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Impact of Discontinuation of Fall-Risk-Increasing Drugs on Falls in Multimorbid Older Patients With Polypharmacy

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Keywords: accidental falls | deprescribing | fall interventions | FRID

ABSTRACT

Background: Falls are a major concern in the older population. An important cause of falls is fall-risk-increasing drugs (FRID). However, it is not known if the discontinuation of FRID leads to a reduction of falls. Therefore, the aim of this study was to assess the association between discontinuation of FRID and the occurrence of falls and recurrent falls.

Methods: This study included adults aged ≥ 70 years with multimorbidity and polypharmacy who were enrolled in a cluster randomized controlled trial assessing hospital pharmacotherapy optimization (OPERAM). Participants who were using FRID at baseline, were alive after 2 months of follow-up, and provided data on fall occurrence were included. FRID discontinuation was defined as discontinuation of ≥ 1 FRID within 2 months after inclusion, including the following groups: antidepressants, antiepileptics, antihistamines, antipsychotics, benzodiazepines and z-drugs, diuretics, opioids, and alpha-blockers. Multivariable cox regression analysis, using inverse probability weighting, was performed to assess the association between FRID discontinuation and the occurrence of falls.

Results: Our analysis included 1546 participants, with a median age of 79 years (IQR 74–84) and 45% female. After 2 months of follow-up, FRID were discontinued in 878 (57%) participants. Among all participants, 378 (24%) experienced a fall within 1 year of follow-up, with 137 (9%) of the participants experiencing two or more falls, and 199 (13%) participants experiencing a serious fall. No association was found between FRID discontinuation and the occurrence of falls. In a subgroup of participants with a previous fall, discontinuation of antipsychotics was associated with a lower occurrence of falls (HR 0.32 [CI 0.12–0.84], $p = 0.02$).

Conclusions: In multimorbid older patients using FRID, falls are highly prevalent. No association was found between discontinuation of FRID and the risk of falls, except for the discontinuation of antipsychotics in patients who experienced a previous fall.

1 | Introduction

Falls are a major concern in the older population. Prior research estimated that approximately one-third of people aged 65 years or older fall every year and that the fall rate further increases with higher age, particularly in institutionalized patients [1, 2]. Considering that the population is aging, falls will be an increasing problem in the upcoming years. They can lead to serious injury, fear of falling, functional decline, and decreased quality of life [3, 4]. Furthermore, falls are the leading cause of death due to unintentional injuries in older adults [5]. They also impose a major economic burden on society [6].

Falls are mostly multifactorial, with the risk of falls increasing with the number of risk factors [7–10]. Important risk factors include age, sex, multimorbidity, polypharmacy, and cognitive impairment [11]. Unfortunately, not all risk factors are modifiable. A risk factor that is modifiable and could potentially lead to a reduction of falls is the discontinuation of fall-risk-increasing drugs (FRID). Previously, a large systematic review and meta-analysis demonstrated a higher risk of falls with the use of multiple drugs [12–14]. Subsequently, the Screening Tool of Older Persons Prescriptions in older adults with high fall risk (STOPPFall) was developed to support clinicians in the management of FRID [15]. This tool was created based on evidence from meta-analyses and national fall prevention guidelines in Europe, utilizing an expert Delphi consensus process [15].

Although it seems plausible that FRID discontinuation may lead to a reduction of falls, a meta-analysis showed no effect of FRID discontinuation as a single intervention on the occurrence of falls [16]. However, the evidence was sparse and of very low quality, consisting of only a few randomized controlled trials ($n = 5$), with small sample sizes (FRID discontinuation in fewer than 120 patients) or focusing exclusively on nursing home populations [16]. Therefore, the primary aim of this study was to assess the association of FRID discontinuation, by using the STOPPFall screening tool, with falls in multimorbid older patients with polypharmacy. Furthermore, we assessed whether discontinuation was associated with a decrease in recurrent falls.

2 | Methods

2.1 | Setting, Study Population and Study Design

We used the data from the OPERAM trial: Optimizing thErapy to prevent Avoidable hospital admissions in Multimorbid older people (OPERAM). This cluster randomized controlled trial was conducted in four European countries (Belgium, Ireland, the Netherlands, and Switzerland) and assessed if a structured medication review could prevent drug-related hospital admissions. Participants of 70 years and older with multimorbidity (≥ 3 chronic conditions) and polypharmacy (≥ 5 daily drugs used for > 30 days before eligibility assessment) who were admitted between December 2016 and October 2018 in four medical centers were enrolled. Data were collected at hospital admission (baseline), and after two, six, and 12 months. More detailed information on the study protocol and intervention was previously published [17, 18].

In the current study, participants who were using at least one FRID at baseline, were alive after 2 months of follow-up, and provided data on fall occurrence were included.

The OPERAM trial was conducted in accordance with the declaration of Helsinki and was approved by the medical ethics review boards of all participating sites and registered under trial registration number NCT02986425. As the current study used the same data, no additional ethical approval was needed.

2.2 | Data Collection

The following data were extracted from the database: age, sex, history of falls according to participant, polyneuropathy, Parkinson's disease, depression, dementia, stroke, vertigo/dizziness, body mass index (BMI), and dependency in activities of daily living (ADL) (defined as ≥ 1 dependency in ADL according to the Katz ADL index [19]). For diagnosis information, we used the 10th version of the International Classification of diseases (ICD). A full list of used ICD-10 codes is provided in Data S1. For comorbidity burden, we used the Elixhauser comorbidity index, an instrument that assesses comorbidity burden based on 30 comorbidities [20]. Scores were calculated using the comorbidity package in R, based on ICD-10 codes [21].

2.3 | FRID

All participants who were using FRID at enrollment were included in this study. Considering there is no worldwide consensus on which medications are classified as FRID, FRID were chosen a priori according to the STOPPFall and included the use of antidepressants (tricyclic antidepressants, selective serotonin reuptake inhibitors), antiepileptics, antihistamines, antipsychotics, benzodiazepines and z-drugs, diuretics, opioids, alpha-blockers, medication used for urinary frequency and incontinence, and vasodilators used in cardiac disease.

FRID were identified in the database through Anatomical Therapeutic Chemical codes (ATC-codes). The ATC-codes used are provided in Data S1. Discontinuation of FRID was defined as the use of a specific type of FRID at baseline (index hospitalization) and no longer used at 2 months of follow-up, as reported by the study participant. If this information was unclear, it was confirmed by contacting the participant's pharmacy or primary care provider. The two-month criterion was chosen to align with the OPERAM study [17], as this was the first follow-up point in the OPERAM study, allowing sufficient time for the implementation of any medication advice provided.

Summary

- Key points
  - This study did not find an overall association between the discontinuation of FRID and the occurrence of falls.
  - In participants that already experienced a fall, discontinuation of antipsychotics was associated with a lower risk of falls.
- Why does this paper matter?
  - Falls are a major concern in the older population.
  - A risk factor that is modifiable and could potentially lead to a reduction of falls is the discontinuation of fall-risk-increasing drugs (FRID).
  - More understanding of whether the discontinuation (certain types) of FRID leads to a decrease in falls can help tailor interventions to improve patient safety and outcomes.

FRID restart was defined as the re-initiation of a FRID during the follow-up period, after it had been discontinued at baseline, and before the occurrence of the first fall. This was regardless of the duration of FRID use after the restart.

2.4 | Falls

During the study, participants were interviewed by telephone at two, six, and 12 months after inclusion and asked about falls during follow-up. Falls were defined as one or more falls in the period of 2 months after inclusion through 12 months of follow-up. Participants that fell two or more times were defined as "recurrent fallers". Furthermore, a serious fall was defined as a fall resulted in fracture, hospitalization and/or death. All fall outcomes were analyzed as dichotomous variables (yes/no).

2.5 | Statistical Analysis

Categorical variables were reported as proportions, and continuous variables as means with standard deviation (SD) or medians with interquartile range (IQR) for nonparametric data. Differences between groups were assessed by chi-squared test, the unpaired t-test for parametric continuous data, and Wilcoxon signed rank test for nonparametric continuous data. A two-sided probability of $p < 0.05$ was considered statistically significant. Outcomes were calculated with a 95% confidence interval (95% CI). Data were analyzed using R software (version 4.2.0).

2.6 | Inverse Probability Weighting

Inverse probability weighting (IPW) by the propensity score (PS) was used to obtain adjusted hazard ratio estimates. The following equation was used to calculate the IPW by the PS: *(type of)* FRID/propensity + (1-*(type of)* FRID)/(1-propensity) [22]. The distribution of IPW weights was graphically inspected to ensure appropriate balancing of covariates and to avoid instability due to extreme weighting. To minimize the impact of extreme values, the IPW weights were truncated at a maximum value of 10. The propensity score was calculated based on potential confounders identified in the literature [7, 10, 23], and was divided into two sets:

- *Simplified set*: Age, sex, history of falls, Elixhauser comorbidity index, dependency in ADL, the number of medications, and the intervention group.
- *Comprehensive set*: All variables in the simplified set, plus depression, dementia, Parkinson's disease, stroke, polyneuropathy, and vertigo.

2.7 | Primary Outcome

To investigate the association between discontinuation of (types of) FRID and falls, cox multivariable proportional hazard analysis was performed using inverse probability weighting (IPW) by the propensity score (PS) to obtain adjusted hazard ratio estimates. In this analysis, falls were used as the dependent variable and discontinuation of FRID as the independent variable.

Due to the smaller number of events and participants in the different types of FRID, for the primary analysis, the simplified set was used to ensure consistency and model stability across all analyses.

2.8 | Secondary Outcomes

Logistic regression was performed for the secondary outcome of recurrent falls also by using the calculated IPW by the PS. Furthermore, a post hoc subgroup analysis was conducted among participants who experienced a fall before inclusion, specifically to examine the effect of FRID discontinuation in the highest-risk population. This analysis utilized a cox multivariable proportional hazard analysis using IPW to assess the association between FRID discontinuation and falls.

2.9 | Sensitivity Analysis

To test the robustness of the results, two sensitivity analyses were conducted for the overall discontinuation of FRID. First, a sensitivity analysis was performed using the comprehensive IPW model. Second, a sensitivity analysis was performed with the intervention as an interaction factor.

3 | Results

Overall, 2008 participants were included in the OPERAM trial, of whom 1705 participants were using FRID. Of these participants, 129 died and 30 participants withdrew or were lost to follow-up within the first 2 months, and were therefore excluded from this study, leaving 1546 participants for analysis. Baseline characteristics are shown in Table 1. The median age was 79 years (IQR 74–84) and 45% were female ($n = 688$). FRID that were most

TABLE 1 | Baseline characteristics.

	All OPERAM participants with FRID ($n=1546$)	Continuation of FRID ($n=679$)	Discontinuation of ≥1 FRID ($n=867$)	p
Age (median, IQR)	79 (74–84))	78 (74–83)	79 (74–85)	0.002
Female	688 (45%)	284 (42%)	404 (47%)	0.07
Site of inclusion				
Bern	636 (41%)	184 (27%)	452 (52%)	<0.001
Cork	284 (18%)	163 (24%)	121 (14%)	
Louvain	287 (19%)	139 (21%)	148 (17%)	
Utrecht	339 (22%)	193 (28%)	146 (17%)	
Intervention group	741 (48%)	283 (42%)	458 (53%)	<0.001
Control group	805 (52%)	396 (58%)	409 (47%)	
Type of admission				
Elective	367 (24%)	170 (25%)	197 (23%)	0.32
Non-elective	1179 (76%)	509 (75%)	670 (77%)	
Occurrence of fall(s) in the previous year	608 (39%)	242 (36%)	366 (42%)	0.008
Medical history				
Dementia	97 (6%)	34 (5%)	63 (7%)	0.09
Depression	160 (10%)	59 (9%)	101 (12%)	0.07
Polyneuropathy	143 (9%)	46 (7%)	97 (11%)	0.003
Vertigo/dizziness	41 (3%)	21 (3%)	20 (2%)	0.427
Stroke	273 (18%)	138 (20%)	135 (16%)	0.018
Parkinsons disease	51 (3%)	24 (4%)	27 (3%)	0.75
Elixhauser comorbidity index (mean ± SD)	3.9 (2.2)	3.5 (1.9)	4.3 (2.3)	<0.001
Clinical parameters				
eGFR (median, IQR)	58 (40–76)	60 (41–79)	56 (39–75)	0.037
Systolic blood pressure < 110 mmHg	230 (15%)	85 (13%)	145 (17%)	0.032
BMI (mean ± SD)	27.2 (5.6)	27.2 (5.5)	27.3 (5.6)	0.64
ADL dependency	858 (56%)	360 (53%)	498 (57%)	0.12
Medication				
Number of medications at baseline (median, IQR)	10 (8–13)	9 (7–12)	11 (8–14)	<0.001
Different types of FRID at baseline (median, IQR)	2 (1–3)	1 (1–2)	2 (1–3)	<0.001

Note: The following variables had missing data: previous falls (0.9%), BMI (8.1%), diabetes (0.06%), dementia (0.06%), diabetes (0.06%), depression (0.06%), Parkinsons disease (0.05%), ADL dependency (1.5%), eGFR (12%), hypotension (2.8%).
Abbreviations: ADL; activities of daily living, BMI; body mass index, eGFR; estimated glomerular filtration rate, FRID; fall-risk-increasing drugs, IQR; interquartile range, SD; standard deviation.

frequently used were diuretics ($n=991$, 64%), followed by benzodiazepines and z-drugs ($n=424$, 27%) and antidepressants ($n=424$, 27%). Of all participants that were using FRID, 39% ($n=608$) reported a fall in the previous year.

After 2 months of follow-up, FRID were discontinued in 867 (56%) participants. FRID use at baseline and 2 months of follow-up is shown in Figure 1. FRID that were most frequently discontinued were opioids ($n=166$, 58%), antipsychotics ($n=51$, 55%) and

diuretics ($n = 495$, 50%). Participants with FRID discontinuation were older (median age 78 years (IQR 74–83) vs. 79 years (IQR 74–85), $p = 0.002$) and more frequently part of the intervention group (53% vs. 42%, $p = < 0.001$). Furthermore, participants with FRID discontinuation were more likely to experience a fall in the year before inclusion (42% vs. 36%, $p = 0.008$).

During follow-up, among all participants who discontinued FRID at baseline, 401 (46%) participants restarted FRID. The median time to restart was 182 days (IQR 94–337). FRID restarts are shown in Table 2, with the most frequently restarted medications being diuretics ($n = 228$, 46% of diuretic users at baseline), benzodiazepines and Z-drugs ($n = 66$, 40%), and antidepressants ($n = 40$, 35%). Among the participants who restarted FRID, 61 (15%) experienced a fall after the restart, compared to 144 (30%) of the participants who did not restart FRID.

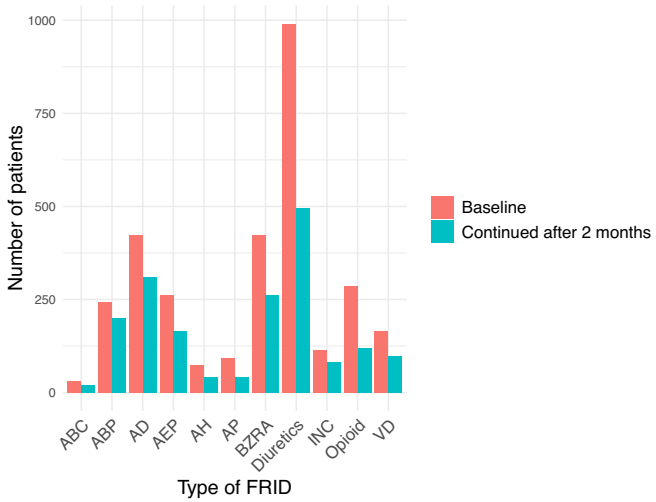

FIGURE 1 | Number of patients using FRID at baseline, and after 2 months. ABC; alpha-blockers prescribed for hypertension, ABP; alpha-blockers prescribed for benign prostatic hyperplasia, AD; antidepressants, AEP; antiepileptics, AH; antihistamines, AP; antipsychotics, BZRA; benzodiazepine receptor agonists, INC; medication used for overactive bladder and incontinence, VD; vasodilators.

3.1 | Discontinuation of FRID and the Occurrence of Falls

The median duration observation time was 352 days (IQR 202–372), during which 210 (14%) participants died (of which 45 participants experienced a fall before death). Among all participants, 378 (24%) experienced a fall, with 137 (9%) experiencing two or more falls, and 199 (13%) experiencing a serious fall. The median time to first fall was 167 days (IQR 109–281). No significant association was found between discontinuation (different types of) FRID and the occurrence of falls (Table 3). Furthermore, no significant association was found between discontinuation (different types of) FRID and the occurrence of recurrent falls (Table 4). All standardized differences of the covariates used, before and after applying IPW, are presented in Data S2. While most standardized differences were less than 0.1, this was not consistently achieved for alpha-blocker prescribed for hypertension and medication used for urinary frequency and incontinence.

3.2 | Subgroup Analysis in Participants That Experienced a Fall Before Inclusion

In participants that experienced a fall before inclusion ($n = 608$), no association was found between discontinuation of FRID and

TABLE 2 | Number of participants who restarted FRID during 10 months of follow-up.

Type of FRID	Use at baseline (*n*, %)	Discontinuation at baseline (*n*, %)	Restart during follow-up after discontinuation at baseline (*n*, %)
All participants with FRID restart (any FRID)	1546 (100%)	867 (56%)	401 (46%)
Alpha-blocker hypertension	32 (2%)	13 (41%)	1 (8%)
Alpha-blocker prostate	243 (16%)	42 (17%)	5 (12%)
Antidepressant	424 (27%)	114 (27%)	40 (35%)
Antiepileptic	261 (17)	97 (37%)	23 (24%)
Antihistamines	75 (5%)	33 (44%)	10 (30%)
Antipsychotic	93 (6%)	51 (55%)	11 (22%)
Benzodiazepines and z drugs	424 (27%)	163 (38%)	66 (40%)
Diuretic	991 (64%)	495 (50%)	228 (46%)
Medication used for urinary frequency and incontinence	113 (7%)	32 (28%)	9 (28%)
Opioid	286 (18%)	166 (58%)	55 (33%)
Vasodilator	165 (11%)	68 (41%)	21 (31%)

Abbreviation: FRID; fall-risk-increasing drugs.

TABLE 3 | Cox regression analysis for the occurrence of falls during a 10-month follow-up period after the discontinuation of FRID (IPW by PS).

Discontinued medication	HR (95% CI)	*p*	Number of falls when FRID discontinued (*n*, %)	Number of falls when FRID continued (*n*, %)
Any FRID	0.86 (0.69–1.06)	0.16	205 (24%)	173 (26%)
Alpha-blocker hypertension	1.95 (0.36–10.51)[a]	0.44	3 (23%)	2 (11%)
Alpha-blocker prostate	1.68 (0.94–3.00)	0.08	16 (38%)	47 (23%)
Antidepressant	0.88 (0.59–1.30)	0.52	37 (33%)	93 (30%)
Antiepileptic	0.99 (0.61–1.61)	0.98	28 (29%)	46 (28%)
Antihistamines	0.49 (0.19–1.29)	0.15	7 (21%)	14 (33%)
Antipsychotic	0.53 (0.25–1.12)	0.10	12 (24%)	17 (41%)
Benzodiazepines and z drugs	0.91 (0.60–1.39)	0.66	41 (25%)	63 (24%)
Diuretic	0.95 (0.73–1.24)	0.72	120 (24%)	122 (25%)
INC	0.77 (0.31–1.94)[a]	0.59	7 (22%)	22 (27%)
Opioid	0.81 (0.51–1.29)	0.37	40 (24%)	33 (28%)
Vasodilator	1.53 (0.74–3.20)	0.25	17 (25%)	15 (16%)

Abbreviations: BZRA; benzodiazepine receptor agonist, CI; confidence interval, FRID; Fall-risk-increasing drugs, HR; hazard ratio, INC; medication used for urinary frequency and incontinence.
[a]Balance was not fully achieved for these variables after applying IPW.

TABLE 4 | The association between multiple falls during the 10-month follow-up period after discontinuation of FRID (IPW by PS).

Discontinued medication	OR (95% CI)	*p*	The occurrence of multiple falls when FRID discontinued (*n*, %)	The occurrence of multiple falls when FRID continued (*n*, %)
Any FRID	1.00 (0.90–1.10)	0.97	72 (35%)	62 (37%)
Alpha-blocker hypertension	0.53 (0.22–1.28)[a]	0.25	1 (33%)	1 (50%)
Alpha-blocker prostate	0.95 (0.74–1.21)	0.67	5 (31%)	18 (38%)
Antidepressant	0.97 (0.83–1.16)	0.78	14 (38%)	36 (39%)
Antiepileptic	1.10 (0.87–1.38)	0.43	13 (46%)	18 (39%)
Antihistamines	0.93 (0.58–1.48)	0.76	3 (43%)	7 (50%)
Antipsychotic	1.25 (0.86–1.81)	0.25	6 (50%)	5 (29%)
Benzodiazepines and z drugs	1.13 (0.94–1.37)	0.20	20 (49%)	23 (37%)
Diuretic	0.97 (0.86–1.55)	0.64	40 (33%)	44 (36%)
INC	1.02 (0.70–1.50)[a]	0.90	3 (43%)	8 (40%)
Opioid	0.84 (0.67–1.05)	0.13	13 (32.5%)	16 (50%)
Vasodilator	1.15 (0.83–1.62)	0.39	6 (35%)	3 (21%)

Abbreviations: CI; confidence interval, BZRA; benzodiazepine receptor agonist, FRID; Fall-risk-increasing drugs, INC; medication used for urinary frequency and incontinence, OR; odds ratio.
[a]Balance was not fully achieved for these variables after applying IPW.

the occurrence of falls (HR 0.78 [CI 0.58–1.05], $p = 0.08$), except for antipsychotics (HR 0.32 [CI 0.11–0.90], $p = 0.03$) (DataS3). However, standardized mean differences were > 0.1 for covariates of alpha-blockers prescribed for hypertension, antihistamines, antipsychotics, medication used for urinary frequency and incontinence, and vasodilators used in cardiac disease (Data S4).

3.3 | Sensitivity Analysis

The association between FRID discontinuation and the occurrence of falls was consistent when conducted using the comprehensive IPW model (HR 0.86, [CI 0.70–1.07], $p = 0.18$) and when repeated with the intervention group included as an interaction factor (group × FRID stop (HR 0.73 [CI 0.47–1.11], $p = 0.139$)).

4 | Discussion

In this large multinational prospective cohort study of multimorbid older patients with polypharmacy, discontinuation of FRID in the first 2 months after hospitalization was highly prevalent. During follow-up, almost a quarter of the participants experienced a fall, of whom 9% experienced multiple falls and 13% experienced a serious fall. No association was found between the discontinuation of FRID and the occurrence of falls. Interestingly, in participants that had already experienced a fall before inclusion, discontinuation of antipsychotics was associated with a 68% lower risk of falls.

To our best knowledge, this is the largest cohort study to date evaluating the effect of FRID discontinuation on falls. Although this post hoc analysis is observational in nature and not specifically designed for this purpose, our findings align with most previous randomized controlled trials, which also found no significant association between FRID discontinuation and the occurrence of falls [24–26, 27]. Remarkably, a previous prospective cohort study assessing 139 patients who had experienced one or more falls in the previous year found that discontinuation of FRID as a single intervention significantly reduced falls [28]. Interestingly, the greatest association was observed when cardiovascular medication was discontinued. This discrepancy in results may be attributed to differences in the risk profile of the study populations. The cohort study included patients referred to a geriatric outpatient clinic who all experienced one or more falls before inclusion and therefore have a very high fall risk. This association was also seen in our own study population, showing a lower hazard ratio for antipsychotics in the sub-analysis in participants that had already experienced a fall before inclusion. Another reason could be that in the aforementioned study, participants that discontinued/reduced the dose of FRID were compared to participants that did not use FRID. This could have led to a higher risk reduction [19]. Furthermore, in our study, we only assessed a selection of cardiovascular medications as suggested by the STOPPFall tool, rather than all cardiovascular medications, which may have led to the exclusion of FRID that could affect falls, potentially missing part of the association in our analysis.

Interestingly, a reduction of falls was especially seen in the participants that discontinued antipsychotics. However, in our propensity score models, complete balance was not achieved, as the group that discontinued antipsychotics had a higher number of medications, which is associated with an increased risk of falls [7]. Despite this imbalance, we observed a significantly lower hazard ratio for falls in this group. This suggests that the protective effect of the discontinuation of antipsychotics may be even stronger if the number of medications were fully balanced. However, residual confounding remains a concern, as we used the simplified propensity score model, which may not have accounted for all relevant covariates. This limitation should be considered when interpreting the findings. Nevertheless, the association between the discontinuation of antipsychotics and a lower risk of falls aligns with a previous randomized controlled trial involving 93 participants, which examined the withdrawal of different types of psychotropic medications on falls over 44 weeks of follow-up and reported a 66% reduction in falls [29]. Unfortunately, no distinction was made between the different types of psychotropic medications in this study, which makes comparison with our study difficult. Other studies that performed a (sub-)analysis on psychotropic medications did not find an association with a reduction of falls [24, 25, 27, 28], but were mostly inadequately powered for the outcome of falls.

The major strengths of this study are the large and multicenter design and the assessment of various types of FRID. Since only a few exclusion criteria were applied, the study population is relatively generalizable to older patients with multimorbidity and polypharmacy. Furthermore, only a few patients were lost to follow-up. However, this study also has several limitations. Firstly, this was a secondary analysis of the OPERAM trial, which was not designed to assess the effect of FRID discontinuation on falls, which may have led to study groups that are not fully comparable. Considering the many risk factors for falls and the lack of clear consensus on which factors play the most significant role, as well as the fact that some IPW models were not fully balanced, some residual confounding may remain. In addition, part of our study population underwent a structured pharmacotherapy optimization intervention as part of the OPERAM study, which could potentially have influenced the results (e.g., in a patient that presented with a fall, discontinuation of FRID in the intervention group will be more likely). However, through the use of the inverse propensity score, we were able to consider many potential confounders and therefore limit this effect. Furthermore, an additional sensitivity analysis showed no significant effect. Secondly, the analyses for the different types of FRID were performed in relatively small groups. Therefore, the multivariate models may have been underpowered, which could have resulted in missing a potential association. Thirdly, the proportion of participants who restarted FRID was high. This could potentially have led to an underestimation of the association between FRID discontinuation and falls. Fourthly, the reasons for (dis)continuing FRID were not assessed in this sub-study. It is possible that, in some patients, a well-considered decision to continue FRID due to a strong medical indication may not increase the risk of falls. For example, in a patient with severe lower urinary tract symptoms due to benign prostatic hyperplasia, the discontinuation of alpha-blockers may lead to recurrence of symptoms and therefore potentially increase the fall risk due to an increase in urinary frequency and urge incontinence. This may therefore outweigh the risk of falls due to orthostatic hypotension in certain patients. More research is needed to assess this personalized decision-making process for the different types of FRID and the relation with falls. Lastly, in this study, falls were self-reported, which could potentially have led to recall bias and subsequently to an underestimation of the effect.

Our study results found that discontinuation of FRID in older patients with multimorbidity and polypharmacy as a single intervention is not associated with a reduction of falls, except for discontinuation of antipsychotics in patients who had fallen previously. The lack of an overall association may be related to adherence to FRID discontinuation and to baseline fall risk. Moreover, the etiology of falls is highly heterogeneous, and medication is not always the only component of fall risk, therefore leading to different risk reductions. Subsequently, reducing fall risk should focus on multifactorial interventions with attention to exercise, assistive technology, environmental strategies, and basic fall risk assessment [30]. Considering a previous fall is the

main risk factor for a recurrent fall, patients with a fall history are likely to benefit most from FRID discontinuation. Further research should focus on FRID discontinuation in high-risk populations, such as patients presenting with a fall to the emergency department or fall clinic. Additionally, examining strategies to improve adherence to discontinuation protocols and understanding the barriers to permanent discontinuation can provide insights into more effective interventions.

In conclusion, in multimorbid older patients with polypharmacy, the occurrence of falls is high. No association was found between discontinuation of (different types of) FRID and the occurrence of falls, except for discontinuation of antipsychotics in patients who experienced a previous fall. Further research should focus on maintaining discontinuation of (different types of) FRID in the population with very high fall risk.

Author Contributions

Namiko A. Goto: conception and design, analysis and interpretation of the data, preparation of the manuscript. **Dayna A. M. van Heel:** analysis and interpretation of the data, revision of the manuscript. **Lauren Dautzenberg:** conception and design, revision of the manuscript. **François-Xavier Sibille:** conception and design, revision of the manuscript. **Emma Jennings:** conception and design, revision of the manuscript. **Douglas C. Bauer:** conception and design, revision of the manuscript. **Carole E. Aubert:** conception and design, revision of the manuscript. **Anne Spinewine:** conception and design, revision of the manuscript. **Nicolas Rodondi:** conception and design, revision of the manuscript. **Huiberdina L. Koek:** conception and design, revision of the manuscript. **Mariëlle H. Emmelot-Vonk:** conception and design, revision of the manuscript. **Wilma Knol:** conception and design, interpretation of the data, revision of the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

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