Are higher antidepressant plasma concentrations associated with fall risk in older antidepressant users?

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Abstract

Aim Antidepressants are well-established fall-risk increasing drugs(FRIDs) and therefore falls should be considered an important adverse drug event(ADE) of antidepressants. However, not all antidepressant users experience fall incidents and factors associated with increased fall risk among antidepressant users are incompletely understood. Our objective was to explore whether antidepressant plasma concentrations are associated with falls in older antidepressant users. Methods For this study, we included antidepressant users of the multicenter B-PROOF study. Fall incidents were recorded prospectively using fall calendars. Antidepressant plasma concentrations were analyzed by Liquid chromatography-mass spectrometry(LC-MS) at baseline and at 2 years follow-up. The associations between the observed antidepressant concentration, or concentration change over time (delta) and fall risk were assessed using Cox proportional hazard and logistic regression models and adjusted for potential confounders. Results In total 93 selective serotonin reuptake inhibitor(SSRI) and 41 antidepressant(TCA) users were identified. There was a significant association between baseline TCA plasma concentration and fall risk within users (HR 2.50, 95% CI 1.07-5.87, crude model). Adjusted there were no significant associations between concentrations of SSRIs and fall risk. Also, for delta concentrations there was no association with fall risk in users. Conclusion There might be an association between plasma concentrations of TCAs and the risk of falling in older users. However, these results needs to be interpreted with caution considering the small sample size and accompanying limitation of confinement to crude analyses. Therefore, replication in a larger cohort, preferably including adjustment for potential confounders and more frequent measures of plasma concentrations is needed.

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Keywords

Accidental falls, Antidepressants, Older adults, Pharmacokinetics, Adverse drug events, Plasma concentration

What is already known about this subject

- Antidepressants have been consistently associated with increased fall risk and different adverse effects of antidepressants can influence fall risk.
- In older adults, there is substantial inter-individual variation in drug pharmacokinetics and – dynamics.
- Whether antidepressant plasma concentrations can predict falls, is unknown.

What this study adds

- Our study shows an association between TCA plasma concentration and fall risk.
- Due to small sample size and only having plasma concentrations available only at certain time points, these analyses should be considered exploratory.
- Replication in a larger cohort is needed, with more frequent measurements of plasma concentrations.

Data availability

Because of restrictions based on privacy regulations and informed consent of the participants, data cannot be made freely available in a public repository. B-PROOF data can be obtained upon request. Requests should be directed towards the principal investigators of the study, who have a protocol for approving data requests.

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Author contribution

A.C.Pronk, L.J.Seppala, K.J.Ploegmakers, E.P.van Poelgeest, R,Mathot, B.Stricker and N.van der Velde were responsible for the conceptualization and methodology of the study. K.Swart, S.C.van Dijk, S.Oliai Araghi, L.C.P.G.M.de Groot and N.M.van Schoor were responsible for data curation.

A.C.Pronk analyzed the data. A.C.Pronk, L.J.Seppala, E.P.van Poelgeest and N.van der Velde were responsible for interpreting the data and wrote the original draft of the manuscript. All authors reviewed the final version and gave approval of the version to be published.

Competing interest

KS is an employee of the PHARMO Institute for Drug Outcomes Research. This independent research institute performs financially supported studies for government and related healthcare authorities and several pharmaceutical companies. The other authors have declared that no competing interest exist.

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Aim

Antidepressants are well-established fall-risk increasing drugs(FRIDs) and therefore falls should be considered an important adverse drug event(ADE) of antidepressants. However, not all antidepressant users experience fall incidents and factors associated with increased fall risk among antidepressant users are incompletely understood. Our objective was to explore whether antidepressant plasma concentrations are associated with falls in older antidepressant users.

Methods

For this study, we included antidepressant users of the multicenter B-PROOF study. Fall incidents were recorded prospectively using fall calendars. Antidepressant plasma concentrations were analyzed by Liquid chromatography-mass spectrometry(LC-MS) at baseline and at 2 years follow-up. The associations between the observed antidepressant concentration, or concentration change over time (delta) and fall risk were assessed using Cox proportional hazard and logistic regression models and adjusted for potential confounders.

Results

In total 93 selective serotonin reuptake inhibitor(SSRI) and 41 antidepressant(TCA) users were identified. There was a significant association between baseline TCA plasma concentration and fall risk within users (HR 2.50, 95% CI 1.07-5.87, crude model). Adjusted there were no significant associations between concentrations of SSRIs and fall risk. Also, for delta concentrations there was no association with fall risk in users.

Conclusion

There might be an association between plasma concentrations of TCAs and the risk of falling in older users. However, these results needs to be interpreted with caution considering the small sample size and accompanying limitation of confinement to crude analyses. Therefore, replication in a larger cohort, preferably including adjustment for potential confounders and more frequent measures of plasma concentrations is needed.

Introduction

Falls in older adults are a major public health problem and associated with substantial health care costs and decreased quality of life[1]. Annually, one-third of individuals over the age of 65 falls at least once and 20% of these falls lead to severe injuries[2]. Well established fall risk factors are fall-risk-increasing drugs (FRIDs) [3] and antidepressants use has consistently been associated with increased fall risk [4]. Therefore, falls should be considered a common adverse drug event (ADE) of antidepressants [5]. However, not all antidepressant users fall and un(der)treated depression also increases fall risk [6, 7]. It is therefore important to identify for whom the risk-benefit ratio of antidepressant use is detrimental. Which individual factors in antidepressant users contribute to fall risk, however, is not completely understood. A dose-response relationship between antidepressants and the incidence of falls has been demonstrated in older adults [8, 9]. However, in older adults there is substantial inter-individual variation in drug pharmacokinetics and –dynamics [10, 11]. Also, often polypharmacy and multimorbidity are present, predisposing to high prevalence of drug-drug and drug-disease interactions[12]. This makes predicting (adverse) drug effects based on given dosage difficult. Therefore, the availability of antidepressant plasma concentrations could be of value in predicting fall risk in antidepressant users.

Measuring drug concentrations to guide dosing of medicines, optimize treatment response and minimizing ADE, is called therapeutic drug monitoring (TDM). Especially within psychiatry this is a widely used approach [13]. Whether antidepressant plasma concentrations is associated with fall risk, however, has not been studied before. Potentially antidepressant plasma concentration measurements could guide clinical decision making in falls prevention. For instance, with regard to decisions on deprescribing or exchanging the antidepressant to a safer alternative. Therefore, our objective was to explore whether fall risk in older adults is related to the antidepressant concentration in plasma. We hypothesized that antidepressant users with higher exposure in plasma would have a higher risk of falling compared to those with lower concentrations.

Methods

Trial design and participants

For this explorative study, antidepressant users from the multicenter B-PROOF (B-Vitamins for the Prevention of Osteoporotic Fractures; ClinicalTrials.gov NCT00696514) study were included. A detailed description of the trial was published previously [14]. In short, B-PROOF was a large multicenter, double-blind, placebo-controlled trial for which persons 65 years and older with mildly elevated homocysteine levels were recruited to participate between 2008 and 2011, for a follow-up period of 2-3 years. A total of 2,919 participants were included. The primary aim was to assess whether the addition of vitamin B12 and folic acid to vitamin D therapy prevented osteoporotic fractures. Because the intervention did not affect fall-related outcomes, data could be used for the current observational study [15]. The Medical Ethics Committee of Wageningen University approved the study protocol of the B-PROOF study [14]. Before entering the study, all participants gave their written informed consent. All experiments were conducted in accordance with the principles of the Declaration of Helsinki.

2.2 Antidepressant usage

Participants were considered antidepressant user based on pharmacy prescription and self-reported usage data. Based on the number of users, participants using TCAs: amitriptyline (N06AA09), nortriptyline (N06AA10), and the SSRIs: citalopram (N06AB04), escitalopram (N06AB10), fluoxetine (N06AB03), fluvoxamine (N06AB08), paroxetine (N06AB05), sertraline (N06AB06) and the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine (N06AX16) [16] were selected.

Usage was defined as having a prescription (based on pharmacy dispensing record data, obtained from the Dutch Foundation for Pharmaceutical Statistics (SFK)). Participants having prescriptions up to 30 days prior blood withdrawal at baseline and/or follow-up visit were selected. To capture more potential users, also participants with a prescription of up to 30 days after the withdrawal date were selected as some participants might have not had a refill in the 30 days before. In case of missing pharmacy data, usage was defined in case of self-reported usage based on questionnaires at baseline and follow-up.

To determine used dosage, defined daily dose (DDD) was used. DDD is a statistical measure of drug consumption and is the assumed average maintenance dose per day for a drug used for its main indication in adults [16]. The average prescribed daily dose was based on the prescription (or self-reported data) in closest proximity to the date of baseline blood sampling.

2.3 Exposure: assessment of antidepressant concentration in plasma

Blood samples were obtained from participants in the morning. Participants were in a fasted state, or had had a light breakfast. Venous blood was drawn in an EDTA tube at both baseline and follow up study visits, and stored at -80°C until analysis.

The plasma concentrations of the following antidepressants and their corresponding (active) metabolites were analyzed using LC-MS with electrospray ionization (Thermo Finnigan TSQ Access, Waltham, MA, USA): amitriptyline, nortriptyline, citalopram and metabolite des(methyl)-citalopram, fluoxetine and metabolite norfluoxetine, fluvoxamine, paroxetine, venlafaxine and metabolite desmethylvenlafaxine and sertraline and metabolite norsertraline. A detailed description of the analysis method can be found in the supporting information**(Supporting information appendix S1**). With regard to the assessment of total drug exposure metabolite concentrations of the parent drug and metabolite were summed as in line with clinical practice. Some amitriptyline and nortriptyline users had plasma concentration below the lower limit of quantification (LLQ) of the LC-MS method. In these samples, it was possible to determine semi-quantitative concentration values **(Supporting information appendix S1)** .

2.4 Outcome

The primary outcome was time to first fall during follow-up. Falls were defined as "an unintentional change in position resulting in coming to rest at a lower level or on the ground" as recommended by the Prevention of Falls Network Europe [17]. Falls were reported prospectively by using fall calendars, which the participants filled in weekly and returned to the research team every three months. Participants were contacted via telephone in case of missing or unclear data. Participants were followed until their first fall incident until their drop-out date or the date of their last calendar, date of death or end of the study, which ever came first [14]. We used the data from fall calendars as a binary variable (yes/no) for the analyses of plasma concentrations at follow-up and delta concentration.

Covariates

Participant data were collected at baseline and follow-up using a questionnaire that included data on age, gender, smoking, alcohol consumption, comorbidities and history of falls. During study visits, data was collected on (self-reported) medication use, body mass index (BMI), blood pressure, serum creatinine, physical performance, handgrip strength, cognitive status, depressive symptoms and presence of pain. For screening of depressive symptoms, the 15-item version of the Geriatric Depression Scale (GDS-15) was used. Cognitive performance was assessed by the mini-mental state examination (MMSE). For pain, the EURoQoL-item 4 was used (pain or other complaints). Baseline use of concomitant medication was grouped based on the ATC coding system, and polypharmacy was defined as usage of five or more medications[18]. Serum creatinine levels were used to calculate kidney function according to the Cockcroft and Gault formula.

2.6 Statistical analyses

If antidepressant use was reported, and plasma concentration was undetectable, the respective concentration was set at half of the LLQ. For amitriptyline and nortriptyline, where also semi-quantitative concentrations below LLQ were available, half of the lowest detectable concentration was taken. Because the number of participants in the various individual antidepressant groups were too low for the analyses, the individual antidepressants subclasses needed to be pooled into two groups: SSRIs and TCAs. Although venlafaxine is a selective serotonin-norepinephrine reuptake inhibitor (SNRI), we analyzed venlafaxine combined with the

SSRIs. Since the dose of venlafaxine in our cohort did not exceed 150 milligram (mg), SNRIs mainly inhibit reuptake of serotonin and thus closely resemble SSRIs[19].

Relationship between drug exposure and fall risk were analyzed with plasma concentrations expressed on both a continuous and categorical scale. If a participant used two or more antidepressants concomitantly, only the antidepressant with the highest concentration was included in the analyses. First, the continuous plasma concentration levels of the individual antidepressants were analyzed. After that, we standardized the concentrations of the different antidepressants by creating z-scores to be able to combine the continuous concentrations. Second, for each antidepressant the median of the plasma concentration was calculated and the concentrations were reclassified into a binary category (below (which was set as reference) or above the median). Third, to explore the influence of the highest plasma concentrations, the antidepressant plasma concentrations were divided into four categories. The reference category contained the concentrations below the LLQ. After that, the concentrations above LLQ were equally divided into tertiles. For the TCAs, the remaining number of participants per category was too low. Thus the reference category contained the lowest tertile and the concentrations below LLQ and the middle and highest tertile were combined. The same was applied for the SSRI follow-up concentrations. Also, delta concentrations (concentration at follow-up minus concentration at baseline) were calculated, reflecting concentration changes over time. These were reclassified into a binary category, negative (decrease or equal concentration over time) or positive (concentration increase over time)

Baseline characteristics were compared between fallers and non-fallers in antidepressant users. Differences between groups were tested using chi-square test, t-test or a Mann-Whitney U test (categorical and continuous non-normally and normally distributed data, respectively). To study the association between the antidepressant plasma concentration at baseline and falls during follow-up, Cox proportional hazard models were used to calculate hazard ratios (HRs). First, we built a model adjusted for age and gender (model 1). Second, the following covariates were selected as potential confounders based on a Directed Acyclic Graph (DAG) and included in the models if they changed the HR of the association by [?]10% (model 2): region, BMI, smoking, alcohol, pain, depressive symptoms, MMSE, number of medication and estimated glomerular filtration rate (eGFR). If covariates could not be added, due to the lack of 10 fall events per covariate [20], only the unadjusted model is presented. For follow-up visit and delta concentrations, logistic regression models were used to calculate odds ratios (ORs) for the association between concentration and fall risk prior to follow-up visit. The same models as described for the Cox proportional hazard models were applied.

To assess whether antidepressant plasma concentrations were correlated with dosage, we calculated Pearson correlation coefficients. Since there were no signs of multicollinearity (correlation coefficient <0.5) between plasma concentration and dosage, as a possible marker for example for disease severity, was added to model 2 to test whether dosage could be a confounder.

P-values <0.05 were considered statistically significant. Statistical analyses were performed in SPSS (version 28.0, IBM, Armonk, NY, USA).

3. Results

3.1 Study population

A total of 132 antidepressant users were identified from the B-PROOF cohort. Of those, 59.8% reported a fall during follow up. In**Table 1,** the baseline characteristics of fallers and non-fallers in antidepressant users are shown. Fallers were more often female, experienced more falls in the 12 months prior to study enrollment and more frequently used benzodiazepines concomitantly. The antidepressants most often used were paroxetine (34.6%) and amitriptyline (23.5%). The range of plasma concentrations were fluoxetine: <20 µg/L – 366 µg/L (fluoxetine + norfluoxetine), fluvoxamine: 126-330 µg/L, sertraline: <5 µg/L -91 µg/L, paroxetine: <5 µg/L -370 µg/L, (es)citalopram: <5 µg/L -174 µg/L, amitriptyline: <22 µg/L -77.7 ug/L (amitriptyline + nortriptyline), nortriptyline: <22 µg/L -329 µg/L. Median concentrations of the individual antidepressants did not differ significantly between fallers and non-fallers, both at baseline and follow-**up (Supporting information Table S1).** In**supporting information Table S2** present an overview of the reference

values for therapeutic and (potential) toxic concentrations. Paroxetine, (es)citalopram plasma concentrations were in therapeutic range, but relatively low. Sertraline and amitriptyline plasma concentration were below therapeutic range. Nortriptyline plasma concentrations were higher in fallers compared to non-fallers (non-significant) and at follow-up above therapeutic range.

Table 1 - Baseline characteristics of antidepressant users

	Non-fallers n= 53	Fallers n= 79	P-value *
Age (years) [a]	73.4 (5.7)	74.4 (5.9)	0.33
Gender [b] male female	22 (41.5) 31 (58.5)	18 (22.8) 61 (77.2)	**0.02**
Body Mass Index (kg/m^2) [a]	27.3 (4.0)	27.0 (3.6)	0.69
Alcohol use (yes) [b]	42 (79.2)	55 (69.6)	0.22
Smoking (current) [b]	12 (22.6)	13 (16.5)	0.67
Depressive symptoms (GDS) [c]	2 (1-3)	2 (1-5)	0.60
MMSE score [c]	28 (27-29)	28 (26-29.5)	0.71
Pain (yes) [b] No pain Some pain Severe pain	20 (37.7) 29 (54.7) 4 (7.5)	25 (31.6) 47 (59.5) 7 (8.9)	0.77
Physical performance [c] #	8 (4-10)	7 (4-9)	0.27
Handgrip strength maximum (kg) [a]	29.6 (9.7)	26.6 (9.1)	0.08
Walking aid use (yes) [b]	15 (28.3)	22 (27.8)	0.96
Number of falls in 12 months prior to study enrolment [b] No falls One fall Two or more falls	31 (75.6) 7 (17.1) 3 (7.3)	26 (41.9) 19 (30.6) 17 (27.4)	**0.002**
eGFR (ml min^{-1} $1.73m^2$) [c]	70.0 (60.1-80.7)	65.3 (54.7-76.8)	0.19
Number of medications [a]	4.1 (2.4)	4.7 (2.3)	0.12
Polypharmacy (yes) [b]	12 (30)	28 (70)	0.12
Benzodiazepine use (yes) [b]	4 (7.5)	20 (25.3)	**0.01**
SSRI use	37 (69.8)	56 (70.9)	0.89
TCA use	17 (32.1)	24 (30.4)	0.84
Opioid use (yes) [b]	2 (3.8)	10 (12.7)	0.08
Antipsychotic use (yes) [b]	4 (7.5)	5 (6.3)	0.79

	Non-fallers n= 53	Fallers n= 79	P-value *
[a] Mean (SD), [b] presented as n (%), [c] Median (IQR; 25%-75%) GDS= Geriatric Depression Scale; MMSE=Mini-Mental State Examination; eGFR=Estimated glomerular filtration rate according to Cockcroft and Gault formula; Polypharmacy: use of five or more medications # physical performance: combined score of the walking test, chair stand test and tandem stand test (maximum=12). * statistically significant at p-value <0.05	[a] Mean (SD), [b] presented as n (%), [c] Median (IQR; 25%-75%) GDS= Geriatric Depression Scale; MMSE=Mini-Mental State Examination; eGFR=Estimated glomerular filtration rate according to Cockcroft and Gault formula; Polypharmacy: use of five or more medications # physical performance: combined score of the walking test, chair stand test and tandem stand test (maximum=12). * statistically significant at p-value <0.05	[a] Mean (SD), [b] presented as n (%), [c] Median (IQR; 25%-75%) GDS= Geriatric Depression Scale; MMSE=Mini-Mental State Examination; eGFR=Estimated glomerular filtration rate according to Cockcroft and Gault formula; Polypharmacy: use of five or more medications # physical performance: combined score of the walking test, chair stand test and tandem stand test (maximum=12). * statistically significant at p-value <0.05	[a] Mean (SD), [b] presented as n (%), [c] Median (IQR; 25%-75%) GDS= Geriatric Depression Scale; MMSE=Mini-Mental State Examination; eGFR=Estimated glomerular filtration rate according to Cockcroft and Gault formula; Polypharmacy: use of five or more medications # physical performance: combined score of the walking test, chair stand test and tandem stand test (maximum=12). * statistically significant at p-value <0.05

3.2 SSRI concentration at baseline & time to first fall

The results of the association between plasma concentrations of SSRIs at baseline and time to first fall are presented in **Table 2** . There were no significant associations between baseline plasma concentration and time to first fall in SSRI users.

Table 2. Association between baseline SSRI plasma concentration and time to first fall

Category
Concentration divided on median
Concentrations below LLQ
Lowest tertile
Middle tertile
Highest tertile
Z-score
Data is presented in Hazard Ratio with 95% confidence interval. N = number of plasma concentration. Number of events=

3.3 SSRI concentration at follow-up visit & fall risk

The results of the association between plasma concentrations of SSRIs at follow-up and fall risk prior study visit are presented in Supporting information **Table S3.** An increased fall risk was found for users with concentrations in the middle tertile compared to users with the lowest concentrations (OR 4.67, 95% CI 1.09-19.9). However, after adjusting for confounders this association disappeared.

3.4 TCA concentration at baseline & time to first fall

The results of the association between plasma concentrations of TCAs and time to first fall are presented in **Table 3.** A significantly increased fall risk was seen for higher TCA plasma concentrations compared to the lowest plasma concentrations (HR 2.50 (1.07-5.87).

Table 3. Association between TCA baseline plasma concentration and time to first fall

Concentration divided on median	
Concentrations below LLQ & lowest tertile concentrations	
Middle & highest tertile concentrations	
Z-score	
Data is presented in Hazard ratio with 95% confidence interval. N = number of plasma concentration samples. Number of e	

3.5 TCA concentration at follow-up visit & fall risk

There were no significant associations between plasma concentrations at follow-up visit and fall risk prior to study visit (**Supporting information table S4)** .

3.6 Plasma concentration over time

To investigate if change in plasma concentration over time was associated with fall risk, we analyzed 73 SSRI and 27 TCA samples with complete data. An increase of concentration over time was not significantly associated with fall risk (**Supporting information table S5**).

3.7 Role of dosage

No dose-response association was found for the different antidepressant groups regarding fall risk in antidepressant users **(Supporting information table S6)** .

4. Discussion

Our results showed that the risk of falling in older users of TCAs is possibly associated with drug exposure, whereas no association was found in users of SSRIs. These results need to be interpreted with caution considering the small sample size and subsequently confinement to unadjusted analysis for the TCA users.

To our knowledge, this is the first study to assess whether antidepressant blood concentrations are associated with fall risk within antidepressant users. Falls have been established to be an important ADE in community-dwelling older persons. Previous studies have consistently established the association between antidepressant use and falls[4]. However, literature linking antidepressant plasma concentrations and falls is scarce. A first indication that measuring antidepressant plasma concentrations might be of value in falls prevention was demonstrated in a case series of patients with drug-induced falls. This study suggested that TDM may help identify patients with drug-induced falls and confirm clinical suspicion of an ADE [21]. The observed possible association between TCA concentrations and fall risk is in line with earlier studies that addressed the role of antidepressant plasma concentrations in fall-related outcomes, e.g. orthostatic hypotension (OH)[22]. Significant correlations between serum concentrations of amitriptyline and fluvoxamine and orthostatic blood pressure drop have been demonstrated [22]. OH is considered an important fall risk factor and pathway in drug-related falls [23]. OH results in transient cerebral hypoperfusion upon standing, which may result in a syncope and/or fall. OH is a prevalent ADE in antidepressants, best known for TCAs, but also seen with SSRIs [7]. Furthermore, anticholinergic activity, which can increase fall risk, by among others risk of delirium and visual disturbances, increases with increasing plasma concentrations of nortriptyline (even at therapeutic levels) [24].

We observed a possible increased fall risk for users with higher plasma concentrations of TCA , which is in line with our hypothesis. However, the sample size was small. Furthermore, especially for amitriptyline the measured concentrations were below reference range for therapeutic effect or in therapeutic range, thus we

cannot generalize our findings to potentially toxic concentrations. However, older adults are more at risk for adverse events due to altered pharmacokinetics and – dynamics[25]. TDM for TCAs is well-established in clinical practice, both for therapeutic effect and toxicity[26-29]. For SSRIs, the clinical use of TDM is less frequently employed, especially in older adults [30]. For most SSRIs therapeutic reference ranges are wide, evidence for a relationship between drug concentration and therapeutic outcome is weak and risk for toxicity is relatively low compared to TCAs[29, 31, 32]. So in general, available data do not suggest benefit for (routine) monitoring of SSRI plasma concentrations[31]. However, TDM for SSRIs is recommended in specific populations like advanced age [13, 32]. Since, studies have shown higher exposure to antidepressant concentrations compared to younger patients [33, 34]. And also adequate use of TDM has been shown to be cost effective in older adults [35, 36]. Thus, the lack of applying TDM and lack of lower blood concentrations as target, can possibly contribute to the risk of falls, an important ADE.

An important strength of our study is the prospective nature, using fall calendars. In falls research this method is considered the golden standard to avoid recall bias [37]. Also, data on medication use was collected thoroughly, using both pharmacy prescription data and self-reported medication lists. Our study also has some important limitations. First, limited power was a problem. Despite the large B-PROOF database, the remaining group of participants that met the inclusion criteria was small as prevalence of antidepressant usage was low. Due to small groups, we needed to pool the data and needed to standardize and categorize the plasma concentrations. Second, information about plasma concentrations during the fall incident was not available, since such an unplanned event cannot be anticipated for. Thus we only had blood samples from baseline and follow-up study visit. Baseline or follow-up plasma concentrations might not be representative for the plasma concentration at the time of the fall incidents. Also, for some participants follow-up samples were missing. Thus it was unsure whether they were an actual antidepressant user at the time of the fall incident. However, this issue probably did not affect our results, since when repeating the analyses in the participants with baseline and follow-up samples, the results did not change significantly (data not shown). Third, for the association between delta concentrations and fall risk cannot be ruled out that concentrations changes did not reflect clinical relevant differences. By coding them binary (either increase or decrease) it could be that not relevant changes are mixed with clinical relevant changes. Fourth, our cohort consisted of relatively healthy community-dwelling older people. Frail older adults, can exhibit different patient characteristics, different pharmacokinetics which could lead to different results [25].

5.Conclusion

Our explorative study showed a possible association between plasma concentrations and fall risk in older TCA users, but not in SSRI users. However, this needs to be interpreted with caution due to the small sample size and accompanying impossibility to perform multivariate analyses in this group. The current study has no direct clinical implications as our findings should be further re-evaluated in a larger cohort. Ideally replication would not only include multivariate assessment, but also include information about medication adherence and concentration measurements around the fall incident. However, this topic is important since it would give us more detailed insight in risk factors determining medication related fall risk and has the potential to personalize clinical decision making, maximizing benefit and minimizing harm in antidepressant use for older persons at risk of falling.

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