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# Risk of falls after withdrawal of fall-risk-increasing drugs: a prospective cohort study

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**What is already known about this subject**

- In observational studies, several drugs have been associated with an increased fall risk. A meta-analysis in 1999 found a significant association for neuroleptics, antidepressants, sedatives, diuretics, type IA antiarrhythmics, and digoxin.
- Nevertheless, knowledge on the effect of withdrawal of these drugs on fall risk is scarce. Only one randomized controlled trial has been carried out in 1999, showing a significantly lowered fall risk after withdrawal of sedatives and antidepressants in community-dwelling older persons.

**What this study adds**

- This study indicates that withdrawal of all fall-risk-increasing drugs, including both cardiovascular and psychotropic drugs, is an effective intervention for lowering of falls incidence. This effect appears to be highest for withdrawal of cardiovascular drugs.

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**Aims**
Falling in older persons is a frequent and serious clinical problem. Several drugs have been associated with increased fall risk. The objective of this study was to identify differences in the incidence of falls after withdrawal (discontinuation or dose reduction) of fall-risk-increasing drugs as a single intervention in older fallers.

**Methods**
In a prospective cohort study of geriatric outpatients, we included 139 patients presenting with one or more falls during the previous year. Fall-risk-increasing drugs were withdrawn, if possible. The incidence of falls was assessed within 2 months of follow-up after a set 1 month period of drug withdrawal. Multivariate adjustment for potential confounders was performed with a Cox proportional hazards model.

**Results**
In 67 patients, we were able to discontinue a fall-risk-increasing drug, and in eight patients to reduce its dose. The total number of fall incidents during follow-up was significantly lower in these 75 patients, than in those who continued treatment (mean number of falls: 0.3 *vs.* 3.6; *P* value 0.025). The hazard ratio of a fall during follow-up was 0.48 (95% confidence interval (CI) 0.23, 0.99) for overall drug withdrawal, 0.35 (95% CI 0.15, 0.82) for cardiovascular drug withdrawal and 0.56 (95% CI 0.23, 1.38) for psychotropic drug withdrawal, after adjustment for age, gender, use of fall-risk-increasing drugs, baseline falls frequency, comorbidity, Mini-Mental State Examination score, and reason for referral.

**Conclusions**
Withdrawal of fall-risk-increasing drugs appears to be effective as a single intervention for falls prevention in a geriatric outpatient setting. The effect was greatest for withdrawal of cardiovascular drugs.

## Introduction

Falls are a major public health challenge for countries with ageing populations. Approximately 30% of people aged over 65 years and 50% aged over 80 years will fall in a given year [1]. In addition to the morbidity and mortality associated with the injuries they cause, falls are a principal reason for emergency attendance at the hospital, hospital bed utilization, and transfer to nursing home care [2]. Altogether, falls can have a large negative impact on functioning and quality of life of older persons.

Since falling is a symptom, not a diagnosis, it can be caused by many different factors. In addition, there are often multiple causes for falling in one patient. Therefore, most trials have addressed multifactorial assessment and intervention [3, 4]. This multifactorial assessment has been shown to lower risk of falling, with a risk ratio of 0.82 (0.72, 0.94) in a recent meta-analysis [5]. However, with the exception of mobility training, it is still unclear which parts of the multifactorial assessment are effective and how large the effect on fall risk is for every single intervention [2].

One of the possible single interventions is withdrawal (discontinuation or dose reduction) of fall-risk-increasing drugs (FRID) [5]. Although there are hardly any data about the effectiveness of this single intervention, many associations between falls and drugs have been reported. In particular, psychotropic drugs such as antipsychotics, antidepressants, and sedatives [6–9], and cardiovascular drugs such as diuretics, type IA antiarrhythmics, and digoxin [10] are considered as risk factors. To our knowledge, only one study has addressed the effect of withdrawal of FRID. In 1999 a randomized-controlled trial was published, showing that discontinuation of a subgroup of possible FRID, i.e. antidepressants and sedatives, lowered fall risk [11]. However, this study did not address other possible FRID, and moreover it did not target geriatric patients with a history of falls, but relatively healthy and fit community-dwelling older persons. Therefore, we performed a prospective cohort study in our population of geriatric outpatients, in which we investigated whether withdrawal of FRID was associated with a decrease in fall risk.

## Methods

### *Study participants*

All new consecutive referrals to our geriatric outpatient clinic and the diagnostic day centre were considered to be eligible if they were 65 years or over, had a history of falling, had a Mini-Mental State Examination score (MMSE) of 21 points or higher (out of 30 points) [12, 13] and were able to walk 10 metres without a walking aid. The study protocol was approved by the Medical Ethics Committee of the Erasmus MC and written informed consent was obtained from all patients. Patient recruitment started 1 April 2003 and ended 30 November 2004. During the study period 201 fallers were eligible, 141 gave informed consent and 139 completed follow-up. Non-participants were older ($80.2 \pm 7.3$ years). The main reason for refusing participation was the burden of the extra visits to the clinic.

### *Assessment of drug use*

Before the baseline assessment of the study, a list of drug use during the preceding year was obtained from both the general practitioner and the patient's pharmacist. During baseline assessment the patient, and if applicable a partner or main carer, were consulted on actual drug use, dosages and duration of use. The medication list was checked on a patient basis for use of FRID and for known drug–drug interactions [5–11, 14]. During the second assessment after 3 months, the patient was asked whether changes in drug use had occurred. If so, date and changes in dosage were registered. This was crosschecked with information from letters of consulting physicians, and if there was any doubt a new list was obtained from the pharmacy.

### *Intervention: withdrawal of FRID*

All potential FRID were considered for withdrawal, i.e. anxiolytics/hypnotics (benzodiazepines and others), neuroleptics (dopamine $D_2$-receptor agonists and serotonin dopamine receptor antagonists), antidepressants (tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors and monoamine oxidase inhibitors), antihypertensives (diuretics, β-adrenoceptor blockers, α-adrenoceptor blockers, centrally acting antihypertensives, calcium channel blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers), antiarrhythmics, nitrates and other vasodilators, digoxin, β-adrenoceptor blocker eye drops, analgesics (mainly opioid analgesics), anticholinergic drugs, antihistamines, antivertigo drugs, and hypoglycaemics. Subsequently, in all fallers FRID were stopped if considered redundant, or otherwise if safely possible, reduced in dose over a 1 month period. The prescribing physicians were consulted if drug changes were intended. During follow-up, no other interventions were performed.

### *Falls history and falls follow-up*

A fall was defined as coming to rest unintentionally on the ground or a lower level with or without losing consciousness, but not induced by acute medical conditions,

e.g. stroke, or exogenous factors, e.g. a traffic accident [15]. At baseline, falls history was considered positive if at least one fall had occurred within the previous year. Other questions concerning falls history were whether more than one fall had occurred in the past year and whether the patient fell on average on a yearly, monthly or weekly basis.

For every participant, we assessed fall incidents during a fixed follow-up period of 2 months, after a set 1 month period, during which we stopped or decreased the dose of FRID. For registration of fall incidents during follow-up, respondents were asked to report their falls weekly on a falls calendar and to mail the calendar page at the end of every month. Every participant was called by the first author to check compliance with these calendar pages.

### *Baseline characteristics*

Functional status was measured with the Activities of Daily Living measurement (ADL) [16] and the Instrumental Activities of Daily Living measurement (IADL) [17]. We also recorded whether or not study participants used a walking aid in daily life. Information on comorbidity was obtained in an interview with the study participants at baseline and this was crosschecked with the record of the geriatrics department and information from the general practitioner. The following diseases were recorded: hypertension, myocardial infarction, diabetes mellitus, angina pectoris, heart failure, atrial fibrillation, heart rhythm disorders other than atrial fibrillation, stroke, transient ischaemic attack, arthritis, Parkinson's disease and parkinsonism, chronic obstructive pulmonary disease, delirium, depression, epilepsy, eye disorders, anxiety disorders, sleeping disorders, history of hip fracture, history of nonhip fracture, thyroid disorder, malignancy, Menière's disease, urinary incontinence, other diseases and total number of comorbid diagnoses.

### *Statistical analysis*

Before starting the study, we estimated that we would need 200 subjects, including 130 fallers, to have 80% power for detection of a relative risk of 0.5, taking into account an alpha of 0.05.

At baseline, all persons with a falls history were stratified according to withdrawal (discontinuation or dose reduction) of FRID. To compare potential confounders between the two groups, an independent *t*-test was used for continuous variables, and a chi-square test for dichotomous variables. The adjusted mean number of falls (cumulative incidence) during follow-up was calculated with ANOVA.

The association of falls incidence during follow-up according to FRID withdrawal was evaluated using a standard multivariate Cox proportional hazards model in which we tested for collinearity, proportionality and goodness of fit. We tested for effect modification with interaction terms. Hazard ratios of events (first fall during follow-up) were computed as estimates of relative risk. To account for potential confounding, we computed a multivariate model containing the following variables on the basis of the fact that they changed the point estimate by 5% or more, or because they were considered clinically relevant: age, gender, use of FRID, baseline falls frequency, total number of comorbid conditions, MMSE score and reason for referral. A second Cox proportional hazards analysis was performed in which the confounders were replaced by a propensity score [18]. All statistical analyses were performed using SPSS software (version 10.1, SPSS Inc., Chicago, IL, USA).

## Results

We were able to withdraw one or more FRID in 75 out of the 139 patients. In 67 patients, FRID were discontinued and in eight patients FRID doses were reduced. For the other 64 fallers, FRID withdrawal was not possible, either because they did not use FRID, or because the FRID could not be discontinued. Also in eight patients, FRID withdrawal was attempted but failed. During the 3 months of follow-up (i.e. 1 month of FRID withdrawal plus 2 months of falls registration) one patient died in the FRID-withdrawal group due to cancer.

The baseline characteristics of the study population are shown in Table 1. Table 2 shows a list of use and withdrawal of FRID. In more detail, we withdrew 17 benzodiazepine derivatives, five benzodiazepine related drugs, six selective serotonin reuptake inhibitors, two monoamine oxidase inhibitors, two butyrophenone derivatives, one thioxanthene derivative, nine β-adrenoceptor blockers, two α-adrenoceptor blockers, 14 diuretics, seven calcium channel blockers, two angiotensin converting enzyme inhibitors, four angiotensin receptor blockers, five nitrates, three class III antiarrhythmics, one nicotinic acid derivative, three β-adrenoceptor blocker eye drops, five non-steroidal anti-inflammatory drugs, four opioid analgesics, seven antivertigo preparations, one hypoglycaemic and one urinary antispasmodic.

During the 2 months of fall follow-up, 17 patients (23%) in the FRID-withdrawal group experienced one or more falls compared with 20 (31%) in the group without FRID withdrawal, resulting in a crude attribut-

**Table 1**
Baseline characteristics of the study population ($n$ = 139)

| Characteristic | Fallers with drug change ($n$ = 75) $n$ | % (SD) | Fallers without drug change ($n$ = 64) $n$ | % (SD) | $P$ value |
|---|---|---|---|---|---|
| Mean age (SD) | 78.4 | (5.2) | 78.8 | (5.9) | 0.66 |
| Female gender | 53 | 71% | 52 | 81% | 0.17 |
| Referral for falls | 64 | 85% | 43 | 67% | 0.015* |
| >1 fall last year | 58 | 77% | 47 | 73% | 0.59 |
| ≥1 fall per month | 33 | 43% | 22 | 35% | 0.25 |
| Use of walking aid | 40 | 53% | 32 | 50% | 0.69 |
| Mean ADL (SD) | 0.72 | (1.7) | 0.78 | (1.6) | 0.83 |
| Mean IADL (SD) | 13.65 | (3.1) | 13.59 | (3.5) | 0.92 |
| Mean MMSE (SD) | 27.0 | (2.8) | 27.2 | (2.5) | 0.67 |
| Mean number of drugs (SD) | 6.2 | (2.6) | 4.3 | (2.5) | 0.000* |
| Mean number of FRID (SD) | 2.9 | (1.7) | 1.7 | (1.5) | 0.000* |
| Mean number of comorbidity (SD) | 4.6 | (1.9) | 3.7 | (1.7) | 0.002* |

*SD standard deviation; ADL activities of daily living; IADL instrumental activities of daily living; MMSE Mini-Mental State Examination; FRID fall-risk-increasing drugs. *P < 0.05.*

**Table 2**
Use and withdrawal of fall-risk-increasing drugs ($n$ = 139)

| | Baseline use ($n$ = 126) | | Number of withdrawals ($n$ = 75) | |
|---|---|---|---|---|
| Psychotropic drugs | 33 | (26%) | 29 | (39%) |
| Sedatives | 26 | (21%) | 22 | (29%) |
| Antidepressants | 14 | (11%) | 8 | (11%) |
| Neuroleptics | 3 | (2%) | 2 | (3%) |
| Cardiovascular drugs | 62 | (50%) | 41 | (55%) |
| Antihypertensives | 51 | (41%) | 29 | (39%) |
| Nitrates | 15 | (12%) | 5 | (7%) |
| Anti-arrhythmics | 4 | (3%) | 3 | (4%) |
| Nicotinic acid | 1 | (1%) | 1 | (1%) |
| β-adrenoceptor blocker eye drops | 3 | (2%) | 3 | (4%) |
| Other drugs | 41 | (33%) | 18 | (24%) |
| Analgesics | 68 | (54%) | 9 | (12%) |
| Antivertigo preparations | 11 | (9%) | 7 | (9%) |
| Hypoglycaemics | 20 | (16%) | 1 | (1%) |
| Urinary antispasmodics | 4 | (3%) | 1 | (1%) |

*In the second column, the baseline usage of FRID for the total study population is shown. In total, 126 patients used 262 fall-risk-increasing drugs (FRID). In the third column, the 91 withdrawn FRID in 75 patients are given, clustered in psychotropic, cardiovascular and other drugs.*

able risk of 8%. Mean number of falls during follow-up was 0.8 (95% CI −1.0, 2.6) for the group with FRID withdrawal and 3.1 (95% CI 1.1, 5.0) for the group without FRID withdrawal ($P$ value 0.10). After adjustment for age, gender, baseline FRID use, baseline falls frequency, number of comorbid conditions, MMSE-score and reason for referral, the mean number of falls was 0.3 (95% CI −1.6, 2.2) and 3.6 (95% CI 1.6, 5.7),

**Table 3**
Risk of a fall during follow-up according to drug withdrawal in a cohort of older fallers ($n$ = 139)

| | Model 1* | | Model 2† | |
|---|---|---|---|---|
| Drug group | HR | (95% CI) | HR | (95% CI) |
| All FRID ($n$ = 75) | 0.65 | (0.33, 1.28) | 0.48 | (0.23, 0.99)‡ |
| CVD ($n$ = 41) | 0.48 | (0.21, 1.09) | 0.35 | (0.15, 0.82)‡ |
| PTD ($n$ = 29) | 0.71 | (0.31–1.61) | 0.56 | (0.23–1.38) |

*CI confidence interval; FRID fall-risk-increasing drugs; CVD cardiovascular drugs; PTD psychotropic drugs; HR hazard ratio. *Model 1 adjusted for age and gender; †Model 2 adjusted for age, gender, FRID use, baseline falls frequency, MMSE-score, number of comorbid conditions, and reason for referral. ‡$P < 0.05$.*

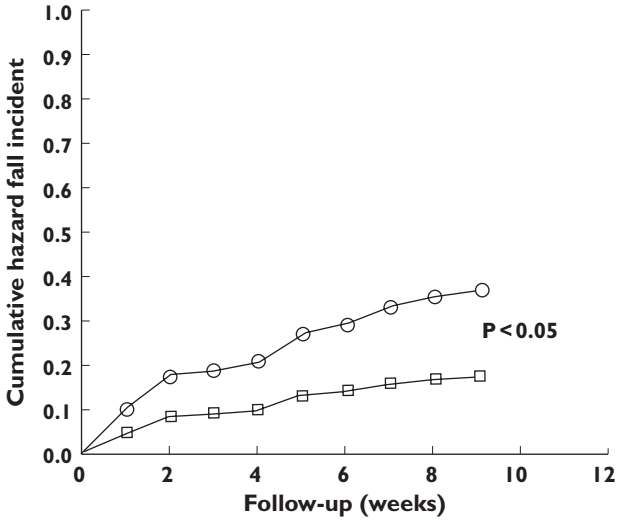


**Figure 1**
Cumulative hazard of a fall incident in 75 patients with FRID withdrawal (□) and 64 patients without FRID withdrawal (○)

respectively ($P$ value 0.025). There was no effect modification by age and gender. Within our FRID-withdrawal group we did not find any known drug–drug interactions, which could have caused a fall as an adverse drug reaction.

For the 139 fallers in our study, overall-FRID withdrawal and cardiovascular-FRID withdrawal were significantly associated with a lower fall risk after adjustment for potential confounders (as mentioned above) (Table 3, model 2). When replacing the confounders with a propensity score, the association was slightly stronger. Figure 1 shows the cumulative proportional hazard of a fall incident during follow-up according to FRID withdrawal, after adjustment for potential confounders. The cumulative hazard of a fall was 0.18 for the FRID-withdrawal group and 0.37 for the group without FRID withdrawal, resulting in an absolute risk reduction of 19% and a relative risk reduction of 49%.

## Discussion

To our knowledge, this is the first prospective cohort study in older fallers in which the effect of withdrawal of all fall-risk-increasing drugs was investigated. During follow-up, the risk of a fall incident was halved ($P < 0.05$).

As expected, because of the observational cohort approach, the two groups differed at baseline in that the group of fallers in whom drug change was possible at baseline used more drugs, more FRID, and also had a higher total number of comorbid conditions (Table 1). Also, this group was significantly more frequently referred for falls and they had a slightly higher fall incidence at baseline. Consequently, the significant reduction of falls during follow-up after withdrawal is clinically very relevant. After all, any confounding by indication would tend to hide a true protective effect, because the discontinuation group had the highest baseline risk of falling, but despite this showed the lowest cumulative hazard of falling during follow-up. In addition to multivariate adjustment, analyses with propensity scores for the likelihood to receive the intervention further increased the protective hazard ratio.

Remarkably, the protective hazard ratio of cardiovascular-FRID withdrawal was stronger than that of psychotropic-FRID withdrawal. This was an unexpected finding, because in earlier studies the strongest associations between fall risk and drug use have always been found for psychotropic drugs, not cardiovascular drugs [6, 10]. This difference may have been caused by a lack of precision in our study, because the psychotropic-FRID withdrawal group was smaller than the cardiovascular-FRID withdrawal group.

### *Limitations of the study*

A potential limitation of our study was the fact that we were not able to perform a randomized double-blind controlled study (RCT) for drug intervention, which would be the ideal research situation to test our hypothesis. The reason we could not do this was that withdrawal of FRID is already implemented in Dutch and international falls guidelines [3, 19], rendering it unethical not to withdraw FRID in patients presenting with a

fall. Therefore, we performed a prospective cohort study in which we compared the effect of drug withdrawal on the incidence of falls with a group of patients in whom FRID withdrawal was not possible. Because of the lack of blinding, we have to consider the possibility of information bias if patients in whom FRID were withdrawn remembered fewer falls than those who continued therapy, or *vice versa*. Information bias by the investigators was unlikely as gathering of data on falling was performed without knowledge of the intervention status. Another potential limitation of our study was the substantial group who declined to participate. On average, these patients were older. Although this might have affected generalizability of our results, we have no reason to suspect that these non-participants would not benefit from FRID withdrawal. Furthermore, in our opinion there was no reason to assume that refusal was differential for the two groups, which makes the possibility of selection bias unlikely.

In conclusion, FRID withdrawal was effective as a single intervention in lowering fall incidence in our study. We have shown that FRID withdrawal is safely possible in a geriatric outpatient setting. The effect on fall incidence was greatest for withdrawal of cardiovascular drugs. On the whole, FRID withdrawal as a single intervention appears to lower fall incidence during short-term follow-up in a frail group of geriatric outpatients. Our findings endorse the guideline advice that withdrawal of FRID should be part of the multifactorial intervention for patients presenting with falls.

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