BMJ Open

Deprescribing Fall-Risk-Increasing Drugs (FRIDs) for the Prevention of Falls and Fall-related Complications: A Systematic Review and Meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-035978
Article Type:	Original research
Date Submitted by the Author:	28-Nov-2019
Complete List of Authors:	Lee, Justin; McMaster University, Division of Geriatric Medicine, Department of Medicine; McMaster University, Department of Health Research Methods, Evidence and Impact Negm, AM; McMaster University Faculty of Health Sciences, School of Rehabilitation Sciences; Hamilton Health Sciences, Geriatric Education and Research in Aging Sciences Centre Peters, Ryan; McMaster University Faculty of Health Sciences, Michael G. DeGroote School of Medicine Wong, Eric; University of Toronto, Division of Geriatric Medicine, Department of Medicine Holbrook, Anne; McMaster University, Division of Clinical Pharmacology and Toxicology, Department of Medicine; McMaster University Faculty of Health Sciences, Department of Health Research Methods, Evidence and Impact
Keywords:	INTERNAL MEDICINE, CLINICAL PHARMACOLOGY, GERIATRIC MEDICINE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

TITLE: Deprescribing Fall-Risk-Increasing Drugs (FRIDs) for the Prevention of Falls and Fall-related Complications: A Systematic Review and Meta-analysis

AUTHORS: Justin Lee, BScPhm, ACPR, MD[1,2,3]

Ahmed Negm, MD, MSc, PhD[3,4]

Ryan Peters, BSc, MD[5]

Eric Wong, BSc, MD[6]

Anne Holbrook, MD, PharmD, MSc[2,7]

[1]Division of Geriatric Medicine, Department of Medicine, McMaster University, Hamilton, Ontario, Canada
[2]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton,
Ontario, Canada
[3]Geriatric Education and Research in Aging Sciences (GERAS) Centre, Hamilton, Ontario, Canada
[4]School of Rehabilitation Sciences, Faculty of Health Sciences, McMaster University, Hamilton Ontario, Canada;
[5]Michael DeGroote School of Medicine, McMaster University, Hamilton, Ontario, Canada
[6]Division of Geriatric Medicine, Department of Medicine, University of Toronto, Toronto, Ontario, Canada
[7]Division of Clinical Pharmacology and Toxicology, Department of Medicine, McMaster University, Hamilton, Ontario, Canada

CORRESPONDING AUTHOR: Justin Lee
Geriatric Education and Research in Aging Sciences Centre
88 Maplewood Avenue, Room 158
Hamilton, Ontario, Canada L8M 1W9
Email: justin.lee@medportal.ca
Telephone: (905) 521-2100

MAIN TEXT WORD COUNT: 3220 (excluding title page, abstract, references, tables)

ABSTRACT:

Objectives: Prevention of falls and fall-related injuries is a priority due to the substantial health and financial burden of falls on patients and healthcare systems. Deprescribing medications known as "fall-risk increasing drugs" (FRIDs) is a common strategy to prevent falls based on retrospective observational associations and presumed benefit. We conducted a systematic review to determine its efficacy for the prevention of falls and fall-related complications.

Design: Systematic review and meta-analysis

Data sources: MEDLINE, EMBASE, CENTRAL, CINAHL and grey literature from inception to March 31, 2019.

Eligibility criteria for selecting studies: Randomized controlled trials of FRID withdrawal compared to usual care evaluating the rate of falls, incidence of falls, fall-related injuries, fall-related fractures, fall-related hospitalization or adverse effects related to the intervention in adults aged ≥65 years.

Data extraction and synthesis: Two reviewers independently performed citation screening, data abstraction, risk of bias assessment and certainty of evidence grading. Random-effects models were used for meta-analyses.

Results: Five trials involving 1305 participants met eligibility criteria for inclusion. Deprescribing FRIDs did not change the rate of falls (rate ratio [RaR] 0.98, 95% CI 0.63 to 1.51), the incidence

of falls (risk difference [RD] 0.01, 95% CI -0.06 to 0.09; relative risk [RR] 1.04, 95% CI 0.86 to 1.26) or rate of fall-related injuries (RaR 0.89, 95% CI 0.57 to 1.39) over a 6 to 12 month follow-up period. No trials evaluated the impact of deprescribing FRIDs on fall-related fractures or hospitalizations.

Conclusion: There is a paucity of robust high-quality evidence to support or refute that a FRID deprescribing strategy is effective at preventing falls or falls-related injury in older adults. Although there may be other reasons to deprescribe FRIDs, our systematic review found that it may result in little to no difference in the rate or risk of falls.

Registration: PROSPERO CRD42016040203

Key Words: Falls, Falls prevention, Fall-risk increasing drug (FRID), Deprescribing, Medication withdrawal, Seniors, Older Adults, Systematic review

Word Count: 298

ARTICLE SUMMARY

Strengths and Limitations of this Study:

- This study's results are based on a systematic review and meta-analysis of randomised controlled trials
- We employed rigorous analytic methods and interpretational approaches including duplicate assessment, subgroup credibility criteria and optimal information size considerations.
- We assessed the certainty in evidence (i.e. quality of evidence) using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Framework.
- Additional studies are needed to reach the optimal information size to reduce uncertainty about this intervention and establish its relative importance in the range of possible fall prevention interventions

INTRODUCTION

Falls and fall-related injuries are significant public health concerns. Every year, 1 in 3 older adults aged ≥65 years falls and 10% of these falls cause serious injury or hospitalization.[1] Falls are estimated to annually cost $50 billion in the United States, $2 billion in Canada, and £2.3 billion in the United Kingdom.[2–4] All jurisdictional levels are making significant investments to implement falls prevention quality improvement initiatives. These include Public Health England's National Falls Prevention Coordinating Group (NFPRCG), the Centers for Disease Control and Prevention (CDC) Stopping Elderly Accidents, Deaths, & Injuries (STEADI) Initiative, and Health Canada's Canadian Patient Safety Institute "Reducing Falls and Injuries from Falls" initiative. National accreditation bodies such as the United States Joint Commission and Accreditation Canada also mandate specific falls prevention activities of healthcare organizations through their required organizational practices and standards.

Since the majority of falls result from multiple factors (e.g. poor strength and balance, visual and cognitive impairment), current practice guidelines and accreditation standards focus on multi-component assessment and intervention strategies.[5] However, the 2018 United States Preventive Services Task Force evidence report recommends that multifactorial interventions only be offered to select patients because the overall net benefit is small.[6] In fact, there is ongoing debate on the relative merits of focusing on single versus multifactorial interventions, and many clinicians and institutions focus on single interventions due to limited resources.[7]

As an individual intervention, only exercise has robust evidence demonstrating reductions in the incidence of fallers and rate of injurious falls.[6,8] It is unclear if other parts of the multi-component strategy are effective, how large is their individual treatment effect, and which components should be prioritized when resources are limited.

Despite limited evidence of effectiveness, deprescribing medications known as "fall-risk increasing drugs" (FRIDs) is common practice and typically included in both multifactorial and single intervention strategies. The justification is based on the belief that certain medications increase the risk for falls. These include anti-hypertensives, anti-arrhythmics, anti-cholinergics, anti-histamines, sedatives-hypnotics, anti-psychotics, anti-depressants, opioids and NSAIDs.[9–11] This evidence is based primarily on retrospective observational data with limited adjustment for confounders, dosage or duration of therapy. It is therefore unclear whether the associated increase in falls is truly related to such drug use versus the underlying conditions or patients for which the drugs are treating.

To justify the common practice of deprescribing FRIDs, confirmation of its effectiveness as a fall prevention strategy in older adults is needed. To the best of our knowledge, no previous systematic review has addressed this specific question nor incorporated new data from the largest RCT of FRID withdrawal to date.[12] We therefore conducted this systematic review to evaluate the deprescribing of FRIDs to prevent falls and clarify its evidence base.

METHODS

This review was developed using the Cochrane Handbook and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13,14] The protocol was registered in PROSPERO (CRD42016040203) and previously published and described in detail.[15]

Search Strategy

MEDLINE, EMBASE, CINAHL and the Cochrane Central Register of Controlled Trials (CENTRAL) electronic databases were searched from inception to March 31, 2019 using a combination of Medical Subject Headings, controlled and free-text terms synonymous for the intervention. The MEDLINE search strategy is shown in Supplementary Figure S1. This strategy was modified for use in other databases.

Reference lists of relevant studies, reviews and guidelines were reviewed to identify additional studies. Trial registries and geriatric medicine conference abstracts were also reviewed.

Study Eligibility Criteria

After pilot testing the eligibility criteria, pairs of reviewers independently conducted screening. A third reviewer resolved disagreements.

Studies were included if they were RCTs evaluating FRID deprescribing or withdrawal with the intent of reducing falls. FRID deprescribing was defined as the planned and supervised discontinuation or dose reduction of single or multiple medications thought to independently increase falls risk.[9–11]

The comparator could be usual care (i.e. no change in usual activities and/or no FRID withdrawal) or a control intervention not thought to reduce falls. Studies focused on adults aged ≥65 years from all settings were included. Studies involving FRID withdrawal within multi-component interventions were excluded if the effect of FRID withdrawal could not be isolated.

The primary outcomes of this review were the (1) rate of falls (defined as the total number of falls per unit of person time that falls were monitored) and (2) incidence of falls (i.e. number of fallers). Secondary outcomes included the incidence of (1) fall-related fractures, (2) fall-related

injuries, (3) fall-related hospitalization, (4) adverse effects related to the withdrawal intervention (e.g. disease relapse, symptomatic withdrawal).

Data Extraction and Quality Assessment

Two reviewers independently abstracted data on general study characteristics, study participants, interventions, comparisons, and outcomes using standardized electronic data extraction forms. Disagreements were resolved through consensus.

Two reviewed independently conducted risk of bias (RoB) assessments using the Cochrane Risk of Bias tool.[16] A previously published modification to the RoB assessment was employed to estimate unclearly reported study methods and allow for sensitivity analysis.[17] This modification involved a structured approach where a score of "definitely low risk", "probably low risk", "probably high risk", or "definitely high risk" was assigned to each RoB criterion. "Definitely" and "probably" scores were collapsed for both low- and high-risk of bias score. Disagreements were resolved through consensus.

Data Synthesis and Analysis

The rate of falls was reported as a rate ratio (RaR) with a 95% confidence interval (CI). Dichotomous outcomes (i.e. incidences of falls, fall-related fracture, fall-related injury, fall-related hospitalization and adverse effects related to the withdrawal intervention) have been reported as risk ratios (RR) with 95% CIs.

We used RevMan 5.3 and the intention-to-treat principle for all statistical analyses. We conducted meta-analyses using the generic inverse variance method to allow pooling of effect estimates. A random effects model was used given expected between-trial variations in

methodological, participant and medication characteristics between studies. We had originally planned to pool data at various pre-specified time intervals, but all included studies had follow-up between 6 to 12 months.

We assessed heterogeneity through visual inspection of forest plots and statistical tests. A two-tailed test with p-value <0.10 was considered significant for all Chi-square analyses as per recommendations from the Cochrane Handbook and the I^2 was interpreted using the Cochrane Collaboration thresholds.[13]

Heterogeneity was explored in subgroup analyses based on five a priori hypotheses (Supplementary Table S1).[15] These included differences in baseline propensity for falls as influenced by (1) a history of recurrent falls (e.g., known faller or not) or (2) place of residence or care (e.g., community, long-term care); differences in the intervention as influenced by (3) specific medication class(es) chosen for withdrawal and (4) preceding medication review by clinician for FRID withdrawal appropriateness; as well as differences in methodology based on (5) definitions used for "falls" (e.g., observed vs. self-reported). We assessed the credibility of any apparent subgroup effects using eleven previously published criteria recommended by the Cochrane Handbook.[18]

A priori sensitivity analyses were conducted to explore the impact of low vs. high RoB based on blinding and attrition. Studies did not report per-protocol results that would allow for our planned intention-to-treat vs. per-protocol sensitivity analysis. The impact of using a fixed vs. random effects model was explored in a post hoc sensitivity analysis.

The confidence in effect estimates for each reported outcome was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.[19]

Patient and Public Involvement

Patients and the public were not involved in this review.

RESULTS

Of 819 citations identified, 28 were relevant for full text review and 6 met eligibility criteria (κ=0.79, 95% CI 0.51-1.00, substantial agreement). One study was available as an abstract, but it did not report its falls data.[20] Data was requested from the authors, but we did not receive a response. The PRISMA flow diagram summarizing our search results is shown in Figure 1.

Study Characteristics

The included trials in our review are described in Table 1.

Table 1: Characteristics of Included Studies

Author,	Study Design	Population	Sample Size	Age, Mean (SD)	Intervention	Control	Study Outcomes
Blalock et al, 2010 [21]	RCT	1) Community setting 2) Age ≥ 65 3) Speak, read English 4) ≥ 4 prescription medications 5) ≥ 1 high falls-risk medication 6) ≥ 1 fall not attributable to syncope within 1 year preceding randomization	186 (93 I/93 C)	74.8 (6.9)	1) Pharmacist medication review 2) Physician coordinated medication changes 3) Fall brochure, home safety checklist	1) Fall brochure, home safety checklist	1) Rate of falls 2) Incidence of falls
Campbell et al, 1999 [22]	RCT	1) Community setting 2) Age ≥ 65 3) Using benzodiazepine, other hypnotic, anti-depressant or major tranquilizer 4) Ambulatory 5) No physiotherapy 6) General practitioner thought psychotropic medication withdrawal beneficial	93 Arm 1: 24 (I) Arm 2: 24 (I) Arm 3: 21 (C)* Arm 4: 24 (C)*	74.7 (7.2)	Arm 1 1) Withdrawal of psychotropic medication over 14 weeks 2) Placebo substitution 3) Home exercise programme Arm 2 1) Psychotropic medication withdrawal 2) Placebo substitution 3) No home exercise programme	Arm 3 1) No change in psychotropic medication 2) Home exercise programme Arm 4 1) No change in psychotropic medication 2) No exercise programme	1) Rate of falls 2) Incidence of falls
Mott et al, 2016 [23]	Cluster RCT	1) Community setting 2) Age ≥ 65 3) English-speaking 4) Fall in last 12 months/fear falling 5) Workshop participation 6) Capable of consent	80 (39 I/41 C)	75.6 (6.5)	1) FRID pharmacist review 2) Medication-related action plan (MAP) developed by pharmacist for patient 3) Pharmacist follow-up 4) Patient given pamphlet 5) describing the role of medications in falls and monthly falls calendars	1) Medications in falls pamphlet	1) Rate of falls 2) Incidence of falls
Patterson et al, 2010 [24]	Cluster RCT	1) Nursing home setting with ≥ 30 beds; not exclusive care of terminally ill 2) Age ≥ 65	334 (173 I/161 C)	82.7 (8.4)	1) Monthly medication review via pharmacist for appropriateness 2) Nurse and prescriber collaboration to improve medications	1) Usual care	1) Rate of falls
Boyé et al, 2017 [12]	RCT	1) Acute care emergency department setting; attended due to fall incident 2) Age ≥ 65 3) ≥ 1 FRID for ≥ 2 weeks prior to the fall 4) MMSE ≥ 21/30 5) Ambulates independently 6) Community dwelling 7) Informed consent by patient	612 (319 I/293 C)	80.2 (7.3)	1) Investigator conducted FRID assessment, proposed changes 2) Changes discussed with geriatrician and general practitioner/prescribing doctor 3) If consensus, FRID discontinued, reduced dosage, substituted for potentially safer option	1) Usual care	1) Rate of falls 2) Incidence of falls

Abbreviations: FRID = Fall-risk-increasing drug, I = Intervention, C = Control
* Arm 3 and Arm 4 classified as controls due to lack of FRID withdrawal in these arms of the factorial design

Three studies were individually randomized, while two studies were cluster randomized by either nursing home or health centre. Studies ranged in size from 80 to 612 participants. With exception of one study[23], studies were multi-centre involving 144 sites and 4 countries. All were conducted in the community setting except for one conducted in long-term care.[24] Follow-up periods ranged from 6 to 12 months.

Overall, there were 1305 participants across all trials. Most were female (>70%) and had a falls history (78.9%). Several key confounders were not reported in the studies including: (1) baseline number and types of FRIDs, (2) baseline number of medications, and (3) baseline number and types of co-morbidities. All these factors are thought to potentially modify falls risk.[25,26]

All interventions included a preceding assessment for FRID deprescribing appropriateness. This was conducted by physicians in 2 trials and pharmacists in 3 trials. Three trials tried to withdraw any FRID, while others focused on sedative-hypnotics, antipsychotics, or antidepressants. Successful discontinuation and adherence to deprescribing protocols were low in all studies. Rates of complete discontinuation of at least one FRID ranged from 10 to 40%.

In terms of our study outcomes, 4 trials measured the rate of falls and 4 measured falls incidence. One trial reported fall-related injuries.[21] Fall-related fractures, fall-related hospitalization or deprescribing-related adverse effects were not measured by any of the trials.

Summary of Findings

Rate and Incidence of Falls

Four studies reported the effect of deprescribing FRIDs on the rate of falls. Deprescribing FRIDs did not reduce the rate of falling (RaR 0.98, 95% CI 0.63 to 1.51; Figure 2 – Analysis 1.1).

Considerable statistical heterogeneity was present (χ^2=17.47, p=0.0006, I^2=83%) and subsequently explored in subgroup analysis.

Four studies reported the effect of deprescribing FRIDs on the risk of falls as measured by falls incidence. Deprescribing FRIDs did not reduce the incidence of falls (RR 1.04, 95% CI 0.86 to 1.26, I^2 = 19%, χ^2=3.70, p = 0.30; Figure 2 – Analysis 2.1). In absolute terms, there was a non-significant risk difference increase of 0.01 (95% CI -0.06 to 0.09, I^2 = 22%, p=0.76; Figure 2 – Analysis 2.2)

Rate of Injurious Falls

One trial reported the effect of deprescribing FRIDs on fall-related injuries.[21] Deprescribing FRIDs did not reduce the rate of fall-related injuries (RaR 0.89, 95% CI 0.57 to 1.39; Figure 2 – Analysis 3.1). This trial did not report data that would allow for any of our pre-planned subgroup analyses.

Risk of Bias Assessment

Figure 3 summarizes our RoB assessments. All studies were deemed high risk of bias in at least one domain. The overall mean weighted kappa across all assessments was 0.67 (moderate agreement). For individual RoB assessments, kappa ranged from 0 to 0.85. Inter-rater agreement is actually higher than indicated by the calculated scores due the "kappa co-efficient paradox".[27,28] Low kappas (e.g. κ=0) occurred despite high levels of observed agreement (e.g. $\geq$ 80% agreement) for two RoB assessments. True agreement is falsely attributed to chance agreement by the kappa calculation when there is substantial imbalance in marginal ratings.

Publication Bias

Since less than 10 eligible studies were found, a funnel plot was not constructed due to an inability to make meaningful conclusions about publication bias.

Subgroup Analyses and Exploration of Heterogeneity

Our pre-specified subgroup analyses did not adequately explain the statistical heterogeneity observed results for the rate and incidence of falls (Supplementary Figure S2). Deprescribing FRIDs appeared more effective when a preceding medication review was conducted by physicians compared to pharmacists (p=0.0004, I^2=91.9%, Analysis 1.5), while psychotropic withdrawal appeared more effective than strategies withdrawing any FRID (p=0.08, I^2=67.8%, Analysis 2.3). However, in both analyses, only 6 of 11 subgroup credibility criteria were met and each subgroup was limited to one trial with less than 100 participants (Supplementary Table S2). We therefore judged the credibility that these subgroup effects are real as poor and uncertain.

The available data did not permit subgroup analyses by place of residence or falls ascertainment method. The other subgroup analyses showed no evidence of difference beyond that due to chance.

Sensitivity Analyses

Our sensitivity analyses are shown in Supplementary Figure S3. The incorporation of trials with high risk of performance bias appeared to mask the potential benefit of deprescribing FRIDs on reducing the incidence and rate of falls, while the trials with high risk of attrition bias appeared to mask a potential increase in falls rate with deprescribing FRIDs. These results should be interpreted cautiously and definitive conclusions cannot be made. Data from trials with low risk

of performance bias were limited to one trial with less 100 participants, and data from trials with low risk of attrition bias were limited to two trials with less than 450 participants overall.

A post-hoc sensitivity analysis examining the impact of using a fixed vs. random effects model did not change conclusions regarding the effect of deprescribing FRIDs on the rate or incidence of falls.

Quality of Evidence

The GRADE evidence profile is shown in Table 2.

Table 2: GRADE Quality of Evidence Assessment

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**FRID deprescribing strategy**	**usual care**	**Relative (95% CI)**	**Absolute (95% CI)**		
Falls Rate												
4	randomised trials	serious [a]	serious [b]	not serious	serious [c]	none	353	340	**Rate ratio 0.98** (0.63 to 1.51)	-	⨁◯◯◯ VERY LOW	IMPORTANT
Falls Incidence												
4	randomised trials	serious [a]	serious [d]	not serious	serious [c]	none	190/499 (38.1%)	170/472 (36.0%)	**RR 1.04** (0.86 to 1.26)	**14 more per 1,000** (from 50 fewer to 94 more)	⨁◯◯◯ VERY LOW	IMPORTANT
								33.7%		**13 more per 1,000** (from 47 fewer to 88 more)		
Fall-Related Injuries												
1	randomised trials	serious [a]	not serious	not serious	serious [c]	none	93	93	**Rate ratio 0.89** (0.57 to 1.39)	-	⨁⨁◯◯ LOW	CRITICAL

We judged the quality of evidence to be low or very low for all outcomes (falls rates, falls incidence and fall-related injuries) after rating down for risk of bias, inconsistency and imprecision.

We believe the optimal information size (OIS) to make definitive conclusions on the effect of deprescribing FRIDs has not yet been met as the body of evidence is based on fewer than 2000 participants and less than 400 events.[29,30] This is based on the OIS calculation figure recommended by the GRADE guidelines using a well-established control falls event rate of 30% described in the literature and conservative relative risk reduction (RRR) of 20% (assuming $\alpha = 0.05$ and $\beta = 0.2$).[30,31]

DISCUSSION

This systematic review found that there is a lack of robust high-quality evidence to support or refute the deprescribing of FRIDs as an effective fall prevention strategy. Incorporating data from 5 RCTs involving 1305 participants aged ≥65 years, our meta-analyses indicate that a FRID deprescribing strategy did not significantly change the rate of falls (RaR 0.98, 95% CI 0.63 to 1.51) nor the risk of falling (RD 0.01, 95% CI -0.06 to 0.09) over a 6 to 12-month follow-up period. Although the intervention focused on those medications thought to be associated with falls, the results and conclusions are similar to previous systematic reviews evaluating the effect of generic (non-FRID focused) medication reviews.[32]

There is also a significant absence of evidence for clinically- and patient-important outcomes such as fall-related injuries, fractures and hospitalizations. The only trial to date that evaluated the rate of fall-related injuries did not demonstrate a statistically significant effect (RaR 0.89, 95% CI 0.57-1.39).[21] Our search found no trials measuring the impact on fall-related fractures, fall-related hospitalizations or adverse effects related to a FRID deprescribing strategy.

Based on low-quality evidence, it is unclear whether deprescribing FRIDs leads to any appreciable clinically important benefit or harm. In fact, our current best effect estimates for falls rate and incidence are centred around no appreciable difference (i.e. RaR ≈ 1, RR ≈ 1, RD ≈ 0). Although seemingly logical to assume, reducing risk factors may not necessarily lead to reduction in falls and fall-related complications. The absence of change in the incidence of hip fractures after statewide regulatory action on benzodiazepine prescribing in the United States that reduced benzodiazepine use by 60.3% is a real-world example of this phenomena and the complexity of exposure-outcome relationships.[33] Furthermore, it is unclear as to what degree a particular risk factor or combination of risk factors (e.g. specific FRIDs) must be reduced to produce an appreciable change in falls. This likely reflects the multi-factorial nature of falls and the varying risk of different FRIDs.

Only one trial[22] included in our review demonstrated a statistically significant benefit with deprescribing FRIDs. This was also the only trial to use study capsules to operationalize blinded deprescribing of FRIDs in participants, research personnel and outcome assessors. Its results might be more reflective of the potential effect of deprescribing FRIDs. However, the magnitude of benefit achievable in the "real world" setting may be closer to those seen in the unblinded trials due to the strong mitigating factors preventing successful deprescribing.

These results raise several questions about current practice and the presumed effectiveness of deprescribing FRIDs as a falls prevention strategy. Given the amount of resources being invested into falls prevention initiatives around the world, clinicians and organizations should re-examine: (1) what is the strength of evidence supporting their current activities, (2) whether these activities are cost-effective, and (3) whether resources are being appropriately prioritized to those interventions shown to provide the most value. This should also be applied to what is being

required of healthcare organizations in national accreditation standards (e.g. Joint Commission, Accreditation Canada) to help direct and encourage optimal use of limited healthcare resources.

Clinicians and policy-makers should acknowledge the lack of strong evidence for this intervention for the specific purpose of reducing falls, particularly in patients who may be very reluctant or who have strong indications for specific FRIDs. As with prescribing medications, deprescribing is a skill and comes with the potential for harm as well as benefit.[34] Thoughtful consideration of the goals, appropriateness and safety of deprescribing is important. Despite insufficient evidence to support or refute the deprescribing of FRIDs for falls prevention, it should be noted that there may be other reasons to deprescribe these medications. These include avoidance of adverse drug events, improvements in cognition, increased medication adherence and drug costs savings.

Our review highlights the need for future FRID deprescribing trials that evaluate patient-important outcomes (e.g. injuries, fractures and hospitalizations). Greater attention to optimal design and reporting is needed to minimize risk of bias. Examples include improved reporting of confounding baseline characteristics and intervention fidelity (e.g. number and types of FRIDs, degree and duration of dose reduction). Deprescribing is challenging and extra measures are likely needed to improve successful intervention adherence and follow-up.

STRENGTHS AND LIMITATIONS

Our review has limitations. There was variation in the operationalization of FRID deprescribing and degree of success achieved (e.g. dose reduction only, completion discontinuation, non-adherence). This presumably makes the detection of any potential benefit less likely and our conclusions more conservative. However, the effect estimates are likely more

indicative of what might be expected outside of the research setting. These phenomena likely represent the real-life challenges of deprescribing (especially with certain types of FRIDs such as psychotropics or opioids). Moreover, our ability to assess for confounders modifying falls risk was limited due to inconsistent reporting of relevant baseline characteristics and lack of patient-level data. Lastly, our ability to make definitive conclusions is limited because the total sample size across studies for each outcome did not yet meet our calculated estimate for the required optimal information size.

Our review has several strengths. First, our search was comprehensive and we included a rigorous grey literature search for unpublished studies. Second, we employed optimal analytical and interpretational approaches including duplicate assessment, subgroup credibility criteria and optimal information size considerations. Third, unlike previous medication-focused reviews, we applied the GRADE approach to assess the quality of evidence and our degree of confidence in the results.

CONCLUSIONS

Our systematic review found that deprescribing FRIDs results in little to no difference in the rate and risk of falls or falls-related injuries, but the evidence is still sparse and very low quality. Additional well-designed studies are needed to reach the optimal information size to reduce uncertainty about this intervention and establish its relative importance in the range of possible interventions that can be employed by clinicians and health systems to reduce falls.

Acknowledgements:

The authors would like to thank Lois Cottrell, medical librarian at St. Joseph's Healthcare Hamilton, Charlton Campus, Hamilton, Ontario, Canada and Andrea McLellan, Head of Collection and Technical Services, School of Medicine liaison, at McMaster University, Hamilton, Ontario, Canada, for their assistance with the development of the search strategy.

Author Contributions:

JL conceptualized the study. JL and AH designed and developed the protocol. RP and EW assisted with citation review. RP and AN assisted with data extraction, risk of bias assessment and certainty of evidence grading. All authors contributed to the analysis and interpretation of results. JL drafted the initial manuscript and all authors contributed to its revision and final approval.

Funding:

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing Interests:

The authors have no potential conflicts of interest to declare.

Patient Consent for Publication:

None required.

Data Sharing Statement:

No unpublished data are available.

REFERENCES:

1 Hill KD, Wee R. Psychotropic drug-induced falls in older people: a review of interventions aimed at reducing the problem. *Drugs Aging* 2012;**29**:15–30. doi:10.2165/11598420-000000000-00000

2 Florence CS, Bergen G, Atherly A, *et al.* Medical Costs of Fatal and Nonfatal Falls in Older Adults. *J Am Geriatr Soc* 2018;**66**:693–8. doi:10.1111/jgs.15304

3 National Institute for Health and Care Excellence. Falls in older people: assessing risk and prevention. 2013.

4 Public Health Agency of Canada. Seniors' Falls in Canada. 2014.

5 Summary of the Updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons. *J Am Geriatr Soc* 2011;**59**:148–57. doi:10.1111/j.1532-5415.2010.03234.x

6 Guirguis-Blake JM, Michael YL, Perdue LA, *et al.* Interventions to Prevent Falls in Older Adults. *JAMA* 2018;**319**:1705. doi:10.1001/jama.2017.21962

7 Campbell AJ, Robertson MC. Fall Prevention: Single or Multiple Interventions? Single Interventions for Fall Prevention. *J Am Geriatr Soc* 2013;**61**:281–4. doi:10.1111/jgs.12095_2

8 Tricco AC, Thomas SM, Veroniki AA, *et al.* Comparisons of Interventions for Preventing Falls in Older Adults. *JAMA* 2017;**318**:1687. doi:10.1001/jama.2017.15006

9 Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: I. Psychotropic drugs. *J Am Geriatr Soc* 1999;**47**:30–9.

10 Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: II. Cardiac and analgesic drugs. *J Am Geriatr Soc* 1999;**47**:40–

50.

11 Woolcott JC, Richardson KJ, Wiens MO, *et al.* Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Arch Intern Med* 2009;**169**:1952–60. doi:10.1001/archinternmed.2009.357

12 Boyé NDA, van der Velde N, de Vries OJ, *et al.* Effectiveness of medication withdrawal in older fallers: results from the Improving Medication Prescribing to reduce Risk Of FALLs (IMPROveFALL) trial. *Age Ageing* 2017;**46**:142–6. doi:10.1093/ageing/afw161

13 The Cochrane Collaboration. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]*. 2011.

14 Moher D, Liberati A, Tetzlaff J, *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;**151**:264–9, W64.

15 Lee JY, Holbrook A. The efficacy of fall-risk-increasing drug (FRID) withdrawal for the prevention of falls and fall-related complications: protocol for a systematic review and meta-analysis. *Syst Rev* 2017;**6**:33.

16 Higgins JPT, Altman DG, Gøtzsche PC, *et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;**343**:d5928.

17 Akl EA, Sun X, Busse JW, *et al.* Specific instructions for estimating unclearly reported blinding status in randomized trials were reliable and valid. *J Clin Epidemiol* 2012;**65**:262–7. doi:10.1016/j.jclinepi.2011.04.015

18 Sun X, Briel M, Walter SD, *et al.* Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. *BMJ* 2010;**340**:c117.

19 Guyatt G, Oxman AD, Akl EA, *et al.* GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;**64**:383–94.

20 Streim JE, Filippo S, Have T, *et al.* Antidepressant discontinuation associated with cognitive decline in older adult residents of long-term care facilities. *Am J Geriatr psychiatry* 2012;**20**:S147–8. doi:10.1097/01.JGP.0000413064.91948.aa

21 Blalock SJ, Casteel C, Roth MT, *et al.* Impact of enhanced pharmacologic care on the prevention of falls: a randomized controlled trial. *Am J Geriatr Pharmacother* 2010;**8**:428–40. doi:10.1016/j.amjopharm.2010.09.002

22 Campbell AJ, Robertson MC, Gardner MM, *et al.* Psychotropic medication withdrawal and a home-based exercise program to prevent falls: a randomized, controlled trial. *J Am Geriatr Soc* 1999;**47**:850–3.

23 Mott DA, Martin B, Breslow R, *et al.* Impact of a medication therapy management intervention targeting medications associated with falling: Results of a pilot study. *J Am Pharm Assoc (2003)* 2016;**56**:22–8.

24 Patterson SM, Hughes CM, Crealey G, *et al.* An evaluation of an adapted U.S. model of pharmaceutical care to improve psychoactive prescribing for nursing home residents in northern ireland (fleetwood northern ireland study). *J Am Geriatr Soc* 2010;**58**:44–53. doi:10.1111/j.1532-5415.2009.02617.x

25 Tinetti M, Kumar C. The Patient Who Falls. *JAMA J Am Med Assoc* 2010;**303**:273–4. doi:10.1001/jama.2009.2024

26 Chen Y, Zhu L-L, Zhou Q. Effects of drug pharmacokinetic/pharmacodynamic properties, characteristics of medication use, and relevant pharmacological interventions on fall risk in elderly patients. *Ther Clin Risk Manag* 2014;**10**:437–48. doi:10.2147/TCRM.S63756

27 Feinstein AR, Cicchetti D V. High agreement but low kappa: I. The problems of two paradoxes. *J Clin Epidemiol* 1990;**43**:543–9.

28 Tang W, Hu J, Zhang H, *et al.* Kappa coefficient: a popular measure of rater agreement. *Shanghai Arch psychiatry* 2015;**27**:62–7. doi:10.11919/j.issn.1002-0829.215010

29 Ioannidis J, Lau J. Evolution of treatment effects over time: empirical insight from recursive cumulative metaanalyses. *Proc Natl Acad Sci U S A* 2001;**98**:831–6. doi:10.1073/pnas.021529998

30 Guyatt GH, Oxman AD, Kunz R, *et al.* GRADE guidelines 6. Rating the quality of evidence--imprecision. *J Clin Epidemiol* 2011;**64**:1283–93. doi:10.1016/j.jclinepi.2011.01.012

31 O'Loughlin JL, Robitaille Y, Boivin JF, *et al.* Incidence of and risk factors for falls and injurious falls among the community-dwelling elderly. *Am J Epidemiol* 1993;**137**:342–54.

32 Gillespie LD, Robertson MC, Gillespie WJ, *et al.* Interventions for preventing falls in older people living in the community. *Cochrane database Syst Rev* 2012;**9**:CD007146. doi:10.1002/14651858.CD007146.pub3

33 Wagner AK, Ross-Degnan D, Gurwitz JH, *et al.* Effect of New York State regulatory action on benzodiazepine prescribing and hip fracture rates. *Ann Intern Med* 2007;**146**:96–103.

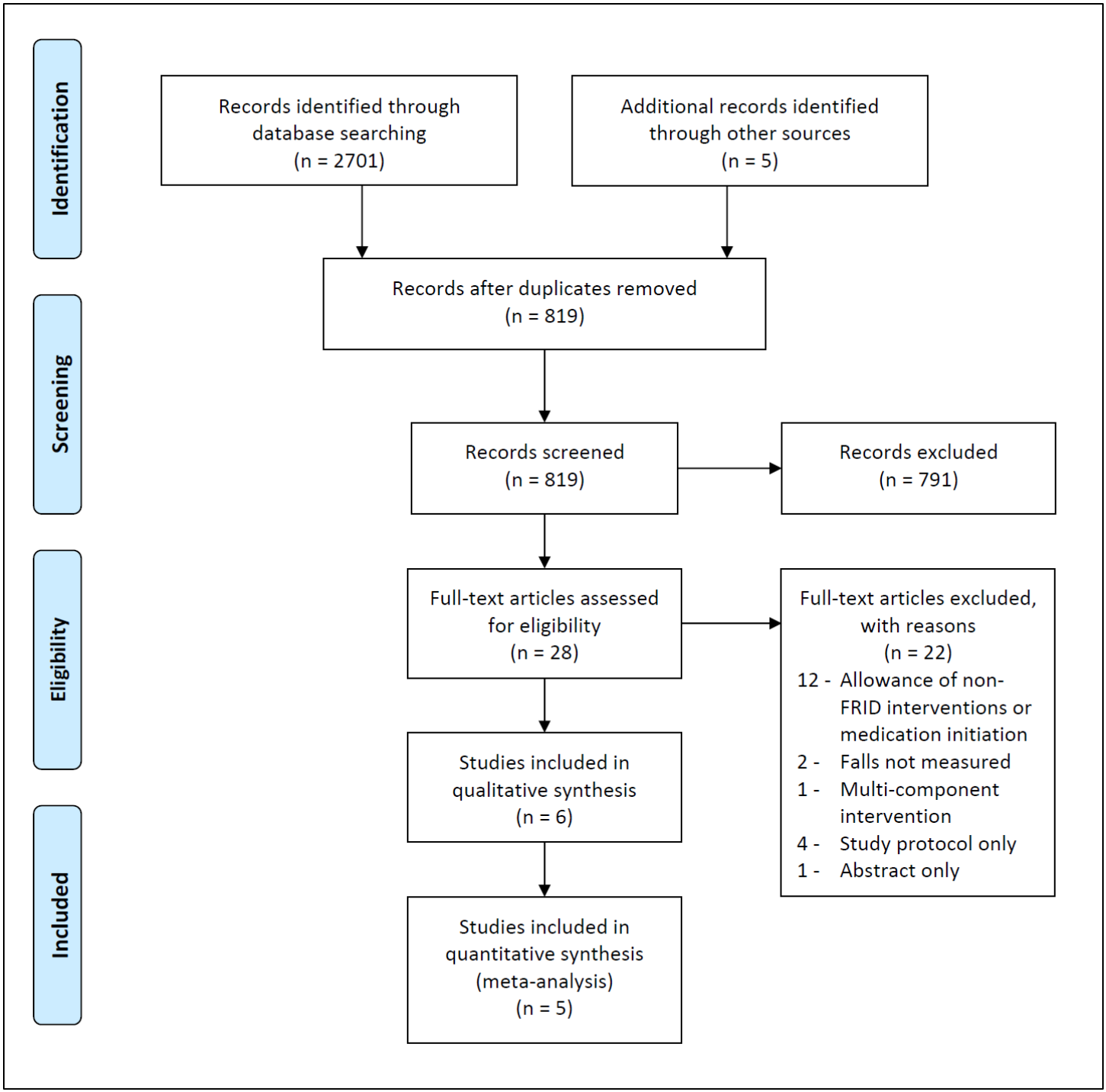
34 Reeve E, Moriarty F, Nahas R, *et al.* A narrative review of the safety concerns of deprescribing in older adults and strategies to mitigate potential harms. *Expert Opin Drug Saf* 2018;**17**:39–49. doi:10.1080/14740338.2018.1397625

FIGURES

Figure 1: PRISMA Flow Diagram of Study Selection Process

Figure 2: Forest Plots of FRID Withdrawal versus Usual Care

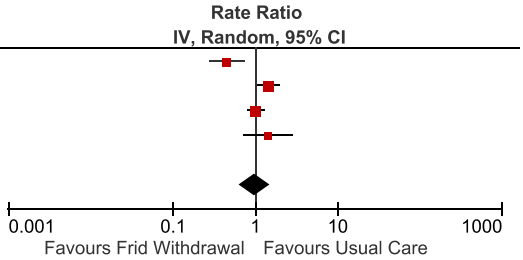
Figure 3: Risk of Bias Assessments


Identification
Screening
Eligibility
Included
Records identified through database searching (n = 2701)
Additional records identified through other sources (n = 5)
Records after duplicates removed (n = 819)
Records screened (n = 819)
Records excluded (n = 791)
Full-text articles assessed for eligibility (n = 28)
Full-text articles excluded, with reasons (n = 22)
12 - Allowance of non-FRID interventions or medication initiation
2 - Falls not measured
1 - Multi-component intervention
4 - Study protocol only
1 - Abstract only
Studies included in qualitative synthesis (n = 6)
Studies included in quantitative synthesis (meta-analysis) (n = 5)

1.1 Falls Rate

Study or Subgroup	log[Rate Ratio]	SE	FRID Withdrawal Total	Usual Care Total	Weight	Rate Ratio IV, Random, 95% CI	Year
Campbell 1999	-0.8023	0.2434	48	45	23.4%	0.45 [0.28, 0.72]	1999
Patterson 2010	0.3549	0.1465	173	161	28.4%	1.43 [1.07, 1.90]	2010
Blalock 2010	0.003	0.1117	93	93	29.9%	1.00 [0.81, 1.25]	2010
Mott 2016	0.3379	0.3416	39	41	18.4%	1.40 [0.72, 2.74]	2016
Total (95% CI)			**353**	**340**	**100.0%**	**0.98 [0.63, 1.51]**	

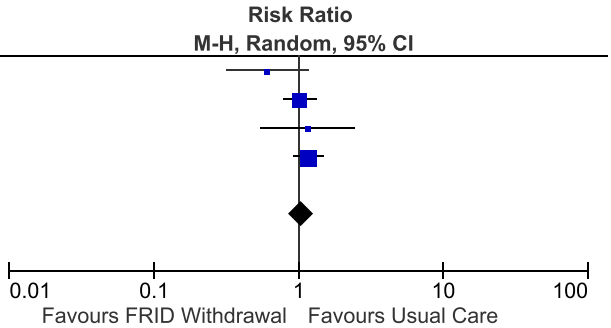
Heterogeneity: Tau² = 0.15; Chi² = 17.47, df = 3 (P = 0.0006); I² = 83%
Test for overall effect: Z = 0.11 (P = 0.92)



2.1 Falls Incidence – Risk Ratio

Study or Subgroup	FRID Withdrawal Events	Total	Usual Care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Campbell 1999	11	48	17	45	8.4%	0.61 [0.32, 1.15]
Blalock 2010	53	93	52	93	39.3%	1.02 [0.79, 1.31]
Mott 2016	11	39	10	41	6.4%	1.16 [0.55, 2.41]
Boyé 2017	115	319	91	293	45.9%	1.16 [0.93, 1.45]
Total (95% CI)		**499**		**472**	**100.0%**	**1.04 [0.86, 1.26]**
Total events	190		170			

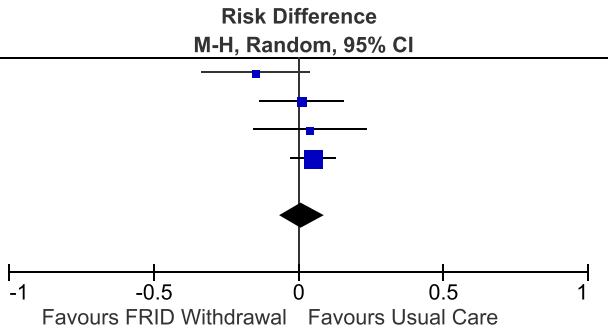
Heterogeneity: Tau² = 0.01; Chi² = 3.70, df = 3 (P = 0.30); I² = 19%
Test for overall effect: Z = 0.44 (P = 0.66)



2.2 Falls Incidence – Risk Difference

Study or Subgroup	FRID Withdrawal Events	Total	Usual Care Events	Total	Weight	Risk Difference M-H, Random, 95% CI
Campbell 1999	11	48	17	45	14.2%	-0.15 [-0.33, 0.04]
Blalock 2010	53	93	52	93	21.8%	0.01 [-0.13, 0.15]
Mott 2016	11	39	10	41	13.2%	0.04 [-0.15, 0.23]
Boyé 2017	115	319	91	293	50.9%	0.05 [-0.02, 0.12]
Total (95% CI)		**499**		**472**	**100.0%**	**0.01 [-0.06, 0.09]**
Total events	190		170			

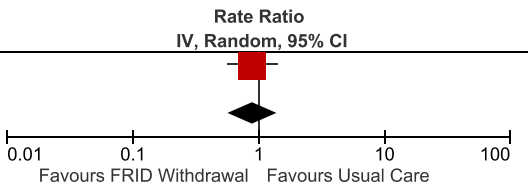
Heterogeneity: Tau² = 0.00; Chi² = 3.86, df = 3 (P = 0.28); I² = 22%
Test for overall effect: Z = 0.31 (P = 0.76)

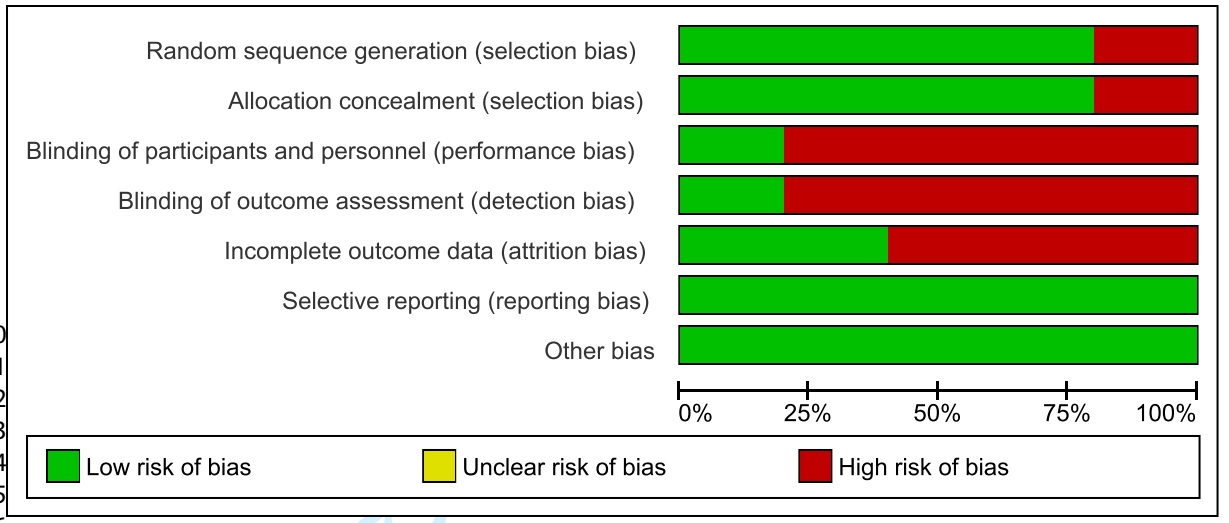


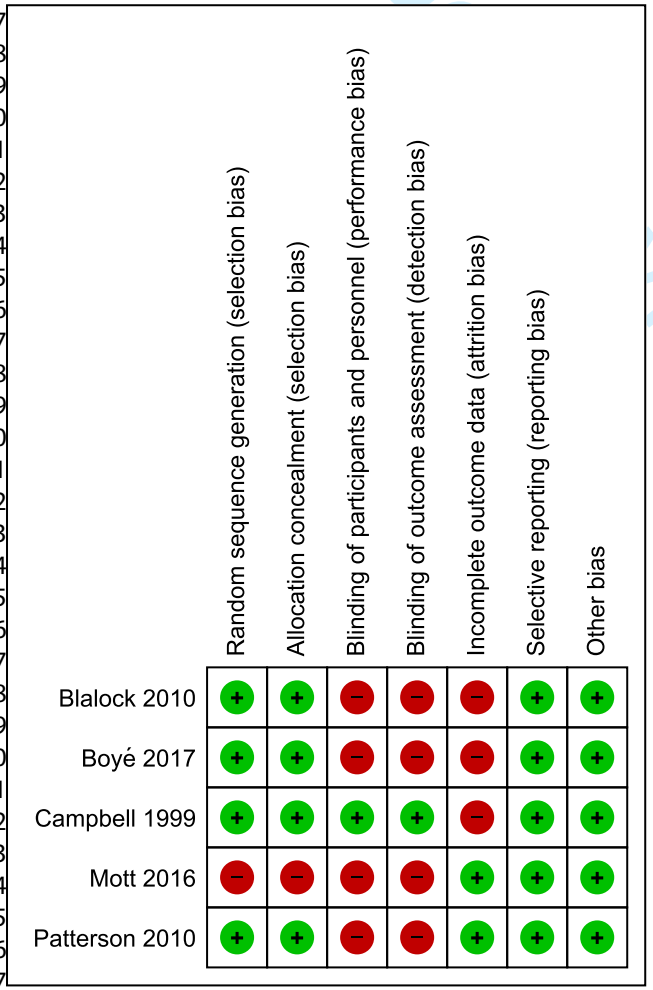
3.1 Fall-Related Injuries

Study or Subgroup	log[Rate Ratio]	SE	FRID Withdrawal Total	Usual Care Total	Weight	Rate Ratio IV, Random, 95% CI	Year
Blalock 2010	-0.1165	0.2273	93	93	100.0%	0.89 [0.57, 1.39]	2010
Total (95% CI)			**93**	**93**	**100.0%**	**0.89 [0.57, 1.39]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.51 (P = 0.61)







Supplementary Figure S1: OVID Medline Search Strategy

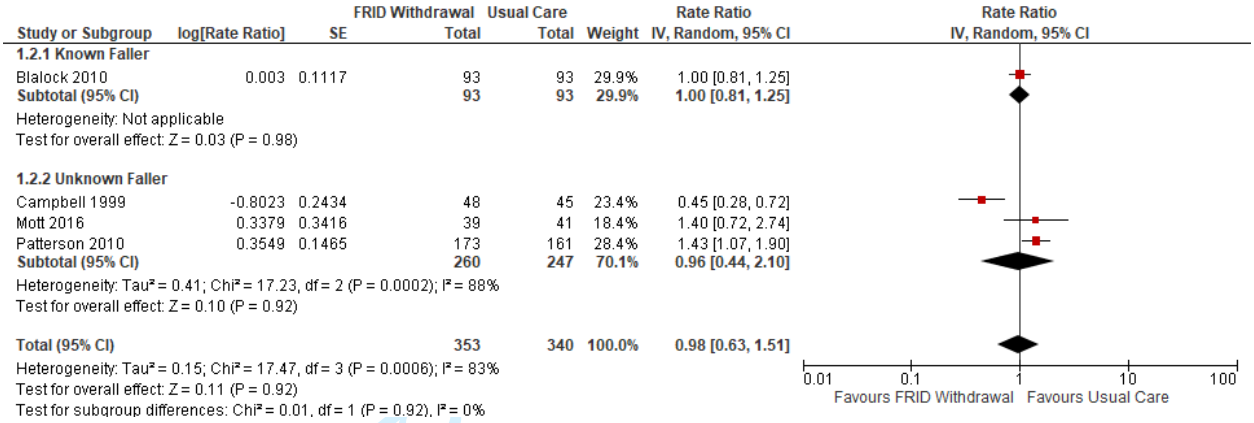
Database(s): OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

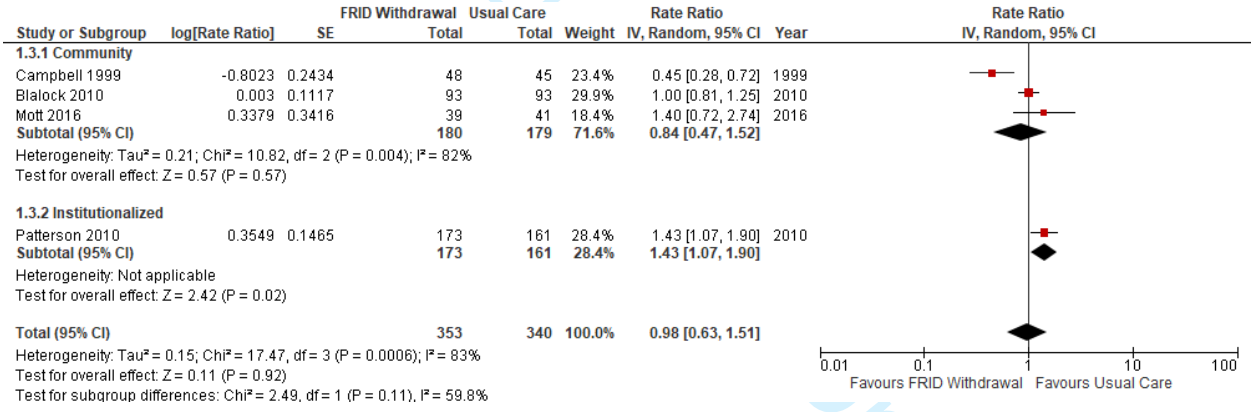
#	Searches
1	exp Accidental Falls/pc [Prevention & Control]
2	fall.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
3	falls.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
4	exp Deprescriptions/
5	((medicat* or drug*) adj3 (deprescrib* or withdraw* or cessat* or stop* or discontin*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
6	((antihypertensive* or diuretic* or beta-blocker* or sedative* or hypnotic* or neuroleptic* or antipsychotic* or antidepressant* or benzodiazepine* or narcotic* or opioid* or narcotic* or NSAID*) adj3 (deprescrib* or withdraw* or cessat* or stop* or discontin*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
7	fall-risk increasing drugs.mp.
8	FRID.mp.
9	((medicat* or drug*) adj3 (review* or improv* or program*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
10	exp "Drug-Related Side Effects and Adverse Reactions"/pc [Prevention & Control]
11	exp Medication Therapy Management/ or exp "Drug Utilization Review"/
12	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13	1 or 2 or 3
14	12 and 13
15	remove duplicates from 14
16	exp Clinical Trial/
17	(randomized or randomised).ab,ti.
18	placebo.ab,ti.
19	randomly.ab,ti.
20	groups.ab,ti.
21	randomized controlled trial.pt.
22	controlled clinical trial.pt.
23	16 or 17 or 18 or 19 or 20 or 21 or 22
24	15 and 23

Supplementary Figure S2: Subgroup Analyses

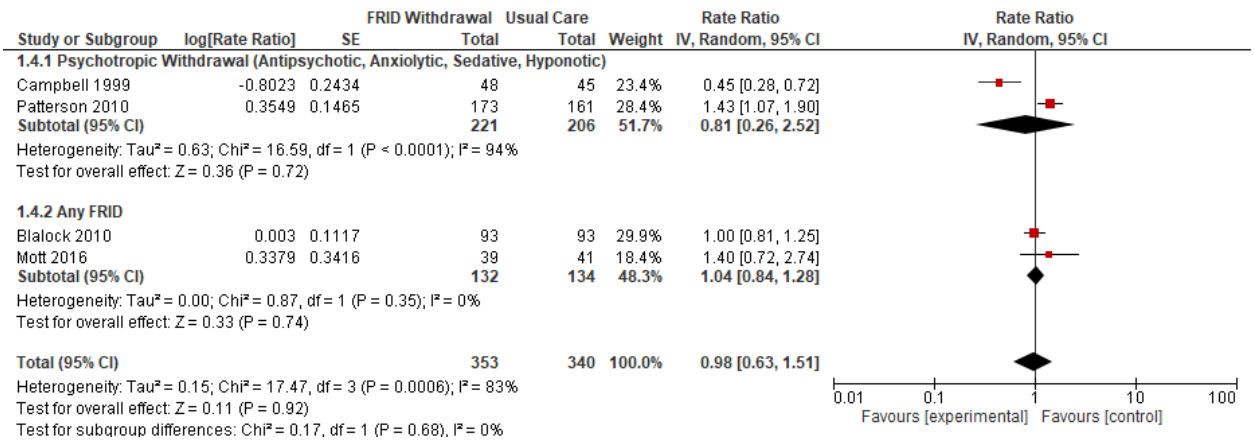
1.2 Falls Rate - Known vs. Unknown Faller



1.3 Falls Rate - Community vs. Institutionalized

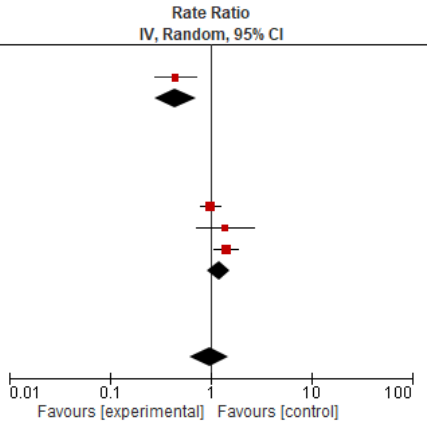


1.4 Falls Rate - Psychotropic Withdrawal vs. Any FRID Withdrawal



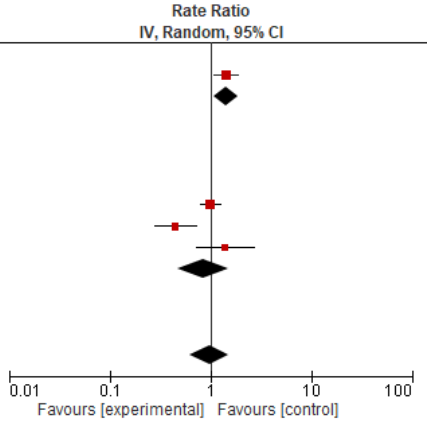
1.5 Falls Rate - Physician vs. Pharmacist Medication Review

Study or Subgroup	log[Rate Ratio]	SE	FRID Withdrawal Total	Usual Care Total	Weight	Rate Ratio IV, Random, 95% CI
1.5.1 Physician Medication Review						
Campbell 1999	-0.8023	0.2434	48	45	23.4%	0.45 [0.28, 0.72]
Subtotal (95% CI)			**48**	**45**	**23.4%**	**0.45 [0.28, 0.72]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.30 (P = 0.0010)						
1.5.2 Pharmacist Medication Review						
Blalock 2010	0.003	0.1117	93	93	29.9%	1.00 [0.81, 1.25]
Mott 2016	0.3379	0.3416	39	41	18.4%	1.40 [0.72, 2.74]
Patterson 2010	0.3549	0.1465	173	161	28.4%	1.43 [1.07, 1.90]
Subtotal (95% CI)			**305**	**295**	**76.6%**	**1.20 [0.92, 1.58]**
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 3.99$, df = 2 (P = 0.14); $I^2 = 50\%$						
Test for overall effect: Z = 1.33 (P = 0.18)						
Total (95% CI)			**353**	**340**	**100.0%**	**0.98 [0.63, 1.51]**
Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 17.47$, df = 3 (P = 0.0006); $I^2 = 83\%$						
Test for overall effect: Z = 0.11 (P = 0.92)						
Test for subgroup differences: $Chi^2 = 12.41$, df = 1 (P = 0.0004), $I^2 = 91.9\%$						

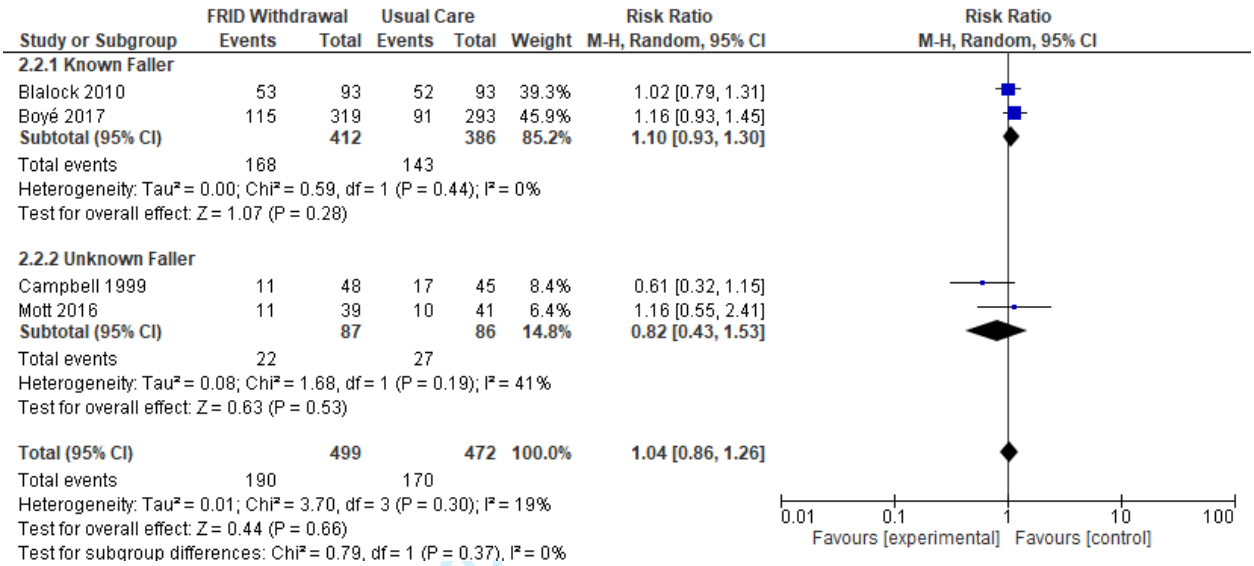


1.6 Falls Rate - Observed vs. Self-Reported Falls

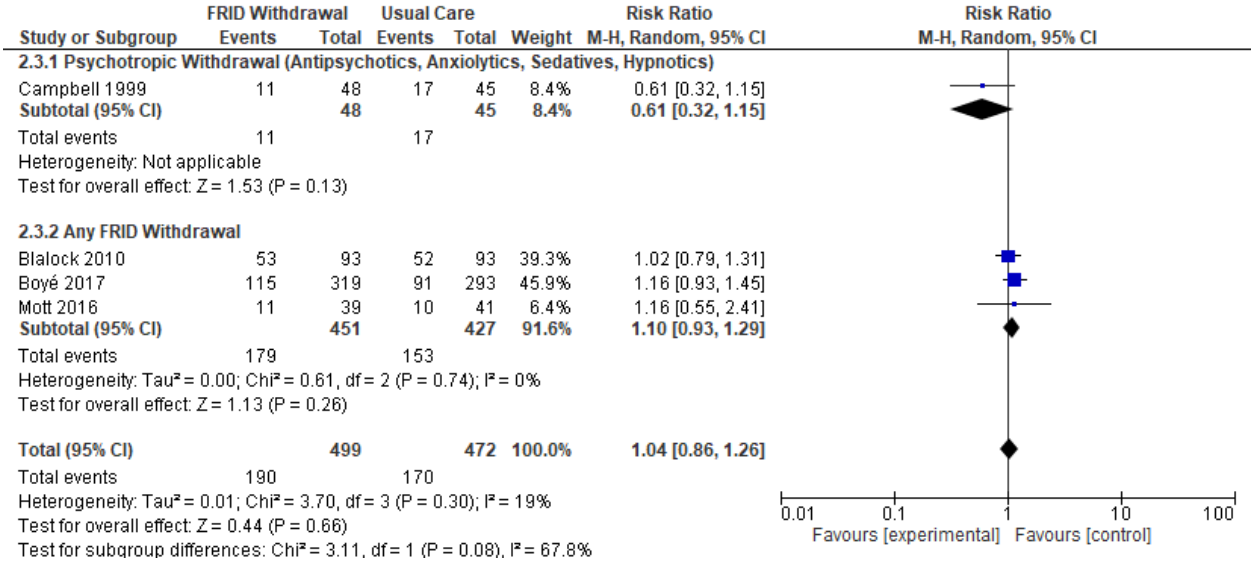
Study or Subgroup	log[Rate Ratio]	SE	FRID Withdrawal Total	Usual Care Total	Weight	Rate Ratio IV, Random, 95% CI
1.6.1 Observed Falls						
Patterson 2010	0.3549	0.1465	173	161	28.4%	1.43 [1.07, 1.90]
Subtotal (95% CI)			**173**	**161**	**28.4%**	**1.43 [1.07, 1.90]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.42 (P = 0.02)						
1.6.2 Self-Reported Falls						
Blalock 2010	0.003	0.1117	93	93	29.9%	1.00 [0.81, 1.25]
Campbell 1999	-0.8023	0.2434	48	45	23.4%	0.45 [0.28, 0.72]
Mott 2016	0.3379	0.3416	39	41	18.4%	1.40 [0.72, 2.74]
Subtotal (95% CI)			**180**	**179**	**71.6%**	**0.84 [0.47, 1.52]**
Heterogeneity: $Tau^2 = 0.21$; $Chi^2 = 10.82$, df = 2 (P = 0.004); $I^2 = 82\%$						
Test for overall effect: Z = 0.57 (P = 0.57)						
Total (95% CI)			**353**	**340**	**100.0%**	**0.98 [0.63, 1.51]**
Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 17.47$, df = 3 (P = 0.0006); $I^2 = 83\%$						
Test for overall effect: Z = 0.11 (P = 0.92)						
Test for subgroup differences: $Chi^2 = 2.49$, df = 1 (P = 0.11), $I^2 = 59.8\%$						



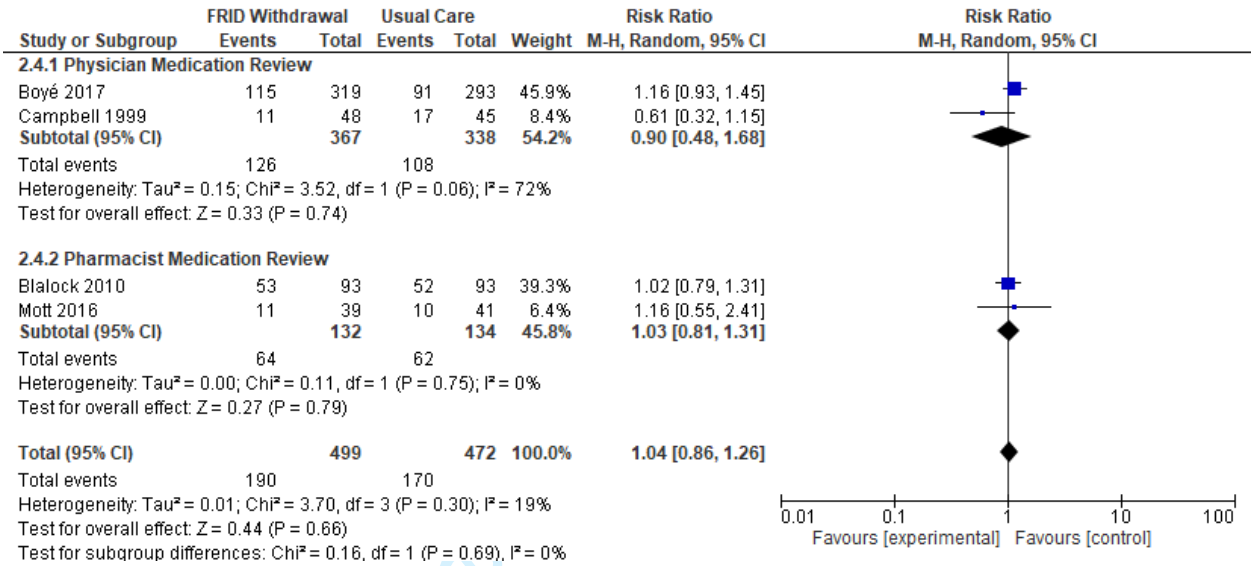
2.2 Falls Incidence - Known vs. Unknown Faller



2.3 Falls Incidence - Psychotropic Withdrawal vs. Any FRID Withdrawal



2.4 Falls Incidence - Physician vs. Pharmacist Medication Review



Supplementary Table S1: Subgroup Credibility Assessments

Physician vs. Pharmacist Medication Review Subgroup for Falls Rate

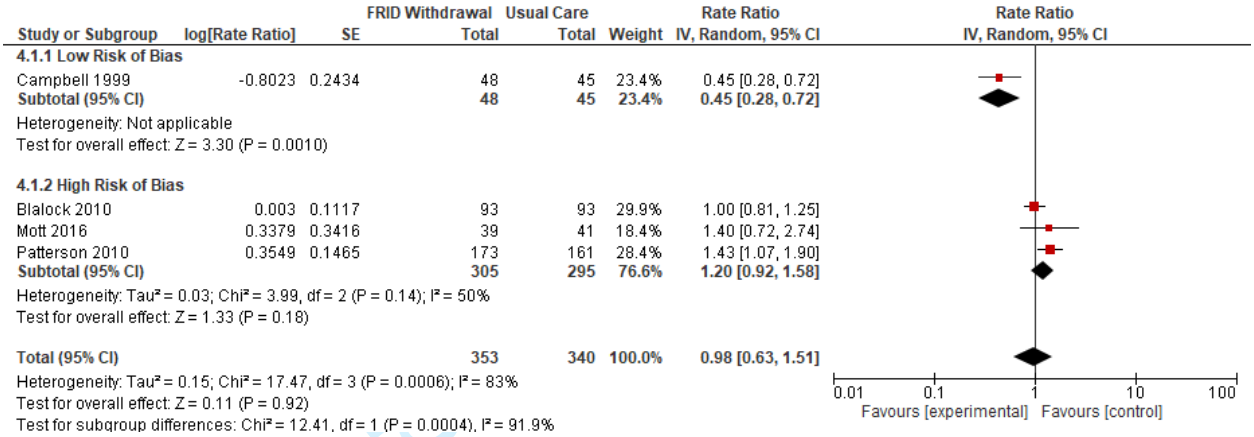
Design	Criteria Met?
Is the subgroup variable a characteristic measured at baseline or after randomization?	Yes – Variable determined at baseline
Is the effect suggested by comparisons within rather between studies?	No – Comparison between studies
Was the hypothesis specified a priori?	Yes
Was the direction of the subgroup effect specified a priori?	No
Was the subgroup effect one of a small number of hypothesized effects tested?	Yes – 1 of 5 analyses
Analysis	
Does the interaction test suggest a low likelihood that chance explains the apparent subgroup effect?	Yes – p =0.0004
Is the significant subgroup effect independent?	Yes
Context	
Is the size of the subgroup effect large?	Yes – RaR 0.45 vs. 1.20
Is the interaction consistent across studies?	No
Is the interaction consistent across closely related outcomes within the study?	No – Subgroup interaction was not seen for incidence of falls
Is there indirect evidence that supports the hypothesized interaction (biological rationale)?	No - No compelling external evidence supporting subgroup hypothesis

Antipsychotic vs. Any FRID Withdrawal for Falls Incidence

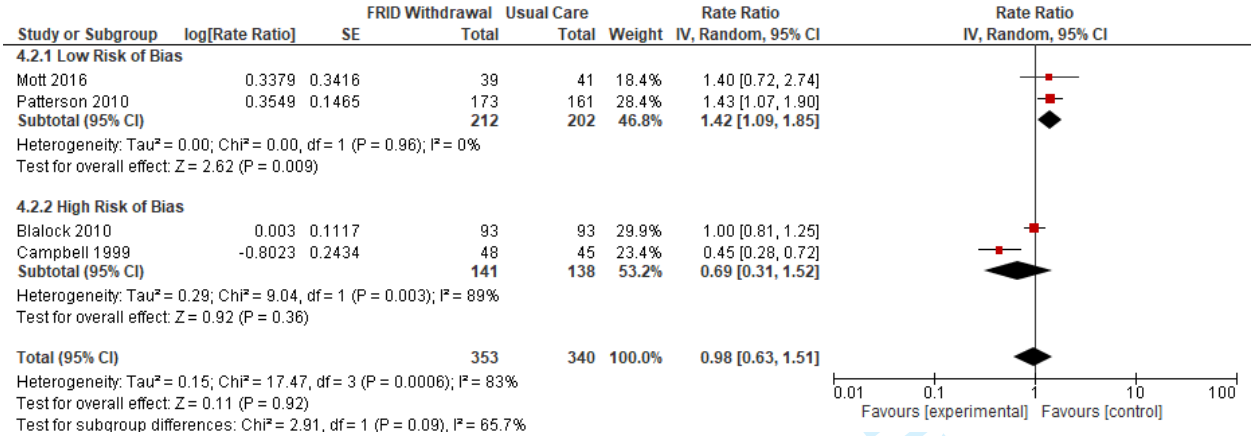
Design	**Criteria Met?**
Is the subgroup variable a characteristic measured at baseline or after randomization?	Yes – Variable determined at baseline
Is the effect suggested by comparisons within rather between studies?	No – Comparison between studies
Was the hypothesis specified a priori?	Yes
Was the direction of the subgroup effect specified a priori?	No
Was the subgroup effect one of a small number of hypothesized effects tested?	Yes – 1 of 3 analyses
Analysis	
Does the interaction test suggest a low likelihood that chance explains the apparent subgroup effect?	Yes – p=0.06
Is the significant subgroup effect independent?	No
Context	
Is the size of the subgroup effect large?	Yes – RR 0.61 vs. 1.14
Is the interaction consistent across studies?	No
Is the interaction consistent across closely related outcomes within the study?	No – Subgroup interaction was not seen for rate of falls
Is there indirect evidence that supports the hypothesized interaction (biological rationale)?	Yes – Antipsychotics associated with one of highest risks of falls. The withdrawal of any FRID may involve withdrawal of those with lower risks and limit potential benefit.

Supplementary Figure S3: Sensitivity Analyses

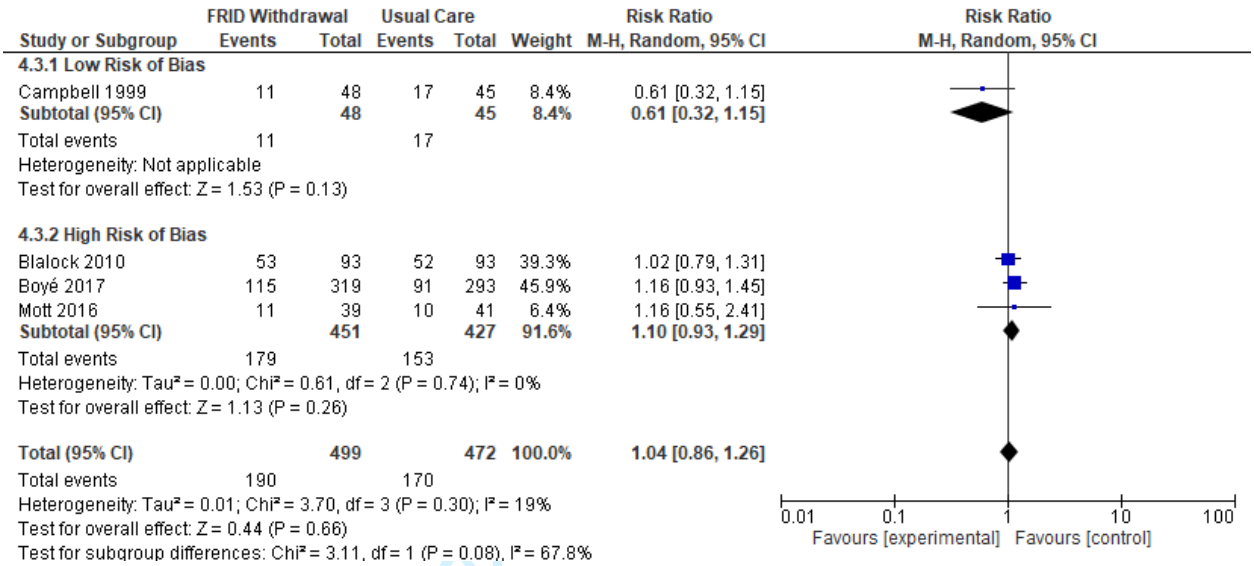
4.1 Falls Rate - Low vs. High Risk of Bias due to Blinding



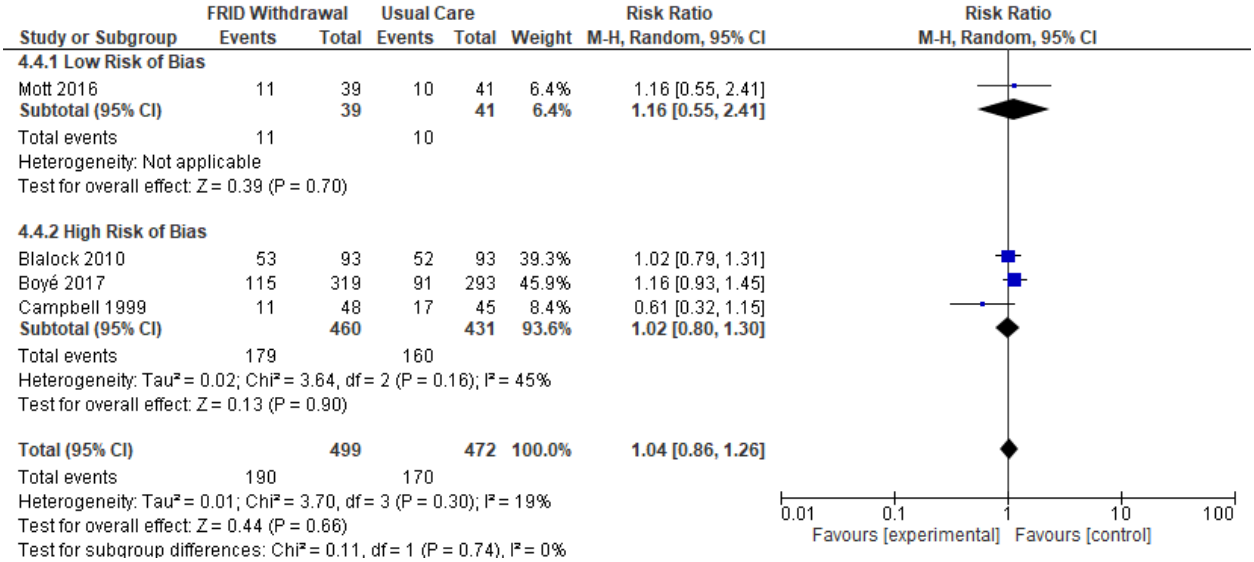
4.2 Falls Rate - Low vs. High Risk of Bias due to Attritional Bias



4.3 Falls Incidence - Low vs. High Risk of Bias due to Blinding



4.4 Falls Incidence - Low vs. High Risk of Bias due to Attrition Bias

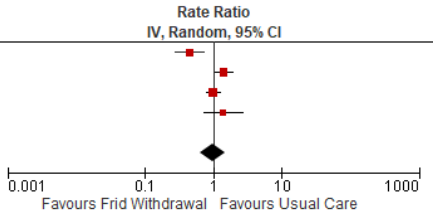


4.5 Falls Rate – Random vs. Effects Model

Random Effects Model

Study or Subgroup	log[Rate Ratio]	SE	FRID Withdrawal Total	Usual Care Total	Weight	Rate Ratio IV, Random, 95% CI	Year
Campbell 1999	-0.8023	0.2434	48	45	23.4%	0.45 [0.28, 0.72]	1999
Patterson 2010	0.3549	0.1465	173	161	28.4%	1.43 [1.07, 1.90]	2010
Blalock 2010	0.003	0.1117	93	93	29.9%	1.00 [0.81, 1.25]	2010
Mott 2016	0.3379	0.3416	39	41	18.4%	1.40 [0.72, 2.74]	2016
Total (95% CI)			**353**	**340**	**100.0%**	**0.98 [0.63, 1.51]**	

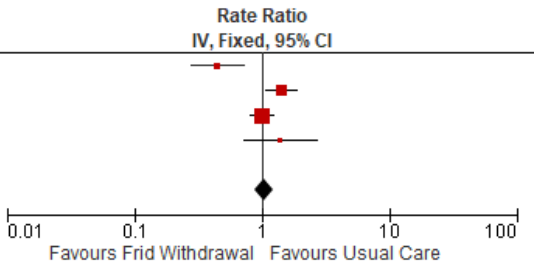
Heterogeneity: Tau² = 0.15; Chi² = 17.47, df = 3 (P = 0.0006); I² = 83%
Test for overall effect: Z = 0.11 (P = 0.92)



Fixed Effects Model

Study or Subgroup	log[Rate Ratio]	SE	Weight	Rate Ratio IV, Fixed, 95% CI	Year
Campbell 1999	-0.8023	0.2434	11.1%	0.45 [0.28, 0.72]	1999
Patterson 2010	0.3549	0.1465	30.6%	1.43 [1.07, 1.90]	2010
Blalock 2010	0.003	0.1117	52.7%	1.00 [0.81, 1.25]	2010
Mott 2016	0.3379	0.3416	5.6%	1.40 [0.72, 2.74]	2016
Total (95% CI)			**100.0%**	**1.04 [0.89, 1.22]**	

Heterogeneity: Chi² = 17.47, df = 3 (P = 0.0006); I² = 83%
Test for overall effect: Z = 0.50 (P = 0.62)

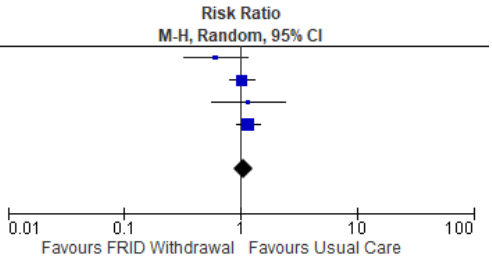


4.6 Falls Incidence – Random vs. Fixed Effects Model

Random Effects Model

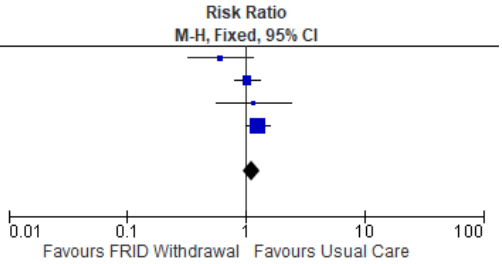
Study or Subgroup	FRID Withdrawal Events	FRID Withdrawal Total	Usual Care Events	Usual Care Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Campbell 1999	11	48	17	45	8.4%	0.61 [0.32, 1.15]	1999
Blalock 2010	53	93	52	93	39.3%	1.02 [0.79, 1.31]	2010
Mott 2016	11	39	10	41	6.4%	1.16 [0.55, 2.41]	2016
Boyé 2017	115	319	91	293	45.9%	1.16 [0.93, 1.45]	2017
Total (95% CI)		**499**		**472**	**100.0%**	**1.04 [0.86, 1.26]**	
Total events	190		170				

Heterogeneity: Tau² = 0.01; Chi² = 3.70, df = 3 (P = 0.30); I² = 19%
Test for overall effect: Z = 0.44 (P = 0.66)



Study or Subgroup	FRID Withdrawal Events	FRID Withdrawal Total	Usual Care Events	Usual Care Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Campbell 1999	11	48	17	45	10.3%	0.61 [0.32, 1.15]	1999
Blalock 2010	53	93	52	93	30.5%	1.02 [0.79, 1.31]	2010
Mott 2016	11	39	10	41	5.7%	1.16 [0.55, 2.41]	2016
Boyé 2017	115	308	91	308	53.4%	1.26 [1.01, 1.58]	2017
Total (95% CI)		**488**		**487**	**100.0%**	**1.12 [0.95, 1.31]**	
Total events	190		170				

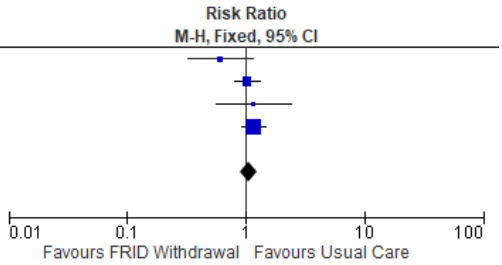
Heterogeneity: Chi² = 5.16, df = 3 (P = 0.16); I² = 42%
Test for overall effect: Z = 1.32 (P = 0.19)



Fixed Effects Model

Study or Subgroup	FRID Withdrawal Events	FRID Withdrawal Total	Usual Care Events	Usual Care Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Campbell 1999	11	48	17	45	10.1%	0.61 [0.32, 1.15]	1999
Blalock 2010	53	93	52	93	29.9%	1.02 [0.79, 1.31]	2010
Mott 2016	11	39	10	41	5.6%	1.16 [0.55, 2.41]	2016
Boyé 2017	115	319	91	293	54.5%	1.16 [0.93, 1.45]	2017
Total (95% CI)		**499**		**472**	**100.0%**	**1.06 [0.90, 1.25]**	
Total events	190		170				

Heterogeneity: Chi² = 3.70, df = 3 (P = 0.30); I² = 19%
Test for overall effect: Z = 0.74 (P = 0.46)



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary Figure S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8-9

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10 Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10-11 Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13 Figure 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12-13, Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12-13 Figure 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	15 Table 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	14-15
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	17-19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17-20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	21

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

PRISMA 2009 Checklist

BMJ Open

Deprescribing Fall-Risk-Increasing Drugs (FRIDs) for the Prevention of Falls and Fall-related Complications: A Systematic Review and Meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-035978.R1
Article Type:	Original research
Date Submitted by the Author:	12-Aug-2020
Complete List of Authors:	Lee, Justin; McMaster University, Division of Geriatric Medicine, Department of Medicine; McMaster University, Department of Health Research Methods, Evidence and Impact Negm, AM; McMaster University Faculty of Health Sciences, School of Rehabilitation Sciences; Hamilton Health Sciences, Geriatric Education and Research in Aging Sciences Centre Peters, Ryan; McMaster University Faculty of Health Sciences, Michael G. DeGroote School of Medicine Wong, Eric; University of Toronto, Division of Geriatric Medicine, Department of Medicine Holbrook, Anne; McMaster University, Division of Clinical Pharmacology and Toxicology, Department of Medicine; McMaster University Faculty of Health Sciences, Department of Health Research Methods, Evidence and Impact
Primary Subject Heading:	Geriatric medicine
Secondary Subject Heading:	Pharmacology and therapeutics, General practice / Family practice
Keywords:	INTERNAL MEDICINE, CLINICAL PHARMACOLOGY, GERIATRIC MEDICINE, PRIMARY CARE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

TITLE: Deprescribing Fall-Risk-Increasing Drugs (FRIDs) for the Prevention of Falls and Fall-related Complications: A Systematic Review and Meta-analysis

AUTHORS: Justin Lee, BScPhm, ACPR, MD[1,2,3]

Ahmed Negm, MD, MSc, PhD[3,4]

Ryan Peters, BSc, MD[5]

Eric Wong, BSc, MD[6]

Anne Holbrook, MD, PharmD, MSc[2,7]

[1]Division of Geriatric Medicine, Department of Medicine, McMaster University, Hamilton, Ontario, Canada
[2]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton,
Ontario, Canada
[3]Geriatric Education and Research in Aging Sciences (GERAS) Centre, Hamilton, Ontario, Canada
[4]School of Rehabilitation Sciences, Faculty of Health Sciences, McMaster University, Hamilton Ontario, Canada;
[5]Michael DeGroote School of Medicine, McMaster University, Hamilton, Ontario, Canada
[6]Division of Geriatric Medicine, Department of Medicine, University of Toronto, Toronto, Ontario, Canada
[7]Division of Clinical Pharmacology and Toxicology, Department of Medicine, McMaster University, Hamilton, Ontario, Canada

CORRESPONDING AUTHOR: Justin Lee
Geriatric Education and Research in Aging Sciences Centre
88 Maplewood Avenue, Room 158
Hamilton, Ontario, Canada L8M 1W9
Email: justin.lee@medportal.ca
Telephone: (905) 521-2100

MAIN TEXT WORD COUNT: 3582 (excluding title page, abstract, references, tables)

ABSTRACT:

Objectives: Prevention of falls and fall-related injuries is a priority due to the substantial health and financial burden of falls on patients and healthcare systems. Deprescribing medications known as "fall-risk increasing drugs" (FRIDs) is a common strategy to prevent falls based on associations in observational studies and presumed benefit. We conducted a systematic review to determine its efficacy for the prevention of falls and fall-related complications.

Design: Systematic review and meta-analysis

Data sources: MEDLINE, EMBASE, CENTRAL, CINAHL and grey literature from inception to August 1, 2020.

Eligibility criteria for selecting studies: Randomized controlled trials of FRID withdrawal compared to usual care evaluating the rate of falls, incidence of falls, fall-related injuries, fall-related fractures, fall-related hospitalizations or adverse effects related to the intervention in adults aged ≥65 years.

Data extraction and synthesis: Two reviewers independently performed citation screening, data abstraction, risk of bias assessment and certainty of evidence grading. Random-effects models were used for meta-analyses.

Results: Five trials involving 1305 participants met eligibility criteria. Deprescribing FRIDs did not change the rate of falls (rate ratio [RaR] 0.98, 95% CI 0.63 to 1.51), the incidence of falls (risk

difference [RD] 0.01, 95% CI -0.06 to 0.09; relative risk [RR] 1.04, 95% CI 0.86 to 1.26) or rate of fall-related injuries (RaR 0.89, 95% CI 0.57 to 1.39) over a 6 to 12 month follow-up period. No trials evaluated the impact of deprescribing FRIDs on fall-related fractures or hospitalizations.

Conclusion: There is a paucity of robust high-quality evidence to support or refute that a FRID deprescribing strategy is effective at preventing falls or falls-related injury in older adults. Although there may be other reasons to deprescribe FRIDs, our systematic review found that it may result in little to no difference in the rate or risk of falls as an isolated falls reduction strategy.

Registration: PROSPERO CRD42016040203

Key Words: Falls, Falls prevention, Fall-risk increasing drug (FRID), Deprescribing, Medication withdrawal, Seniors, Older Adults, Systematic review

Word Count: 300

ARTICLE SUMMARY

Strengths and Limitations of this Study:

- This study's results are based on a systematic review and meta-analysis of randomised controlled trials
- We employed rigorous analytic methods and interpretational approaches including duplicate assessment, subgroup credibility criteria and optimal information size considerations.
- We assessed the certainty in evidence (i.e. quality of evidence) using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Framework.
- Additional studies are needed to reach the optimal information size to reduce uncertainty about this intervention and establish its relative importance in the range of possible fall prevention interventions

INTRODUCTION

Falls and fall-related injuries are significant public health concerns. Every year, 1 in 3 older adults aged ≥65 years falls and 10% of these falls cause serious injury or hospitalization.[1] Falls are estimated to annually cost $50 billion in the United States, $2 billion in Canada, and £2.3 billion in the United Kingdom.[2–4] All jurisdictional levels are making significant investments to implement falls prevention quality improvement initiatives. These include Public Health England's National Falls Prevention Coordinating Group (NFPRCG), the Centers for Disease Control and Prevention (CDC) Stopping Elderly Accidents, Deaths, & Injuries (STEADI) Initiative, and Health Canada's Canadian Patient Safety Institute "Reducing Falls and Injuries from Falls" initiative. National accreditation bodies such as the United States Joint Commission and Accreditation Canada also mandate specific falls prevention activities of healthcare organizations through their required organizational practices and standards.

Since the majority of falls result from multiple factors (e.g. poor strength and balance, visual and cognitive impairment), current practice guidelines and accreditation standards focus on multi-component assessment and intervention strategies.[5] However, the 2018 United States Preventive Services Task Force evidence report recommends that multifactorial interventions only be offered to select patients because the overall net benefit is small.[6] In fact, there is ongoing debate on the relative merits of focusing on single versus multifactorial interventions, and many clinicians and institutions focus on single interventions due to limited resources.[7]

As an individual intervention, only exercise has robust evidence demonstrating reductions in the incidence of fallers and rate of injurious falls.[6,8] It is unclear if other parts of the multi-component strategy are effective, how large is their individual treatment effect, and which components should be prioritized when resources are limited.

Although there is limited evidence of effectiveness, deprescribing medications known as "fall-risk increasing drugs" (FRIDs) is common practice and typically included in both multifactorial and single intervention strategies. The justification is based primarily on observational studies that suggest certain medications are associated with increased falls risk. These include anti-hypertensives, anti-arrhythmics, anti-cholinergics, anti-histamines, sedatives-hypnotics, anti-psychotics, anti-depressants, opioids and NSAIDs.[9–14] Although the mechanisms are not fully understood, these drugs may influence falls risk by adversely affecting the cardiovascular or central nervous system (e.g. orthostatic hypotension, bradycardia, sedation, sleep disturbance, confusion, dizziness).

Key issues affecting the quality of this observational evidence and certainty of a causal relationship include: (1) variable adjustment for confounders, dosage or duration of therapy, (2) medication use confirmed only at baseline (but not throughout follow-up), and (3) potential prescribing bias associated with specific medication classes. Most meta-analyses have also been based on the pooling of unadjusted estimates and thus susceptible to bias including confounding by indication. As a result, it is unclear whether the observed increase in falls is causally related to such drug use versus the underlying conditions or patients for which the drugs are treating.

With the aim of evaluating its effectiveness as a falls prevention strategy, we conducted this systematic review to determine whether deprescribing FRIDs decreases the risk of falls compared to usual care in older adults. To the best of our knowledge, no previous systematic review has addressed this specific question.

METHODS

This review was developed using the Cochrane Handbook and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[15,16] The protocol was registered in PROSPERO (CRD42016040203) and previously published and described in detail.[17]

Search Strategy

MEDLINE, EMBASE, CINAHL and the Cochrane Central Register of Controlled Trials (CENTRAL) electronic databases were searched from inception to August 1, 2020 using a combination of Medical Subject Headings, controlled and free-text terms synonymous for the intervention. The MEDLINE search strategy is shown in Supplementary Figure S1. This strategy was modified for use in other databases.

Reference lists of relevant studies, reviews and guidelines were reviewed to identify additional studies. Trial registries and geriatric medicine conference abstracts were also reviewed.

Study Eligibility Criteria

After pilot testing the eligibility criteria, pairs of reviewers independently conducted screening. A third reviewer resolved disagreements.

Studies were included if they were RCTs evaluating FRID deprescribing or withdrawal with the intent of reducing falls. FRID deprescribing was defined as the planned and supervised discontinuation or dose reduction of single or multiple medications thought to independently increase falls risk.[9–11]

The comparator could be usual care (i.e. no change in usual activities and/or no FRID withdrawal) or a control intervention not thought to reduce falls. Studies focused on adults aged

≥65 years from all settings were included. Studies involving FRID withdrawal within multi-component interventions were excluded if the effect of FRID withdrawal could not be isolated.

The primary outcomes of this review were the (1) rate of falls (defined as the total number of falls per unit of person time that falls were monitored) and (2) incidence of falls (i.e. number of fallers). Secondary outcomes included the incidence of (1) fall-related fractures, (2) fall-related injuries, (3) fall-related hospitalization, (4) adverse effects related to the withdrawal intervention (e.g. disease relapse, symptomatic withdrawal).

Data Extraction and Quality Assessment

Two reviewers independently abstracted data on study characteristics, participants, interventions, comparisons, and outcomes using standardized electronic data extraction forms. Disagreements were resolved through consensus.

Two reviewed independently conducted risk of bias (RoB) assessments using the Cochrane Risk of Bias tool.[18] A previously published modification to the RoB assessment was employed to estimate unclearly reported study methods and allow for sensitivity analysis.[19] This modification involved a structured approach where a score of "definitely low risk", "probably low risk", "probably high risk", or "definitely high risk" was assigned to each RoB criterion. "Definitely" and "probably" scores were collapsed for both low and high RoB scores. Disagreements were resolved through consensus.

Data Synthesis and Analysis

The rate of falls was reported as a rate ratio (RaR) with a 95% confidence interval (CI). Dichotomous outcomes (i.e. incidences of falls, fall-related fracture, fall-related injury, fall-related

hospitalization and adverse effects related to the withdrawal intervention) have been reported as risk ratios (RR) with 95% CIs.

We used RevMan 5.3 and the intention-to-treat principle for all statistical analyses. We conducted meta-analyses using the generic inverse variance method to allow pooling of effect estimates. A random effects model was used given expected between-trial variations in methodological, participant and medication characteristics between studies. We had originally planned to pool data at various pre-specified time intervals, but all included studies had follow-up between 6 to 12 months.

We assessed heterogeneity through visual inspection of forest plots and statistical tests. A two-tailed test with p-value <0.10 was considered significant for all Chi-square analyses as per recommendations from the Cochrane Handbook and the I^2 was interpreted using the Cochrane Collaboration thresholds.[15]

Heterogeneity was explored in subgroup analyses based on five a priori hypotheses (Supplementary Table S1).[17] These included differences in baseline propensity for falls as influenced by (1) a history of recurrent falls (e.g. known faller or not) or (2) place of residence or care (e.g. community, long-term care); differences in the intervention as influenced by (3) specific medication class(es) chosen for withdrawal and (4) preceding medication review by a clinician for FRID withdrawal appropriateness; as well as differences in methodology based on (5) definitions used for "falls" (e.g., observed vs. self-reported). We assessed the credibility of any apparent subgroup effects using eleven previously published criteria recommended by the Cochrane Handbook.[20]

A priori sensitivity analyses were conducted to explore the impact of low vs. high RoB based on blinding and attrition. Studies did not report per-protocol results that would allow for our

planned intention-to-treat vs. per-protocol sensitivity analysis. The impact of using a fixed vs. random effects model was explored in a post hoc sensitivity analysis.

The confidence in effect estimates for each reported outcome was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.[21]

Patient and Public Involvement

Patients and the public were not involved in this review.

RESULTS

Of 891 citations identified, 31 were relevant for full text review and 6 met eligibility criteria (κ=0.79, 95% CI 0.51-1.00, substantial agreement). One study was available as an abstract, but it did not report its falls data.[22] Data were requested from the authors, but we did not receive a response. The PRISMA flow diagram summarizing our search results is shown in Figure 1.

Study Characteristics

The included trials in our review are described in Table 1.

Table 1: Characteristics of Included Studies

Author,	Study Design	Population	Sample Size	Age, Mean (SD)	Intervention	Control	Study Outcomes
Blalock et al, 2010 [23]	RCT	1) Community setting 2) Age ≥ 65 3) Speak, read English 4) ≥ 4 prescription medications 5) ≥ 1 high falls-risk medication 6) ≥ 1 fall not attributable to syncope within 1 year preceding randomization	186 (93 I/93 C)	74.8 (6.9)	1) Pharmacist medication review 2) Physician coordinated medication changes 3) Fall brochure, home safety checklist	1) Fall brochure, home safety checklist	1) Rate of falls 2) Incidence of falls
Campbell et al, 1999 [24]	RCT	1) Community setting 2) Age ≥ 65 3) Using benzodiazepine, other hypnotic, anti-depressant or major tranquilizer 4) Ambulatory 5) No physiotherapy 6) General practitioner thought psychotropic medication withdrawal beneficial	93 Arm 1: 24 (I) Arm 2: 24 (I) Arm 3: 21 (C)* Arm 4: 24 (C)*	74.7 (7.2)	Arm 1 1) Withdrawal of psychotropic medication over 14 weeks 2) Placebo substitution 3) Home exercise programme Arm 2 1) Psychotropic medication withdrawal 2) Placebo substitution 3) No home exercise programme	Arm 3 1) No change in psychotropic medication 2) Home exercise programme Arm 4 1) No change in psychotropic medication 2) No exercise programme	1) Rate of falls 2) Incidence of falls
Mott et al, 2016 [25]	Cluster RCT	1) Community setting 2) Age ≥ 65 3) English-speaking 4) Fall in last 12 months/fear of falling 5) Workshop participation 6) Capable of consent	80 (39 I/41 C)	75.6 (6.5)	1) FRID pharmacist review 2) Medication-related action plan (MAP) developed by pharmacist for patient 3) Pharmacist follow-up 4) Patient given pamphlet 5) describing the role of medications in falls and monthly falls calendars	1) Medications in falls pamphlet	1) Rate of falls 2) Incidence of falls
Patterson et al, 2010 [26]	Cluster RCT	1) Nursing home setting with ≥ 30 beds; not exclusive care of terminally ill 2) Age ≥ 65	334 (173 I/161 C)	82.7 (8.4)	1) Monthly medication review via pharmacist for appropriateness 2) Nurse and prescriber collaboration to improve medications	1) Usual care	1) Rate of falls
Boyé et al, 2017 [27]	RCT	1) Acute care emergency department setting; attended due to fall incident 2) Age ≥ 65 3) ≥ 1 FRID for ≥ 2 weeks prior to the fall 4) MMSE ≥ 21/30 5) Ambulates independently 6) Community dwelling 7) Informed consent by patient	612 (319 I/293 C)	80.2 (7.3)	1) Investigator conducted FRID assessment, proposed changes 2) Changes discussed with geriatrician and general practitioner/prescribing doctor 3) If consensus, FRID discontinued, reduced dosage, substituted for potentially safer option	1) Usual care	1) Rate of falls 2) Incidence of falls

Abbreviations: FRID = Fall-risk-increasing drug, I = Intervention, C = Control
* Arm 3 and Arm 4 classified as controls due to lack of FRID withdrawal in these arms of the factorial design

Three studies were individually randomized, while two studies were cluster randomized by either nursing home or health centre. Studies ranged in size from 80 to 612 participants. With exception of one study[25], studies were multi-centre involving 144 sites and 4 countries. All were conducted in the community setting except for one conducted in long-term care.[26] Follow-up periods ranged from 6 to 12 months.

Overall, there were 1305 participants across all trials. Most were female (>70%) and had a falls history (78.9%). Several key confounders were not reported in the studies including: (1) baseline number and types of FRIDs, (2) baseline number of medications, and (3) baseline number and types of co-morbidities. All these factors are thought to potentially modify falls risk.[28,29]

All interventions included a preceding assessment for FRID deprescribing appropriateness. This was conducted by physicians in 2 trials and pharmacists in 3 trials. Three trials tried to withdraw any FRID, while others focused on sedative-hypnotics, antipsychotics, or antidepressants. Successful discontinuation and adherence to deprescribing protocols were low in all studies. Rates of complete discontinuation of at least one FRID ranged from 10 to 40%.

In terms of our study outcomes, 4 trials measured the rate of falls and 4 measured falls incidence. One trial reported fall-related injuries.[23] Fall-related fractures, fall-related hospitalization or deprescribing-related adverse effects were not measured by any of the trials.

Summary of Findings

Rate and Incidence of Falls

Four studies reported the effect of deprescribing FRIDs on the rate of falls. Deprescribing FRIDs did not reduce the rate of falling (RaR 0.98, 95% CI 0.63 to 1.51; Figure 2 – Analysis 1.1).

Considerable statistical heterogeneity was present (χ^2=17.47, p=0.0006, I^2=83%) and subsequently explored in subgroup analysis.

Four studies reported the effect of deprescribing FRIDs on the risk of falls as measured by falls incidence. Deprescribing FRIDs did not reduce the incidence of falls (RR 1.04, 95% CI 0.86 to 1.26, I^2 = 19%, χ^2=3.70, p = 0.30; Figure 2 – Analysis 2.1). In absolute terms, there was a non-significant risk difference increase of 0.01 (95% CI -0.06 to 0.09, I^2 = 22%, p=0.76; Figure 2 – Analysis 2.2)

Rate of Injurious Falls

One trial reported the effect of deprescribing FRIDs on fall-related injuries.[23] Deprescribing FRIDs did not reduce the rate of fall-related injuries (RaR 0.89, 95% CI 0.57 to 1.39; Figure 2 – Analysis 3.1). This trial did not report data that would allow for any of our pre-planned subgroup analyses.

Risk of Bias Assessment

Figure 3 summarizes our RoB assessments. All studies were deemed at high risk of bias in at least one domain. The overall mean weighted kappa across all assessments was 0.67 (moderate agreement). For individual RoB assessments, kappa ranged from 0 to 0.85. Inter-rater agreement is actually higher than indicated by the calculated scores due to the "kappa co-efficient paradox".[30,31] Low kappas (e.g. κ=0) occurred despite high levels of observed agreement (e.g. $\geq$ 80% agreement) for two RoB assessments. True agreement is falsely attributed to chance agreement by the kappa calculation when there is substantial imbalance in marginal ratings.

For falls rate and incidence, all studies except one[24] were judged at high risk of bias for lack of blinding of participants, personnel and outcome assessors. It is unclear whether blinding could have impacted behaviour or perceptions (e.g. activity risk-level, nocebo effect). Risk of ascertainment bias was high in one study[26] (i.e. no standardized falls definition was used), but all other studies used methods accepted to be low risk of bias (i.e. falls recorded daily on postcards or calendars). Risk of attrition bias was deemed high in three studies based on high or unbalanced lost to follow-up rates.[23,24,27]

Publication Bias

Since less than 10 eligible studies were found, a funnel plot was not constructed due to an inability to make meaningful conclusions about publication bias.

Subgroup Analyses and Exploration of Heterogeneity

Our pre-specified subgroup analyses did not adequately explain the statistical heterogeneity observed results for the rate and incidence of falls (Supplementary Figure S2). Deprescribing FRIDs appeared more effective when a preceding medication review was conducted by physicians compared to pharmacists (p=0.0004, I^2=91.9%, Analysis 1.5), while psychotropic withdrawal appeared more effective than strategies withdrawing any FRID (p=0.08, I^2=67.8%, Analysis 2.3). However, in both analyses, only 6 of 11 subgroup credibility criteria were met and each subgroup was limited to one trial with less than 100 participants (Supplementary Table S2). We, therefore, judged the credibility that these subgroup effects are real as poor and uncertain.

The available data did not permit subgroup analyses by place of residence or falls ascertainment method. The other subgroup analyses showed no evidence of difference beyond that due to chance.

Sensitivity Analyses

Our sensitivity analyses are shown in Supplementary Figure S3. The incorporation of trials with high risk of performance bias appeared to mask the potential benefit of deprescribing FRIDs on reducing the incidence and rate of falls, while the trials with high risk of attrition bias appeared to mask a potential increase in falls rate with deprescribing FRIDs. These results should be interpreted cautiously and definitive conclusions cannot be made. Data from trials with low risk of performance bias were limited to one trial with less than 100 participants, and data from trials with low risk of attrition bias were limited to two trials with less than 450 participants overall.

A post-hoc sensitivity analysis examining the impact of using a fixed vs. random effects model did not change conclusions regarding the effect of deprescribing FRIDs on the rate or incidence of falls.

Quality of Evidence

The GRADE evidence profile is shown in Table 2.

Table 2: GRADE Quality of Evidence Assessment

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**FRID deprescribing strategy**	**usual care**	**Relative (95% CI)**	**Absolute (95% CI)**		
Falls Rate												
4	randomised trials	serious [a]	serious [b]	not serious	serious [c]	none	353	340	**Rate ratio 0.98** (0.63 to 1.51)	-	⨁◯◯◯ VERY LOW	IMPORTANT
Falls Incidence												
4	randomised trials	serious [a]	serious [d]	not serious	serious [c]	none	190/499 (38.1%)	170/472 (36.0%)	**RR 1.04** (0.86 to 1.26)	**14 more per 1,000** (from 50 fewer to 94 more)	⨁◯◯◯ VERY LOW	IMPORTANT
								33.7%		**13 more per 1,000** (from 47 fewer to 88 more)		
Fall-Related Injuries												
1	randomised trials	serious [a]	not serious	not serious	serious [c]	none	93	93	**Rate ratio 0.89** (0.57 to 1.39)	-	⨁⨁◯◯ LOW	CRITICAL

We judged the quality of evidence to be low or very low for all outcomes (falls rates, falls incidence and fall-related injuries) after rating down for risk of bias, inconsistency and imprecision.

We believe the optimal information size (OIS) to make definitive conclusions on the effect of deprescribing FRIDs has not yet been met as the body of evidence is based on fewer than 2000 participants and less than 400 events.[32,33] This is based on the OIS calculation figure recommended by the GRADE guidelines using a well-established control falls event rate of 30% described in the literature and conservative relative risk reduction (RRR) of 20% (assuming $\alpha = 0.05$ and $\beta = 0.2$).[33,34]

DISCUSSION

This systematic review sought to determine whether deprescribing FRIDs decreased the risk of falls in older adults and found that there is a lack of robust high-quality evidence to support or refute the deprescribing of FRIDs as an effective fall prevention strategy. Incorporating data from 5 RCTs involving 1305 participants aged ≥65 years, our meta-analyses indicate that a FRID deprescribing strategy did not significantly change the rate of falls (RaR 0.98, 95% CI 0.63 to 1.51) nor the risk of falling (RD 0.01, 95% CI -0.06 to 0.09) over a 6 to 12-month follow-up period. Although this intervention focuses on those medications thought to be associated with falls, the conclusions are similar to previous systematic reviews evaluating the effectiveness of medication reviews that had a broader focus on reducing polypharmacy and potentially inappropriate prescribing (i.e. not focused solely on FRIDs).[35,36]

There is also a significant absence of evidence for clinically- and patient-important outcomes such as fall-related injuries, fractures and hospitalizations. The only trial to date that evaluated the rate of fall-related injuries did not demonstrate a statistically significant effect (RaR

0.89, 95% CI 0.57-1.39).[23] Our search found no trials measuring the impact on fall-related fractures, fall-related hospitalizations or adverse effects related to a FRID deprescribing strategy. Although this may be rooted in the difficulty of conducting RCTs powered for such outcomes, their measurement and reporting are still important to inform systematic review meta-analyses that could lead to more precise estimates.

Based on low-quality evidence, it is unclear whether deprescribing FRIDs as a stand-alone intervention leads to any appreciable clinically important benefit or harm. Our current best effect estimates for falls rate and incidence are centred around no appreciable difference (i.e. RaR ≈ 1, RR ≈ 1, RD ≈ 0). Although seemingly logical to assume, reducing isolated risk factors may not necessarily lead to a reduction in falls and fall-related complications. The absence of change in the incidence of hip fractures after statewide regulatory action on benzodiazepine prescribing in the United States that reduced benzodiazepine use by 60.3% is a real-world example of this phenomenon and the complexity of exposure-outcome relationships.[37]

Our findings likely reflect the multi-factorial nature of falls and the varying risk of different FRIDs. It is unclear as to what degree a particular risk factor or combination of risk factors (e.g. specific FRIDs) must be reduced to produce an appreciable change in falls. Medications may only have conditional or contributory causality to falls. It may be that medication-related interventions work best in combination with other interventions or only in specific contexts.

Only one trial[24] included in our review demonstrated a statistically significant benefit with deprescribing FRIDs. This was also the only trial to use study capsules to operationalize blinded deprescribing of FRIDs in participants, research personnel and outcome assessors. Its results might be more reflective of the potential physiological effect of deprescribing FRIDs. However, the magnitude of benefit achievable in the "real world" setting may be closer to those

seen in the unblinded trials due to the strong psychological and behavioural factors (e.g. nocebo effect) that may hinder successful deprescribing.

These results raise several questions about the presumed effectiveness of deprescribing FRIDs as an isolated falls prevention strategy. Given the amount of resources being invested into falls prevention initiatives around the world, clinicians and organizations should examine: (1) what is the strength of evidence supporting their current activities, (2) whether these activities are cost-effective, and (3) whether resources are being appropriately prioritized to those interventions shown to provide the most value. This should also be applied to what is being required of healthcare organizations in national accreditation standards (e.g. Joint Commission, Accreditation Canada) to help direct and encourage optimal use of limited healthcare resources.

Clinicians and policy-makers need to consider the lack of strong evidence for deprescribing FRIDs as an isolated intervention for the specific purpose of reducing falls, particularly in patients who may be very reluctant or who have strong indications for specific FRIDs. FRID reduction is one out of many possible interventions that need to be considered. As with prescribing medications, deprescribing is a skill and comes with the potential for harm as well as benefit.[38] Thoughtful consideration of the goals, appropriateness and safety of deprescribing is important.[39] Our results highlight the need for a comprehensive and individualized approach to falls. Multi-component interventions are ideal, but interventions may need to be prioritized depending on time, resources and context.

Despite insufficient evidence to support or refute the deprescribing of FRIDs for falls prevention, our results do not mean that clinicians should avoid deprescribing FRIDs. There may be many other reasons to deprescribe these medications. These include avoidance of adverse drug events, improvements in cognition, increased medication adherence and drug costs savings. It is

also unclear whether medication review and management with a broader focus on reducing polypharmacy and potentially inappropriate prescribing in older adults may be beneficial in preventing falls.

Our review highlights the need for future FRID deprescribing trials that evaluate patient-important outcomes (e.g. injuries, fractures and hospitalizations). Greater attention to optimal design and reporting is needed to minimize risk of bias and enhance our interpretation of the results. Examples include improved reporting of confounding baseline characteristics and intervention fidelity (e.g. number and types of FRIDs, degree and duration of dose reduction). Deprescribing is challenging and extra measures are likely needed to improve successful intervention adherence and follow-up.

STRENGTHS AND LIMITATIONS

Our review has limitations. There was variation in the operationalization of FRID deprescribing and degree of success achieved (e.g. dose reduction only, completion discontinuation, non-adherence). This presumably makes the detection of any potential benefit less likely and our conclusions more conservative. However, the effect estimates are likely more indicative of what might be expected outside of the research setting. These phenomena likely represent the real-life challenges of deprescribing (especially with certain types of FRIDs such as psychotropics or opioids). Moreover, our ability to assess for confounders modifying falls risk was limited due to inconsistent reporting of relevant baseline characteristics and lack of patient-level data. Lastly, our ability to make definitive conclusions is limited because the total sample size across studies for each outcome did not yet meet our calculated estimate for the required optimal information size.

Our review has several strengths. First, our search was comprehensive and we included a rigorous grey literature search for unpublished studies. Second, we employed optimal analytical and interpretational approaches including duplicate assessment, subgroup credibility criteria and optimal information size considerations. Third, unlike previous medication-focused reviews, we applied the GRADE approach to assess the quality of evidence and our degree of confidence in the results.

CONCLUSIONS

Our systematic review found that deprescribing FRIDs as an isolated strategy results in little to no difference in the rate and risk of falls or falls-related injuries, but the evidence is still sparse and very low quality. Additional well-designed studies are needed to reach the optimal information size to reduce uncertainty about this intervention and establish its relative importance in the range of possible interventions that can be employed by clinicians and health systems to reduce falls.

Acknowledgements:

The authors would like to thank Lois Cottrell, medical librarian at St. Joseph's Healthcare Hamilton, Charlton Campus, Hamilton, Ontario, Canada and Andrea McLellan, Head of Collection and Technical Services, School of Medicine liaison, at McMaster University, Hamilton, Ontario, Canada, for their assistance with the development of the search strategy.

Author Contributions:

JL conceptualized the study. JL and AH designed and developed the protocol. RP and EW assisted with citation review. RP and AN assisted with data extraction, risk of bias assessment and certainty of evidence grading. All authors contributed to the analysis and interpretation of results. JL drafted the initial manuscript and all authors contributed to its revision and final approval.

Funding:

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing Interests:

The authors have no potential conflicts of interest to declare.

Patient Consent for Publication:

None required.

Data Sharing Statement:

No unpublished data are available.

REFERENCES:

1 Hill KD, Wee R. Psychotropic drug-induced falls in older people: a review of interventions aimed at reducing the problem. *Drugs Aging* 2012;**29**:15–30. doi:10.2165/11598420-000000000-00000

2 Florence CS, Bergen G, Atherly A, *et al.* Medical Costs of Fatal and Nonfatal Falls in Older Adults. *J Am Geriatr Soc* 2018;**66**:693–8. doi:10.1111/jgs.15304

3 National Institute for Health and Care Excellence. Falls in older people: assessing risk and prevention. 2013.

4 Public Health Agency of Canada. Seniors' Falls in Canada. 2014.

5 Summary of the Updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons. *J Am Geriatr Soc* 2011;**59**:148–57. doi:10.1111/j.1532-5415.2010.03234.x

6 Guirguis-Blake JM, Michael YL, Perdue LA, *et al.* Interventions to Prevent Falls in Older Adults. *JAMA* 2018;**319**:1705. doi:10.1001/jama.2017.21962

7 Campbell AJ, Robertson MC. Fall Prevention: Single or Multiple Interventions? Single Interventions for Fall Prevention. *J Am Geriatr Soc* 2013;**61**:281–4. doi:10.1111/jgs.12095_2

8 Tricco AC, Thomas SM, Veroniki AA, *et al.* Comparisons of Interventions for Preventing Falls in Older Adults. *JAMA* 2017;**318**:1687. doi:10.1001/jama.2017.15006

9 Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: I. Psychotropic drugs. *J Am Geriatr Soc* 1999;**47**:30–9.

10 Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: II. Cardiac and analgesic drugs. *J Am Geriatr Soc* 1999;**47**:40–

50.

11 Woolcott JC, Richardson KJ, Wiens MO, *et al.* Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Arch Intern Med* 2009;**169**:1952–60. doi:10.1001/archinternmed.2009.357

12 de Vries M, Seppala LJ, Daams JG, *et al.* Fall-Risk-Increasing Drugs: A Systematic Review and Meta-Analysis: I. Cardiovascular Drugs. *J Am Med Dir Assoc* 2018;**19**:371.e1-371.e9. doi:10.1016/j.jamda.2017.12.013

13 Seppala LJ, Wermelink AMAT, de Vries M, *et al.* Fall-Risk-Increasing Drugs: A Systematic Review and Meta-Analysis: II. Psychotropics. *J Am Med Dir Assoc* 2018;**19**:371.e11-371.e17. doi:10.1016/j.jamda.2017.12.098

14 Seppala LJ, van de Glind EMM, Daams JG, *et al.* Fall-Risk-Increasing Drugs: A Systematic Review and Meta-analysis: III. Others. *J Am Med Dir Assoc* 2018;**19**:372.e1-372.e8. doi:10.1016/j.jamda.2017.12.099

15 The Cochrane Collaboration. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]*. 2011.

16 Moher D, Liberati A, Tetzlaff J, *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;**151**:264–9, W64.

17 Lee JY, Holbrook A. The efficacy of fall-risk-increasing drug (FRID) withdrawal for the prevention of falls and fall-related complications: protocol for a systematic review and meta-analysis. *Syst Rev* 2017;**6**:33.

18 Higgins JPT, Altman DG, Gøtzsche PC, *et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;**343**:d5928.

19 Akl EA, Sun X, Busse JW, *et al.* Specific instructions for estimating unclearly reported

blinding status in randomized trials were reliable and valid. *J Clin Epidemiol* 2012;**65**:262–7. doi:10.1016/j.jclinepi.2011.04.015

20 Sun X, Briel M, Walter SD, *et al.* Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. *BMJ* 2010;**340**:c117.

21 Guyatt G, Oxman AD, Akl EA, *et al.* GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;**64**:383–94.

22 Streim JE, Filippo S, Have T, *et al.* Antidepressant discontinuation associated with cognitive decline in older adult residents of long-term care facilities. *Am J Geriatr psychiatry* 2012;**20**:S147–8. doi:10.1097/01.JGP.0000413064.91948.aa

23 Blalock SJ, Casteel C, Roth MT, *et al.* Impact of enhanced pharmacologic care on the prevention of falls: a randomized controlled trial. *Am J Geriatr Pharmacother* 2010;**8**:428–40. doi:10.1016/j.amjopharm.2010.09.002

24 Campbell AJ, Robertson MC, Gardner MM, *et al.* Psychotropic medication withdrawal and a home-based exercise program to prevent falls: a randomized, controlled trial. *J Am Geriatr Soc* 1999;**47**:850–3.

25 Mott DA, Martin B, Breslow R, *et al.* Impact of a medication therapy management intervention targeting medications associated with falling: Results of a pilot study. *J Am Pharm Assoc (2003)* 2016;**56**:22–8.

26 Patterson SM, Hughes CM, Crealey G, *et al.* An evaluation of an adapted U.S. model of pharmaceutical care to improve psychoactive prescribing for nursing home residents in northern ireland (fleetwood northern ireland study). *J Am Geriatr Soc* 2010;**58**:44–53. doi:10.1111/j.1532-5415.2009.02617.x

27 Boyé NDA, van der Velde N, de Vries OJ, *et al.* Effectiveness of medication withdrawal

in older fallers: results from the Improving Medication Prescribing to reduce Risk Of FALLs (IMPROveFALL) trial. *Age Ageing* 2017;**46**:142–6. doi:10.1093/ageing/afw161

28 Tinetti M, Kumar C. The Patient Who Falls. *JAMA J Am Med Assoc* 2010;**303**:273–4. doi:10.1001/jama.2009.2024

29 Chen Y, Zhu L-L, Zhou Q. Effects of drug pharmacokinetic/pharmacodynamic properties, characteristics of medication use, and relevant pharmacological interventions on fall risk in elderly patients. *Ther Clin Risk Manag* 2014;**10**:437–48. doi:10.2147/TCRM.S63756

30 Feinstein AR, Cicchetti D V. High agreement but low kappa: I. The problems of two paradoxes. *J Clin Epidemiol* 1990;**43**:543–9.

31 Tang W, Hu J, Zhang H, *et al.* Kappa coefficient: a popular measure of rater agreement. *Shanghai Arch psychiatry* 2015;**27**:62–7. doi:10.11919/j.issn.1002-0829.215010

32 Ioannidis J, Lau J. Evolution of treatment effects over time: empirical insight from recursive cumulative metaanalyses. *Proc Natl Acad Sci U S A* 2001;**98**:831–6. doi:10.1073/pnas.021529998

33 Guyatt GH, Oxman AD, Kunz R, *et al.* GRADE guidelines 6. Rating the quality of evidence--imprecision. *J Clin Epidemiol* 2011;**64**:1283–93. doi:10.1016/j.jclinepi.2011.01.012

34 O'Loughlin JL, Robitaille Y, Boivin JF, *et al.* Incidence of and risk factors for falls and injurious falls among the community-dwelling elderly. *Am J Epidemiol* 1993;**137**:342–54.

35 Gillespie LD, Robertson MC, Gillespie WJ, *et al.* Interventions for preventing falls in older people living in the community. *Cochrane database Syst Rev* 2012;**9**:CD007146. doi:10.1002/14651858.CD007146.pub3

36 Guirguis-Blake JM, Michael YL, Perdue LA, *et al. Interventions to Prevent Falls in*

Community-Dwelling Older Adults: A Systematic Review for the U.S. Preventive Services Task Force. Agency for Healthcare Research and Quality (US) 2018.

37 Wagner AK, Ross-Degnan D, Gurwitz JH, *et al.* Effect of New York State regulatory action on benzodiazepine prescribing and hip fracture rates. *Ann Intern Med* 2007;**146**:96–103.

38 Reeve E, Moriarty F, Nahas R, *et al.* A narrative review of the safety concerns of deprescribing in older adults and strategies to mitigate potential harms. *Expert Opin Drug Saf* 2018;**17**:39–49. doi:10.1080/14740338.2018.1397625

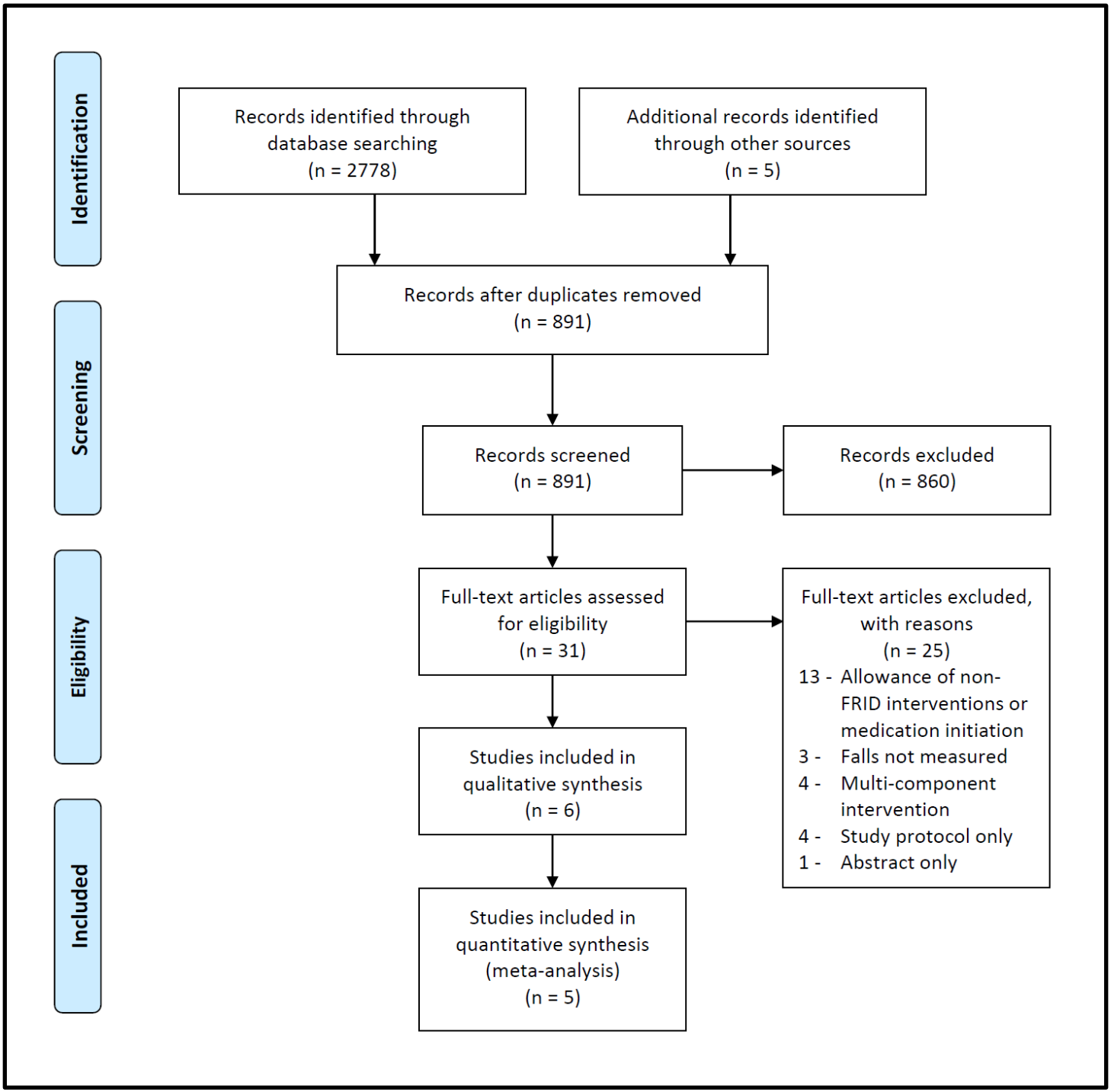
39 Lee JY, Farrell B, Holbrook AM. De-prescribing benzodiazepine receptor agonists taken for insomnia: a review and key messages from practice guidelines. *Polish Arch Intern Med* 2018;**129**:839–45. doi:10.20452/pamw.4391

FIGURES

Figure 1: PRISMA Flow Diagram of Study Selection Process

Figure 2: Forest Plots of FRID Withdrawal versus Usual Care

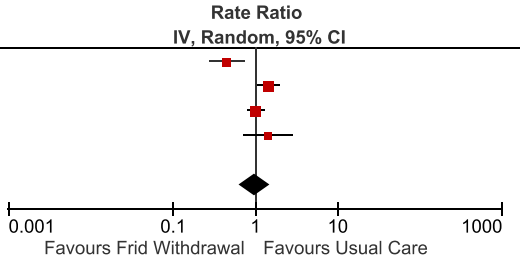
Figure 3: Risk of Bias Assessments


Identification
Screening
Eligibility
Included
Records identified through database searching (n = 2778)
Additional records identified through other sources (n = 5)
Records after duplicates removed (n = 891)
Records screened (n = 891)
Records excluded (n = 860)
Full-text articles assessed for eligibility (n = 31)
Full-text articles excluded, with reasons (n = 25)
13 - Allowance of non-FRID interventions or medication initiation
3 - Falls not measured
4 - Multi-component intervention
4 - Study protocol only
1 - Abstract only
Studies included in qualitative synthesis (n = 6)
Studies included in quantitative synthesis (meta-analysis) (n = 5)

1.1 Falls Rate

Study or Subgroup	log[Rate Ratio]	SE	FRID Withdrawal Total	Usual Care Total	Weight	Rate Ratio IV, Random, 95% CI	Year
Campbell 1999	-0.8023	0.2434	48	45	23.4%	0.45 [0.28, 0.72]	1999
Patterson 2010	0.3549	0.1465	173	161	28.4%	1.43 [1.07, 1.90]	2010
Blalock 2010	0.003	0.1117	93	93	29.9%	1.00 [0.81, 1.25]	2010
Mott 2016	0.3379	0.3416	39	41	18.4%	1.40 [0.72, 2.74]	2016
Total (95% CI)			**353**	**340**	**100.0%**	**0.98 [0.63, 1.51]**	

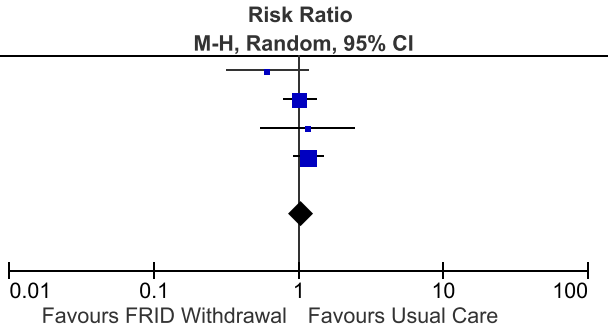
Heterogeneity: Tau² = 0.15; Chi² = 17.47, df = 3 (P = 0.0006); I² = 83%
Test for overall effect: Z = 0.11 (P = 0.92)



2.1 Falls Incidence – Risk Ratio

Study or Subgroup	FRID Withdrawal Events	FRID Withdrawal Total	Usual Care Events	Usual Care Total	Weight	Risk Ratio M-H, Random, 95% CI
Campbell 1999	11	48	17	45	8.4%	0.61 [0.32, 1.15]
Blalock 2010	53	93	52	93	39.3%	1.02 [0.79, 1.31]
Mott 2016	11	39	10	41	6.4%	1.16 [0.55, 2.41]
Boyé 2017	115	319	91	293	45.9%	1.16 [0.93, 1.45]
Total (95% CI)		**499**		**472**	**100.0%**	**1.04 [0.86, 1.26]**
Total events	190		170			

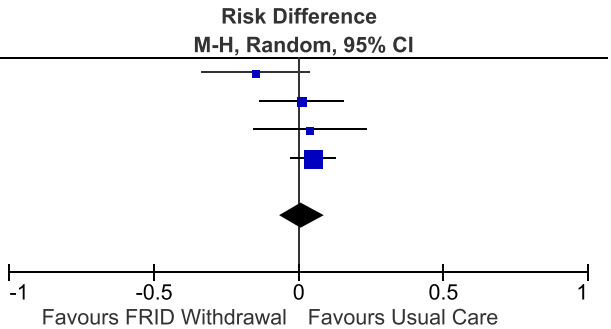
Heterogeneity: Tau² = 0.01; Chi² = 3.70, df = 3 (P = 0.30); I² = 19%
Test for overall effect: Z = 0.44 (P = 0.66)



2.2 Falls Incidence – Risk Difference

Study or Subgroup	FRID Withdrawal Events	FRID Withdrawal Total	Usual Care Events	Usual Care Total	Weight	Risk Difference M-H, Random, 95% CI
Campbell 1999	11	48	17	45	14.2%	-0.15 [-0.33, 0.04]
Blalock 2010	53	93	52	93	21.8%	0.01 [-0.13, 0.15]
Mott 2016	11	39	10	41	13.2%	0.04 [-0.15, 0.23]
Boyé 2017	115	319	91	293	50.9%	0.05 [-0.02, 0.12]
Total (95% CI)		**499**		**472**	**100.0%**	**0.01 [-0.06, 0.09]**
Total events	190		170			

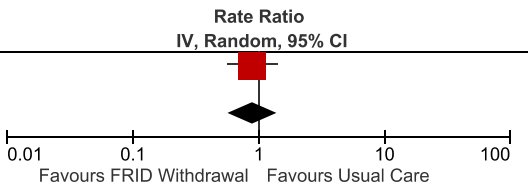
Heterogeneity: Tau² = 0.00; Chi² = 3.86, df = 3 (P = 0.28); I² = 22%
Test for overall effect: Z = 0.31 (P = 0.76)

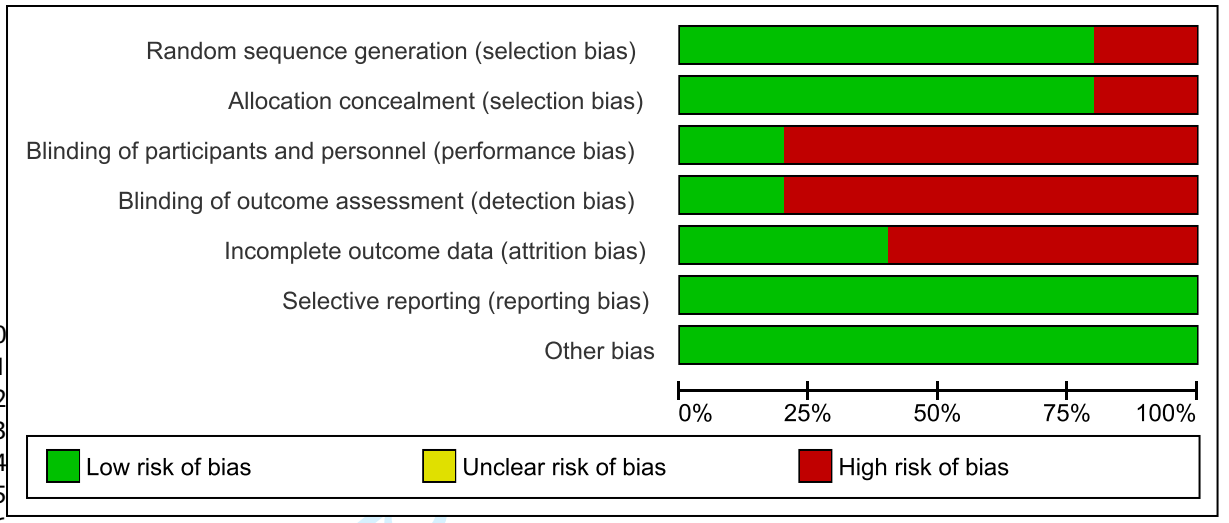


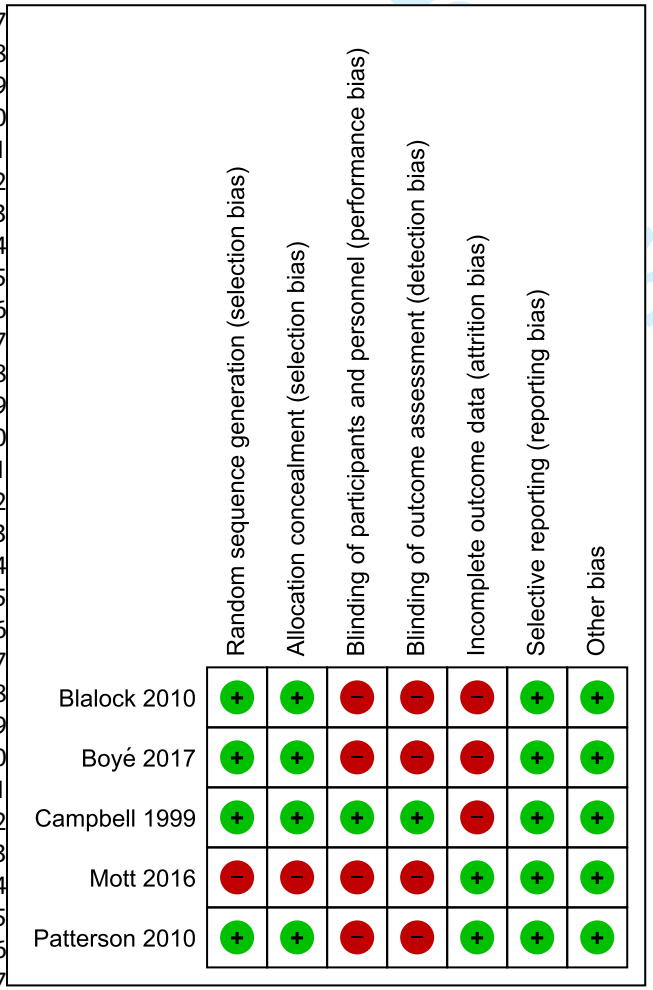
3.1 Fall-Related Injuries

Study or Subgroup	log[Rate Ratio]	SE	FRID Withdrawal Total	Usual Care Total	Weight	Rate Ratio IV, Random, 95% CI	Year
Blalock 2010	-0.1165	0.2273	93	93	100.0%	0.89 [0.57, 1.39]	2010
Total (95% CI)			**93**	**93**	**100.0%**	**0.89 [0.57, 1.39]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.51 (P = 0.61)







Supplementary Figure S1: OVID Medline Search Strategy

Database(s): OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

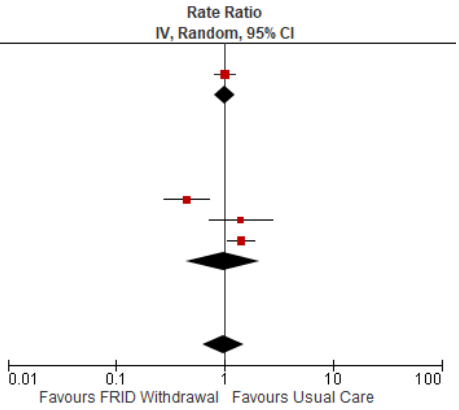
Search Strategy:

#	Searches
1	exp Accidental Falls/pc [Prevention & Control]
2	fall.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
3	falls.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
4	exp Deprescriptions/
5	((medicat* or drug*) adj3 (deprescrib* or withdraw* or cessat* or stop* or discontin*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
6	((antihypertensive* or diuretic* or beta-blocker* or sedative* or hypnotic* or neuroleptic* or antipsychotic* or antidepressant* or benzodiazepine* or narcotic* or opioid* or narcotic* or NSAID*) adj3 (deprescrib* or withdraw* or cessat* or stop* or discontin*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
7	fall-risk increasing drugs.mp.
8	FRID.mp.
9	((medicat* or drug*) adj3 (review* or improv* or program*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
10	exp "Drug-Related Side Effects and Adverse Reactions"/pc [Prevention & Control]
11	exp Medication Therapy Management/ or exp "Drug Utilization Review"/
12	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13	1 or 2 or 3
14	12 and 13
15	remove duplicates from 14
16	exp Clinical Trial/
17	(randomized or randomised).ab,ti.
18	placebo.ab,ti.
19	randomly.ab,ti.
20	groups.ab,ti.
21	randomized controlled trial.pt.
22	controlled clinical trial.pt.
23	16 or 17 or 18 or 19 or 20 or 21 or 22
24	15 and 23

Supplementary Figure S2: Subgroup Analyses

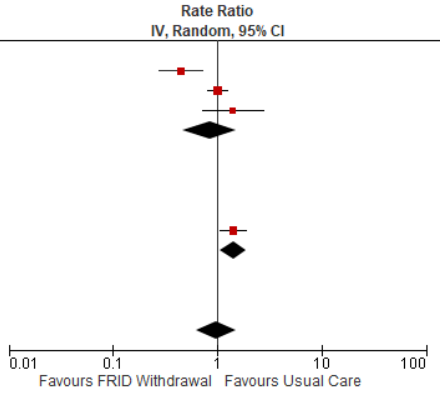
1.2 Falls Rate - Known vs. Unknown Faller

Study or Subgroup	log[Rate Ratio]	SE	FRID Withdrawal Total	Usual Care Total	Weight	Rate Ratio IV, Random, 95% CI
1.2.1 Known Faller						
Blalock 2010	0.003	0.1117	93	93	29.9%	1.00 [0.81, 1.25]
Subtotal (95% CI)			**93**	**93**	**29.9%**	**1.00 [0.81, 1.25]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.03 (P = 0.98)						
1.2.2 Unknown Faller						
Campbell 1999	-0.8023	0.2434	48	45	23.4%	0.45 [0.28, 0.72]
Mott 2016	0.3379	0.3416	39	41	18.4%	1.40 [0.72, 2.74]
Patterson 2010	0.3549	0.1465	173	161	28.4%	1.43 [1.07, 1.90]
Subtotal (95% CI)			**260**	**247**	**70.1%**	**0.96 [0.44, 2.10]**
Heterogeneity: Tau² = 0.41; Chi² = 17.23, df = 2 (P = 0.0002); I² = 88%						
Test for overall effect: Z = 0.10 (P = 0.92)						
Total (95% CI)			**353**	**340**	**100.0%**	**0.98 [0.63, 1.51]**
Heterogeneity: Tau² = 0.15; Chi² = 17.47, df = 3 (P = 0.0006); I² = 83%						
Test for overall effect: Z = 0.11 (P = 0.92)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.92), I² = 0%						



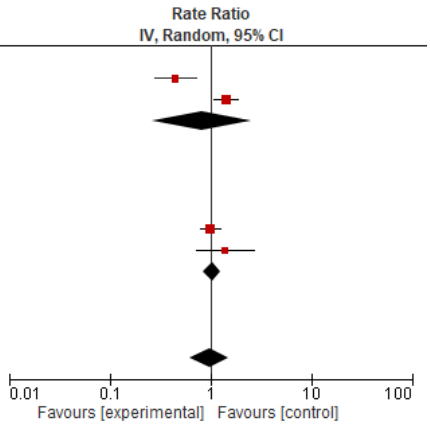
1.3 Falls Rate - Community vs. Institutionalized

Study or Subgroup	log[Rate Ratio]	SE	FRID Withdrawal Total	Usual Care Total	Weight	Rate Ratio IV, Random, 95% CI	Year
1.3.1 Community							
Campbell 1999	-0.8023	0.2434	48	45	23.4%	0.45 [0.28, 0.72]	1999
Blalock 2010	0.003	0.1117	93	93	29.9%	1.00 [0.81, 1.25]	2010
Mott 2016	0.3379	0.3416	39	41	18.4%	1.40 [0.72, 2.74]	2016
Subtotal (95% CI)			**180**	**179**	**71.6%**	**0.84 [0.47, 1.52]**	
Heterogeneity: Tau² = 0.21; Chi² = 10.82, df = 2 (P = 0.004); I² = 82%							
Test for overall effect: Z = 0.57 (P = 0.57)							
1.3.2 Institutionalized							
Patterson 2010	0.3549	0.1465	173	161	28.4%	1.43 [1.07, 1.90]	2010
Subtotal (95% CI)			**173**	**161**	**28.4%**	**1.43 [1.07, 1.90]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.42 (P = 0.02)							
Total (95% CI)			**353**	**340**	**100.0%**	**0.98 [0.63, 1.51]**	
Heterogeneity: Tau² = 0.15; Chi² = 17.47, df = 3 (P = 0.0006); I² = 83%							
Test for overall effect: Z = 0.11 (P = 0.92)							
Test for subgroup differences: Chi² = 2.49, df = 1 (P = 0.11), I² = 59.8%							



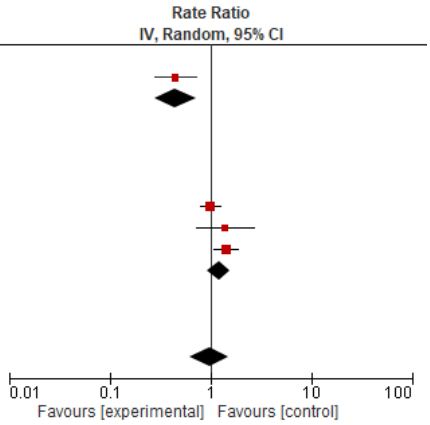
1.4 Falls Rate - Psychotropic Withdrawal vs. Any FRID Withdrawal

Study or Subgroup	log[Rate Ratio]	SE	FRID Withdrawal Total	Usual Care Total	Weight	Rate Ratio IV, Random, 95% CI
1.4.1 Psychotropic Withdrawal (Antipsychotic, Anxiolytic, Sedative, Hyponotic)						
Campbell 1999	-0.8023	0.2434	48	45	23.4%	0.45 [0.28, 0.72]
Patterson 2010	0.3549	0.1465	173	161	28.4%	1.43 [1.07, 1.90]
Subtotal (95% CI)			**221**	**206**	**51.7%**	**0.81 [0.26, 2.52]**
Heterogeneity: Tau² = 0.63; Chi² = 16.59, df = 1 (P < 0.0001); I² = 94%						
Test for overall effect: Z = 0.36 (P = 0.72)						
1.4.2 Any FRID						
Blalock 2010	0.003	0.1117	93	93	29.9%	1.00 [0.81, 1.25]
Mott 2016	0.3379	0.3416	39	41	18.4%	1.40 [0.72, 2.74]
Subtotal (95% CI)			**132**	**134**	**48.3%**	**1.04 [0.84, 1.28]**
Heterogeneity: Tau² = 0.00; Chi² = 0.87, df = 1 (P = 0.35); I² = 0%						
Test for overall effect: Z = 0.33 (P = 0.74)						
Total (95% CI)			**353**	**340**	**100.0%**	**0.98 [0.63, 1.51]**
Heterogeneity: Tau² = 0.15; Chi² = 17.47, df = 3 (P = 0.0006); I² = 83%						
Test for overall effect: Z = 0.11 (P = 0.92)						
Test for subgroup differences: Chi² = 0.17, df = 1 (P = 0.68), I² = 0%						



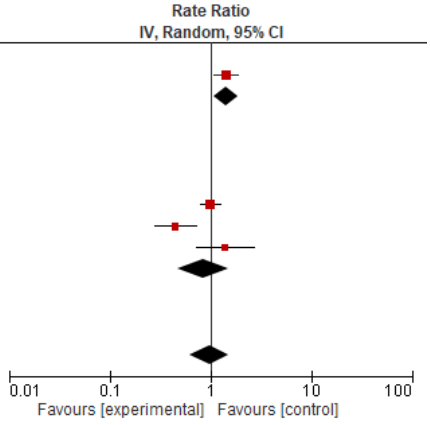
1.5 Falls Rate - Physician vs. Pharmacist Medication Review

Study or Subgroup	log[Rate Ratio]	SE	FRID Withdrawal Total	Usual Care Total	Weight	Rate Ratio IV, Random, 95% CI
1.5.1 Physician Medication Review						
Campbell 1999	-0.8023	0.2434	48	45	23.4%	0.45 [0.28, 0.72]
Subtotal (95% CI)			**48**	**45**	**23.4%**	**0.45 [0.28, 0.72]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.30 (P = 0.0010)						
1.5.2 Pharmacist Medication Review						
Blalock 2010	0.003	0.1117	93	93	29.9%	1.00 [0.81, 1.25]
Mott 2016	0.3379	0.3416	39	41	18.4%	1.40 [0.72, 2.74]
Patterson 2010	0.3549	0.1465	173	161	28.4%	1.43 [1.07, 1.90]
Subtotal (95% CI)			**305**	**295**	**76.6%**	**1.20 [0.92, 1.58]**
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 3.99$, df = 2 (P = 0.14); $I^2 = 50\%$						
Test for overall effect: Z = 1.33 (P = 0.18)						
Total (95% CI)			**353**	**340**	**100.0%**	**0.98 [0.63, 1.51]**
Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 17.47$, df = 3 (P = 0.0006); $I^2 = 83\%$						
Test for overall effect: Z = 0.11 (P = 0.92)						
Test for subgroup differences: $Chi^2 = 12.41$, df = 1 (P = 0.0004), $I^2 = 91.9\%$						

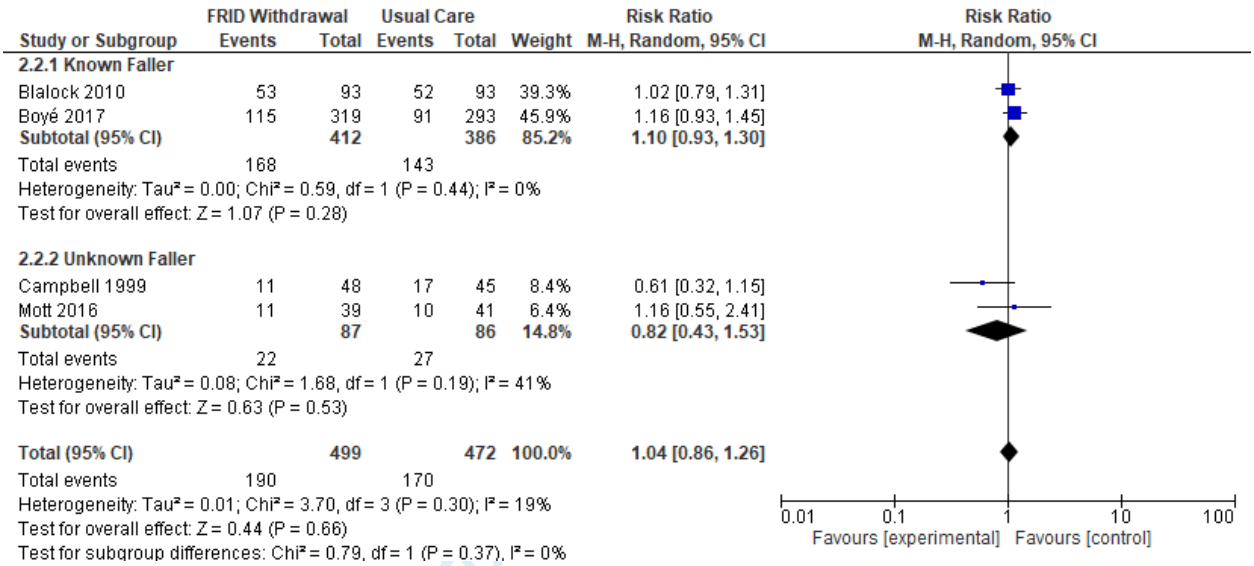


1.6 Falls Rate - Observed vs. Self-Reported Falls

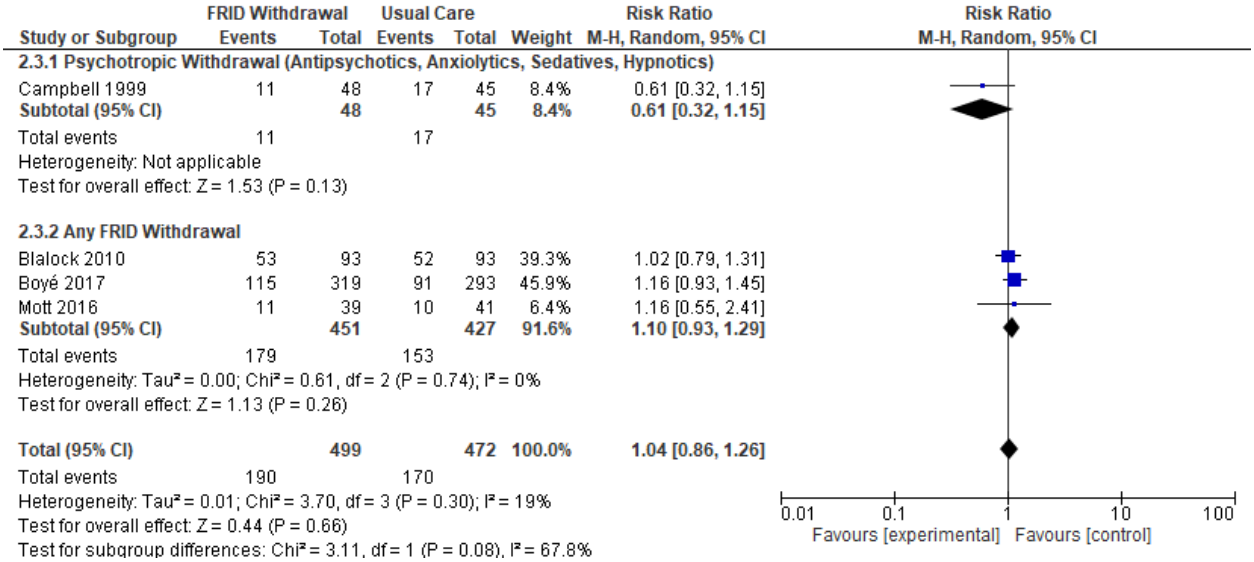
Study or Subgroup	log[Rate Ratio]	SE	FRID Withdrawal Total	Usual Care Total	Weight	Rate Ratio IV, Random, 95% CI
1.6.1 Observed Falls						
Patterson 2010	0.3549	0.1465	173	161	28.4%	1.43 [1.07, 1.90]
Subtotal (95% CI)			**173**	**161**	**28.4%**	**1.43 [1.07, 1.90]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.42 (P = 0.02)						
1.6.2 Self-Reported Falls						
Blalock 2010	0.003	0.1117	93	93	29.9%	1.00 [0.81, 1.25]
Campbell 1999	-0.8023	0.2434	48	45	23.4%	0.45 [0.28, 0.72]
Mott 2016	0.3379	0.3416	39	41	18.4%	1.40 [0.72, 2.74]
Subtotal (95% CI)			**180**	**179**	**71.6%**	**0.84 [0.47, 1.52]**
Heterogeneity: $Tau^2 = 0.21$; $Chi^2 = 10.82$, df = 2 (P = 0.004); $I^2 = 82\%$						
Test for overall effect: Z = 0.57 (P = 0.57)						
Total (95% CI)			**353**	**340**	**100.0%**	**0.98 [0.63, 1.51]**
Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 17.47$, df = 3 (P = 0.0006); $I^2 = 83\%$						
Test for overall effect: Z = 0.11 (P = 0.92)						
Test for subgroup differences: $Chi^2 = 2.49$, df = 1 (P = 0.11), $I^2 = 59.8\%$						



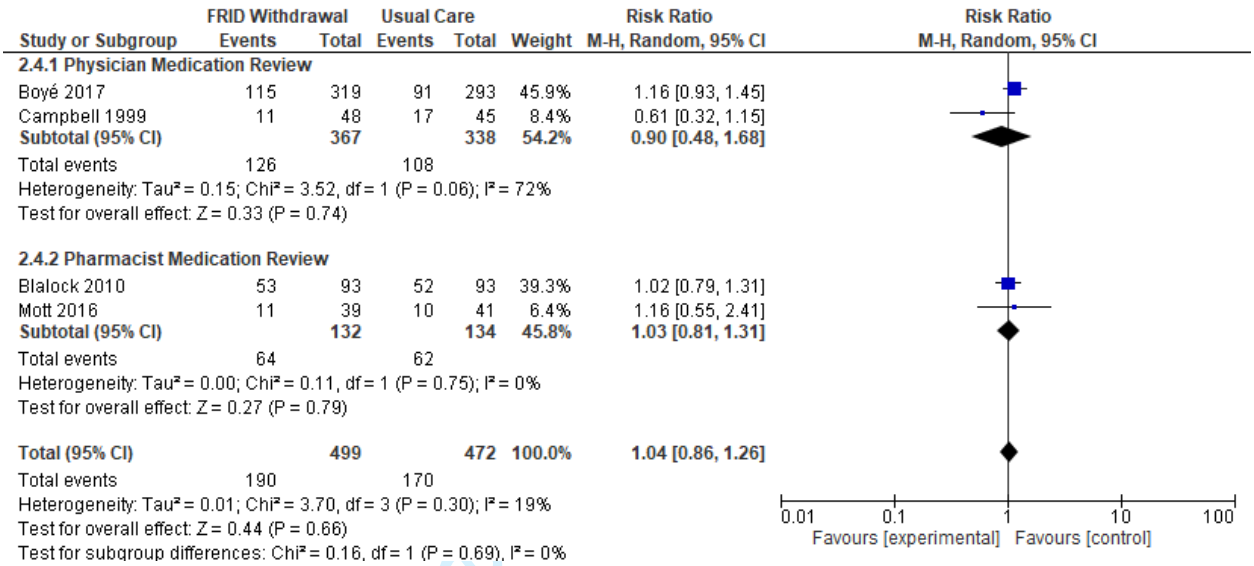
2.2 Falls Incidence - Known vs. Unknown Faller



2.3 Falls Incidence - Psychotropic Withdrawal vs. Any FRID Withdrawal



2.4 Falls Incidence - Physician vs. Pharmacist Medication Review



Supplementary Table S1: Subgroup Credibility Assessment – Clinician Medication Review

Physician vs. Pharmacist Medication Review Subgroup for Falls Rate

Design	**Criteria Met?**
Is the subgroup variable a characteristic measured at baseline or after randomization?	Yes – Variable determined at baseline
Is the effect suggested by comparisons within rather between studies?	No – Comparison between studies
Was the hypothesis specified a priori?	Yes
Was the direction of the subgroup effect specified a priori?	No
Was the subgroup effect one of a small number of hypothesized effects tested?	Yes – 1 of 5 analyses
Analysis	
Does the interaction test suggest a low likelihood that chance explains the apparent subgroup effect?	Yes – p =0.0004
Is the significant subgroup effect independent?	Yes
Context	
Is the size of the subgroup effect large?	Yes – RaR 0.45 vs. 1.20
Is the interaction consistent across studies?	No
Is the interaction consistent across closely related outcomes within the study?	No – Subgroup interaction was not seen for incidence of falls
Is there indirect evidence that supports the hypothesized interaction (biological rationale)?	No - No compelling external evidence supporting subgroup hypothesis

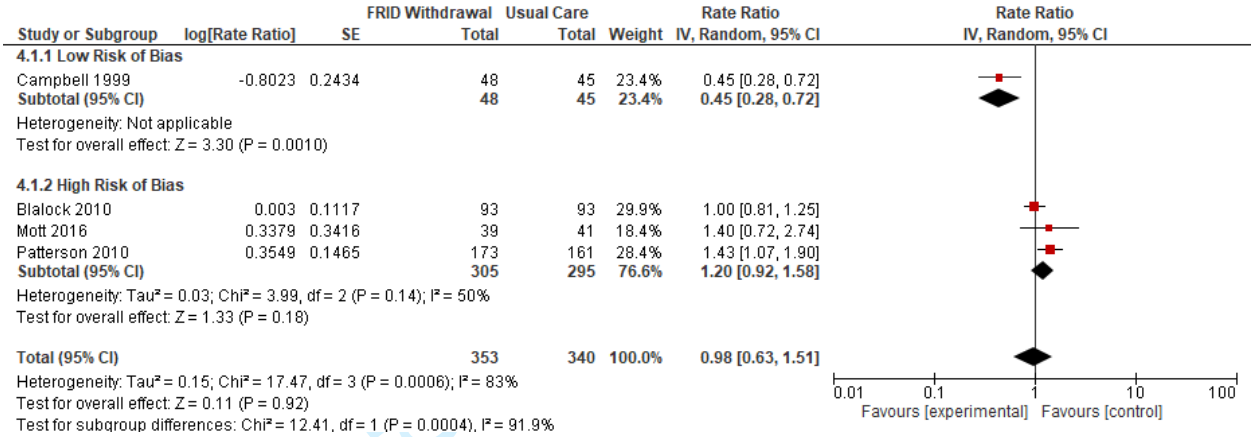
Supplementary Table S2: Subgroup Credibility Assessment – FRID Withdrawal Type

Antipsychotic vs. Any FRID Withdrawal for Falls Incidence

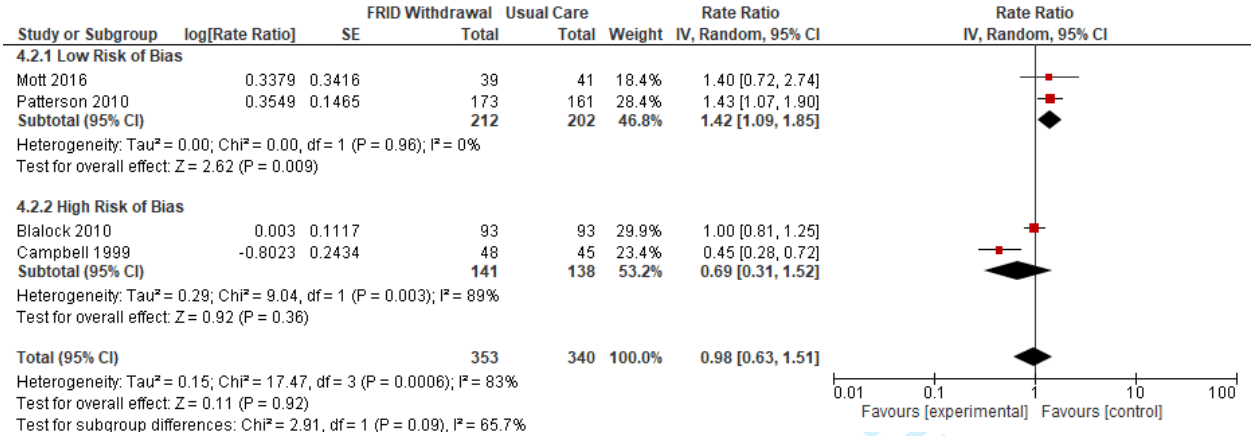
Design	**Criteria Met?**
Is the subgroup variable a characteristic measured at baseline or after randomization?	Yes – Variable determined at baseline
Is the effect suggested by comparisons within rather between studies?	No – Comparison between studies
Was the hypothesis specified a priori?	Yes
Was the direction of the subgroup effect specified a priori?	No
Was the subgroup effect one of a small number of hypothesized effects tested?	Yes – 1 of 3 analyses
Analysis	
Does the interaction test suggest a low likelihood that chance explains the apparent subgroup effect?	Yes – p=0.06
Is the significant subgroup effect independent?	No
Context	
Is the size of the subgroup effect large?	Yes – RR 0.61 vs. 1.14
Is the interaction consistent across studies?	No
Is the interaction consistent across closely related outcomes within the study?	No – Subgroup interaction was not seen for rate of falls
Is there indirect evidence that supports the hypothesized interaction (biological rationale)?	Yes – Antipsychotics associated with one of highest risks of falls. The withdrawal of any FRID may involve withdrawal of those with lower risks and limit potential benefit.

Supplementary Figure S3: Sensitivity Analyses

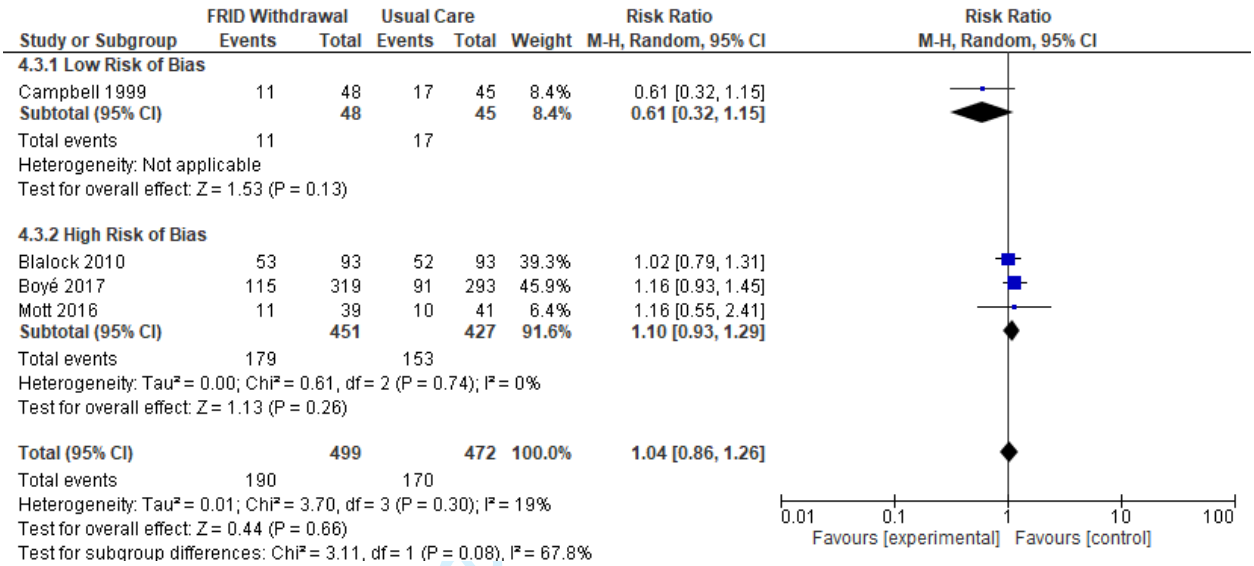
4.1 Falls Rate - Low vs. High Risk of Bias due to Blinding



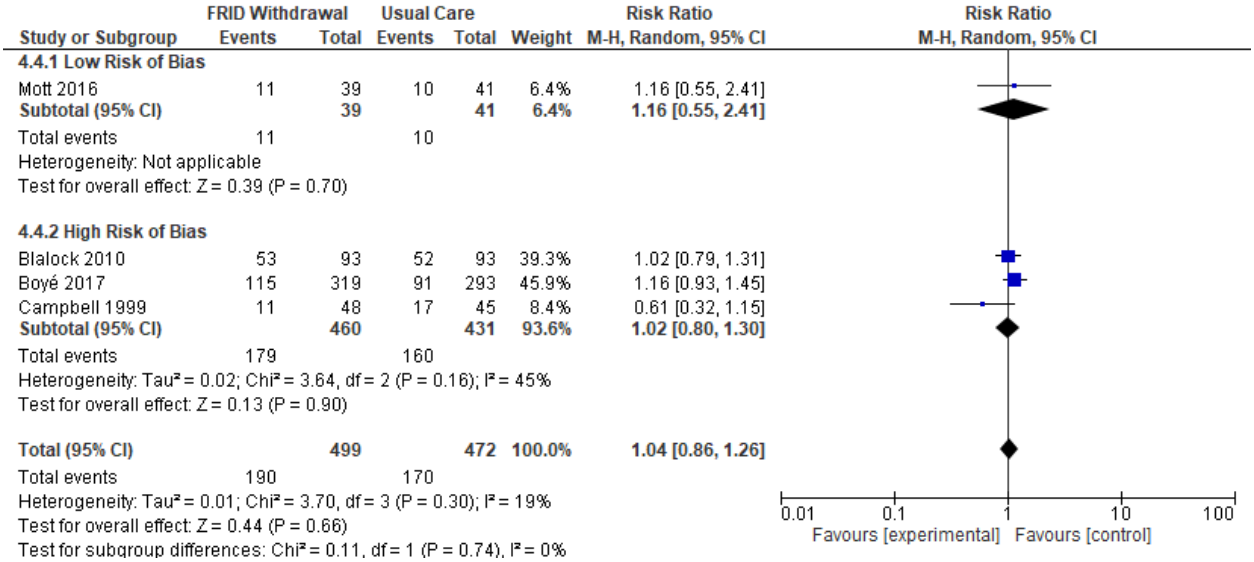
4.2 Falls Rate - Low vs. High Risk of Bias due to Attritional Bias



4.3 Falls Incidence - Low vs. High Risk of Bias due to Blinding



4.4 Falls Incidence - Low vs. High Risk of Bias due to Attrition Bias

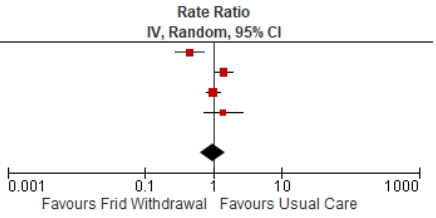


4.5 Falls Rate – Random vs. Effects Model

Random Effects Model

Study or Subgroup	log[Rate Ratio]	SE	FRID Withdrawal Total	Usual Care Total	Weight	Rate Ratio IV, Random, 95% CI	Year
Campbell 1999	-0.8023	0.2434	48	45	23.4%	0.45 [0.28, 0.72]	1999
Patterson 2010	0.3549	0.1465	173	161	28.4%	1.43 [1.07, 1.90]	2010
Blalock 2010	0.003	0.1117	93	93	29.9%	1.00 [0.81, 1.25]	2010
Mott 2016	0.3379	0.3416	39	41	18.4%	1.40 [0.72, 2.74]	2016
Total (95% CI)			**353**	**340**	**100.0%**	**0.98 [0.63, 1.51]**	

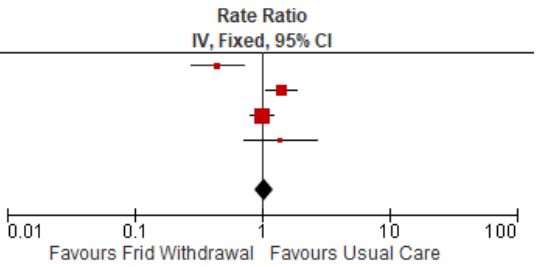
Heterogeneity: Tau² = 0.15; Chi² = 17.47, df = 3 (P = 0.0006); I² = 83%
Test for overall effect: Z = 0.11 (P = 0.92)



Fixed Effects Model

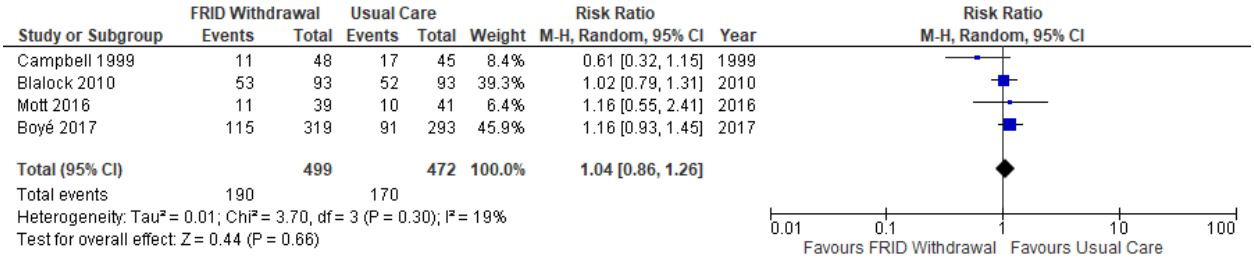
Study or Subgroup	log[Rate Ratio]	SE	Weight	Rate Ratio IV, Fixed, 95% CI	Year
Campbell 1999	-0.8023	0.2434	11.1%	0.45 [0.28, 0.72]	1999
Patterson 2010	0.3549	0.1465	30.6%	1.43 [1.07, 1.90]	2010
Blalock 2010	0.003	0.1117	52.7%	1.00 [0.81, 1.25]	2010
Mott 2016	0.3379	0.3416	5.6%	1.40 [0.72, 2.74]	2016
Total (95% CI)			**100.0%**	**1.04 [0.89, 1.22]**	

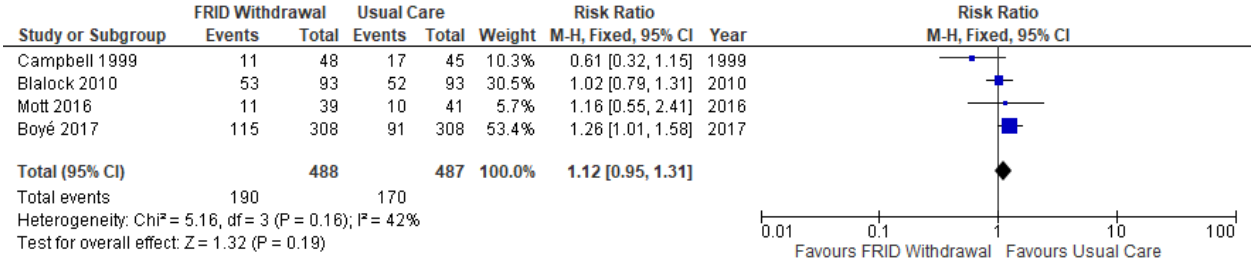
Heterogeneity: Chi² = 17.47, df = 3 (P = 0.0006); I² = 83%
Test for overall effect: Z = 0.50 (P = 0.62)



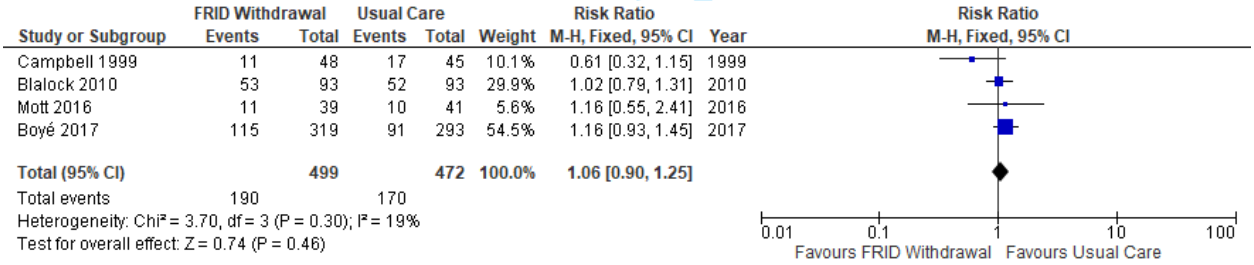
4.6 Falls Incidence – Random vs. Fixed Effects Model

Random Effects Model





Fixed Effects Model



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary Figure S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8-9

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9-10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9-10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10 Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10-11 Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13-14 Figure 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12-13, Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12-13 Figure 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	15-16 Table 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	14-15
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	17-20
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	20-21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	21
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	22

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

PRISMA 2009 Checklist

BMJ Open

Deprescribing Fall-Risk-Increasing Drugs (FRIDs) for the Prevention of Falls and Fall-related Complications: A Systematic Review and Meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-035978.R2
Article Type:	Original research
Date Submitted by the Author:	09-Oct-2020
Complete List of Authors:	Lee, Justin; McMaster University, Division of Geriatric Medicine, Department of Medicine; McMaster University, Department of Health Research Methods, Evidence and Impact Negm, AM; McMaster University Faculty of Health Sciences, School of Rehabilitation Sciences; Hamilton Health Sciences, Geriatric Education and Research in Aging Sciences Centre Peters, Ryan; McMaster University Faculty of Health Sciences, Michael G. DeGroote School of Medicine Wong, Eric; University of Toronto, Division of Geriatric Medicine, Department of Medicine Holbrook, Anne; McMaster University, Division of Clinical Pharmacology and Toxicology, Department of Medicine; McMaster University Faculty of Health Sciences, Department of Health Research Methods, Evidence and Impact
Primary Subject Heading:	Geriatric medicine
Secondary Subject Heading:	Pharmacology and therapeutics, General practice / Family practice
Keywords:	INTERNAL MEDICINE, CLINICAL PHARMACOLOGY, GERIATRIC MEDICINE, PRIMARY CARE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

TITLE: Deprescribing Fall-Risk-Increasing Drugs (FRIDs) for the Prevention of Falls and Fall-related Complications: A Systematic Review and Meta-analysis

AUTHORS: Justin Lee, BScPhm, ACPR, MD[1,2,3]

Ahmed Negm, MD, MSc, PhD[3,4]

Ryan Peters, BSc, MD[5]

Eric Wong, BSc, MD[6]

Anne Holbrook, MD, PharmD, MSc[2,7]

[1]Division of Geriatric Medicine, Department of Medicine, McMaster University, Hamilton, Ontario, Canada
[2]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton,
Ontario, Canada
[3]Geriatric Education and Research in Aging Sciences (GERAS) Centre, Hamilton, Ontario, Canada
[4]School of Rehabilitation Sciences, Faculty of Health Sciences, McMaster University, Hamilton Ontario, Canada;
[5]Michael DeGroote School of Medicine, McMaster University, Hamilton, Ontario, Canada
[6]Division of Geriatric Medicine, Department of Medicine, University of Toronto, Toronto, Ontario, Canada
[7]Division of Clinical Pharmacology and Toxicology, Department of Medicine, McMaster University, Hamilton, Ontario, Canada

CORRESPONDING AUTHOR: Justin Lee
Geriatric Education and Research in Aging Sciences Centre
88 Maplewood Avenue, Room 158
Hamilton, Ontario, Canada L8M 1W9
Email: justin.lee@medportal.ca
Telephone: (905) 521-2100

MAIN TEXT WORD COUNT: 3709 (excluding title page, abstract, references, tables)

ABSTRACT:

Objectives: Prevention of falls and fall-related injuries is a priority due to the substantial health and financial burden of falls on patients and healthcare systems. Deprescribing medications known as "fall-risk increasing drugs" (FRIDs) is a common strategy to prevent falls. We conducted a systematic review to determine its efficacy for the prevention of falls and fall-related complications.

Design: Systematic review and meta-analysis

Data sources: MEDLINE, EMBASE, CENTRAL, CINAHL and grey literature from inception to August 1, 2020.

Eligibility criteria for selecting studies: Randomized controlled trials of FRID withdrawal compared to usual care evaluating the rate of falls, incidence of falls, fall-related injuries, fall-related fractures, fall-related hospitalizations or adverse effects related to the intervention in adults aged ≥65 years.

Data extraction and synthesis: Two reviewers independently performed citation screening, data abstraction, risk of bias assessment and certainty of evidence grading. Random-effects models were used for meta-analyses.

Results: Five trials involving 1305 participants met eligibility criteria. Deprescribing FRIDs did not change the rate of falls (rate ratio [RaR] 0.98, 95% CI 0.63 to 1.51), the incidence of falls (risk difference [RD] 0.01, 95% CI -0.06 to 0.09; relative risk [RR] 1.04, 95% CI 0.86 to 1.26) or rate

of fall-related injuries (RaR 0.89, 95% CI 0.57 to 1.39) over a 6 to 12 month follow-up period. No trials evaluated the impact of deprescribing FRIDs on fall-related fractures or hospitalizations.

Conclusion: There is a paucity of robust high-quality evidence to support or refute that a FRID deprescribing strategy alone is effective at preventing falls or falls-related injury in older adults. Although there may be other reasons to deprescribe FRIDs, our systematic review found that it may result in little to no difference in the rate or risk of falls as an sole falls reduction strategy.

Registration: PROSPERO CRD42016040203

Key Words: Falls, Falls prevention, Fall-risk increasing drug (FRID), Deprescribing, Medication withdrawal, Seniors, Older Adults, Systematic review

Word Count: 295

ARTICLE SUMMARY

Strengths and Limitations of this Study:

- This study's results are based on a systematic review and meta-analysis of randomised controlled trials
- We employed rigorous analytic methods and interpretational approaches including duplicate assessment, subgroup credibility criteria and optimal information size considerations.
- We assessed the certainty in evidence (i.e. quality of evidence) using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Framework.
- Additional studies are needed to reach the optimal information size to reduce uncertainty about this intervention and establish its relative importance in the range of possible fall prevention interventions

INTRODUCTION

Falls and fall-related injuries are significant public health concerns. Every year, 1 in 3 older adults aged ≥65 years falls and 10% of these falls cause serious injury or hospitalization.[1] Falls are estimated to annually cost $50 billion in the United States, $2 billion in Canada, and £2.3 billion in the United Kingdom.[2–4] All jurisdictional levels are making significant investments to implement falls prevention quality improvement initiatives. These include Public Health England's National Falls Prevention Coordinating Group (NFPRCG), the Centers for Disease Control and Prevention (CDC) Stopping Elderly Accidents, Deaths, & Injuries (STEADI) Initiative, and Health Canada's Canadian Patient Safety Institute "Reducing Falls and Injuries from Falls" initiative. National accreditation bodies such as the United States Joint Commission and Accreditation Canada also mandate specific falls prevention activities of healthcare organizations through their required organizational practices and standards.

Since the majority of falls result from multiple factors (e.g. poor strength and balance, visual and cognitive impairment), current practice guidelines and accreditation standards focus on multi-factorial assessment and intervention strategies.[5] These strategies involve the combination of two or more interventions (e.g. exercise, home or environmental modification, vision assessment, education, medication management, vitamin D supplementation). However, the 2018 United States Preventive Services Task Force evidence report recommends that multifactorial interventions only be offered to select patients because the overall net benefit is small.[6] In fact, there is ongoing debate on the relative merits of focusing on single versus multifactorial interventions, and many clinicians and institutions focus on single interventions due to limited resources.[7]

As an individual intervention, only exercise has robust evidence demonstrating reductions in the incidence of fallers and rate of injurious falls.[6,8] It is unclear if other parts of the multi-component strategy are effective, how large is their individual treatment effect, and which components should be prioritized when resources are limited.

Although there is limited evidence of effectiveness, deprescribing medications known as "fall-risk increasing drugs" (FRIDs) is common practice and typically included in both multifactorial and single intervention strategies. The justification is based on observational studies that suggest certain medications are associated with increased falls risk as well as some randomized controlled trials (RCTs) that have shown that medication management interventions (including those with a broader focus of reducing polypharmacy and/or potentially inappropriate prescribing) may reduce the risk of falls.[9] FRIDs include anti-hypertensives, anti-arrhythmics, anti-cholinergics, anti-histamines, sedatives-hypnotics, anti-psychotics, anti-depressants, opioids and NSAIDs.[10–15]. Although the mechanisms are not fully understood, these drugs may influence falls risk by adversely affecting the cardiovascular or central nervous system (e.g. orthostatic hypotension, bradycardia, sedation, sleep disturbance, confusion, dizziness).

Key issues affecting the quality of this observational evidence and certainty of a causal relationship include: (1) variable adjustment for confounders, dosage or duration of therapy, (2) medication use confirmed only at baseline (but not throughout follow-up), and (3) potential prescribing bias associated with specific medication classes. Most meta-analyses have also been based on the pooling of unadjusted estimates and thus susceptible to bias including confounding by indication. As a result, it is unclear whether the observed increase in falls is causally related to such drug use versus the underlying conditions or patients for which the drugs are treating.

With the aim of evaluating its effectiveness as a single falls prevention strategy, we conducted this systematic review to determine whether deprescribing FRIDs decreases the risk of falls compared to usual care in older adults aged ≥ 65 years. To the best of our knowledge, no previous systematic review has addressed this specific research question.

METHODS

This review was developed using the Cochrane Handbook and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[16,17] The protocol was registered in PROSPERO (CRD42016040203) and previously published and described in detail.[18]

Search Strategy

MEDLINE, EMBASE, CINAHL and the Cochrane Central Register of Controlled Trials (CENTRAL) electronic databases were searched from inception to August 1, 2020 using a combination of Medical Subject Headings, controlled and free-text terms synonymous for the intervention. The MEDLINE search strategy is shown in Supplementary Figure S1. This strategy was modified for use in other databases.

Reference lists of relevant studies, reviews and guidelines were reviewed to identify additional studies. Trial registries and geriatric medicine conference abstracts were also reviewed.

Study Eligibility Criteria

After pilot testing the eligibility criteria, pairs of reviewers independently conducted screening. A third reviewer resolved disagreements.

Studies were included if they were RCTs evaluating FRID deprescribing or withdrawal with the intent of reducing falls. FRID deprescribing was defined as the planned and supervised discontinuation or dose reduction of single or multiple medications thought to independently increase falls risk.[10–12]

The comparator could be usual care (i.e. no change in usual activities and/or no FRID withdrawal) or a control intervention not thought to reduce falls. Studies focused on adults aged ≥65 years from all settings were included. Studies involving FRID withdrawal within multi-component interventions were excluded if the effect of FRID withdrawal could not be isolated.

The primary outcomes of this review were the (1) rate of falls (defined as the total number of falls per unit of person time that falls were monitored) and (2) incidence of falls (i.e. number of fallers). Secondary outcomes included the incidence of (1) fall-related fractures, (2) fall-related injuries, (3) fall-related hospitalization, (4) adverse effects related to the withdrawal intervention (e.g. disease relapse, symptomatic withdrawal).

Data Extraction and Quality Assessment

Two reviewers independently abstracted data on study characteristics, participants, interventions, comparisons, and outcomes using standardized electronic data extraction forms. Disagreements were resolved through consensus.

Two reviewed independently conducted risk of bias (RoB) assessments using the Cochrane Risk of Bias tool.[19] A previously published modification to the RoB assessment was employed to estimate unclearly reported study methods and allow for sensitivity analysis.[20] This modification involved a structured approach where a score of "definitely low risk", "probably low risk", "probably high risk", or "definitely high risk" was assigned to each RoB criterion.

"Definitely" and "probably" scores were collapsed for both low and high RoB scores. Disagreements were resolved through consensus.

Data Synthesis and Analysis

The rate of falls was reported as a rate ratio (RaR) with a 95% confidence interval (CI). Dichotomous outcomes (i.e. incidences of falls, fall-related fracture, fall-related injury, fall-related hospitalization and adverse effects related to the withdrawal intervention) have been reported as risk ratios (RR) with 95% CIs.

We used RevMan 5.3 and the intention-to-treat principle for all statistical analyses. We conducted meta-analyses using the generic inverse variance method to allow pooling of effect estimates. A random effects model was used given expected between-trial variations in methodological, participant and medication characteristics between studies. We had originally planned to pool data at various pre-specified time intervals, but all included studies had follow-up between 6 to 12 months.

We assessed heterogeneity through visual inspection of forest plots and statistical tests. A two-tailed test with p-value <0.10 was considered significant for all Chi-square analyses as per recommendations from the Cochrane Handbook and the I^2 was interpreted using the Cochrane Collaboration thresholds.[16]

Heterogeneity was explored in subgroup analyses based on five a priori hypotheses (Supplementary Table S1).[18] These included differences in baseline propensity for falls as influenced by (1) a history of recurrent falls (e.g. known faller or not) or (2) place of residence or care (e.g. community, long-term care); differences in the intervention as influenced by (3) specific medication class(es) chosen for withdrawal and (4) preceding medication review by a clinician for

FRID withdrawal appropriateness; as well as differences in methodology based on (5) definitions used for "falls" (e.g., observed vs. self-reported). We assessed the credibility of any apparent subgroup effects using eleven previously published criteria recommended by the Cochrane Handbook.[21]

A priori sensitivity analyses were conducted to explore the impact of low vs. high RoB based on blinding and attrition. Studies did not report per-protocol results that would allow for our planned intention-to-treat vs. per-protocol sensitivity analysis. The impact of using a fixed vs. random effects model was explored in a post hoc sensitivity analysis.

The confidence in effect estimates for each reported outcome was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.[22]

Patient and Public Involvement

Patients and the public were not involved in this review.

RESULTS

Of 891 citations identified, 31 were relevant for full text review and 6 met eligibility criteria (κ=0.79, 95% CI 0.51-1.00, substantial agreement). One study was available as an abstract, but it did not report its falls data.[23] Data were requested from the authors, but we did not receive a response. The PRISMA flow diagram summarizing our search results is shown in Figure 1.

Study Characteristics

The included trials in our review are described in Table 1.

Table 1: Characteristics of Included Studies

Author, Year	Study Design	Population	Sample Size	Age Mean (SD)	Targeted FRIDs	Intervention	Control	Study Outcomes
Blalock 2010 [24]	RCT	1) Community setting 2) Age ≥ 65 3) Speak, read English 4) ≥ 4 prescription medications 5) ≥ 1 high falls-risk medication 6) ≥ 1 fall not attributable to syncope within previous year	186 (93 I/93 C)	74.8 (6.9)	Benzodiazepines, antidepressants, anticonvulsants, sedative hypnotics, opioid analgesics, antipsychotics, and skeletal muscle relaxants	1) Pharmacist medication review 2) Physician coordinated medication changes 3) Fall brochure, home safety checklist	1) Fall brochure, home safety checklist	1) Rate of falls 2) Incidence of falls
Campbell 1999 [25]	RCT	1) Community setting 2) Age ≥ 65 3) Using benzodiazepine, other hypnotic, anti-depressant or major tranquilizer 4) Ambulatory 5) No physiotherapy 6) General practitioner thought psychotropic medication withdrawal beneficial	93 Arm 1: 24 (I) Arm 2: 24 (I) Arm 3: 21 (C)* Arm 4: 24 (C)*	74.7 (7.2)	Psychotropic medications (e.g. benzodiazepines, hypnotics, antidepressants, tranquilizers)	Arm 1 1) Withdrawal of psychotropic medication over 14 weeks 2) Placebo substitution 3) Home exercise programme Arm 2 1) Psychotropic medication withdrawal 2) Placebo substitution 3) No home exercise programme	Arm 3 1) No change in psychotropic medication 2) Home exercise programme Arm 4 1) No change in psychotropic medication 2) No exercise programme	1) Rate of falls 2) Incidence of falls
Mott 2016 [26]	Cluster RCT	1) Community setting 2) Age ≥ 65 3) English-speaking 4) Fall in last 12 months/fear of falling 5) Workshop participation 6) Capable of consent	80 (39 I/41 C)	75.6 (6.5)	Neuroleptics, benzodiazepines, anti-depressants, sedative-hypnotics, anti-hypertensives, cyclobenzaprine, carisoprodol, sedating antihistamines, oxybutynin, carbamazepine, methocarbamol, prochlorperazine, benztropine, trihexiphenidyl	1) FRID pharmacist review 2) Medication-related action plan (MAP) developed by pharmacist for patient 3) Pharmacist follow-up 4) Patient given pamphlet 5) describing the role of medications in falls and monthly falls calendars	1) Medications in falls pamphlet	1) Rate of falls 2) Incidence of falls
Patterson 2010 [27]	Cluster RCT	1) Nursing home setting with ≥ 30 beds; not exclusive care of terminally ill 2) Age ≥ 65	334 (173 I/161 C)	82.7 (8.4)	Psychoactive medications (i.e. hypnotics, anxiolytics, antipsychotics)	1) Monthly medication review via pharmacist for appropriateness 2) Nurse and prescriber collaboration to improve medications	1) Usual care	1) Rate of falls
Boyé 2017 [28]	RCT	1) Acute care emergency department setting; attended due to fall incident 2) Age ≥ 65 3) ≥ 1 FRID for ≥ 2 weeks prior to the fall 4) MMSE ≥ 21/30 5) Ambulates independently 6) Community dwelling 7) Informed consent by patient	612 (319 I/293 C)	80.2 (7.3)	Anxiolytics/hypnotics, antidepressants, neuroleptics, anti-hypertensives, anti-arrhythmics, NSAIDs, H2 receptor antagonists, opioids, sympathomimetics, anti-histaminics, diuretics	1) Investigator conducted FRID assessment, proposed changes 2) Changes discussed with geriatrician and general practitioner/prescribing doctor 3) If consensus, FRID discontinued, reduced dosage, substituted for potentially safer option	1) Usual care	1) Rate of falls 2) Incidence of falls

Abbreviations: FRID = Fall-risk-increasing drug, I = Intervention, C = Control

* Arm 3 and Arm 4 classified as controls due to lack of FRID withdrawal in these arms of the factorial design

Three studies were individually randomized, while two studies were cluster randomized by either nursing home or health centre. Studies ranged in size from 80 to 612 participants. With exception of one study[26], studies were multi-centre involving 144 sites and 4 countries. All were conducted in the community setting except for one conducted in long-term care.[27] Follow-up periods ranged from 6 to 12 months.

Overall, there were 1305 participants across all trials. Most were female (>70%) and had a falls history (78.9%). Several key confounders were not reported in the studies including: (1) baseline number and types of FRIDs, (2) baseline number of medications, and (3) baseline number and types of co-morbidities. All these factors are thought to potentially modify falls risk.[29,30]

All interventions included a preceding assessment for FRID deprescribing appropriateness. This was conducted by physicians in 2 trials and pharmacists in 3 trials. Three trials tried to withdraw any FRID, while others focused on sedative-hypnotics, antipsychotics, or antidepressants. Successful discontinuation and adherence to deprescribing protocols were low in all studies. Rates of complete discontinuation of at least one FRID ranged from 10 to 40%.

In terms of our study outcomes, 4 trials measured the rate of falls and 4 measured falls incidence. One trial reported fall-related injuries.[24] Fall-related fractures, fall-related hospitalization or deprescribing-related adverse effects were not measured by any of the trials.

Summary of Findings

Rate and Incidence of Falls

Four studies reported the effect of deprescribing FRIDs on the rate of falls. Deprescribing FRIDs did not reduce the rate of falling (RaR 0.98, 95% CI 0.63 to 1.51; Figure 2 – Analysis 1.1).

Considerable statistical heterogeneity was present (χ^2=17.47, p=0.0006, I^2=83%) and subsequently explored in subgroup analysis.

Four studies reported the effect of deprescribing FRIDs on the risk of falls as measured by falls incidence. Deprescribing FRIDs did not reduce the incidence of falls (RR 1.04, 95% CI 0.86 to 1.26, I^2 = 19%, χ^2=3.70, p = 0.30; Figure 2 – Analysis 2.1). In absolute terms, there was a non-significant risk difference increase of 0.01 (95% CI -0.06 to 0.09, I^2 = 22%, p=0.76; Figure 2 – Analysis 2.2)

Rate of Injurious Falls

One trial reported the effect of deprescribing FRIDs on fall-related injuries.[24] Deprescribing FRIDs did not reduce the rate of fall-related injuries (RaR 0.89, 95% CI 0.57 to 1.39; Figure 2 – Analysis 3.1). This trial did not report data that would allow for any of our pre-planned subgroup analyses.

Risk of Bias Assessment

Figure 3 summarizes our RoB assessments. All studies were deemed at high risk of bias in at least one domain. The overall mean weighted kappa across all assessments was 0.67 (moderate agreement). For individual RoB assessments, kappa ranged from 0 to 0.85. Inter-rater agreement is actually higher than indicated by the calculated scores due to the "kappa co-efficient paradox".[31,32] Low kappas (e.g. κ=0) occurred despite high levels of observed agreement (e.g. $\geq$ 80% agreement) for two RoB assessments. True agreement is falsely attributed to chance agreement by the kappa calculation when there is substantial imbalance in marginal ratings.

For falls rate and incidence, all studies except one[25] were judged at high risk of bias for lack of blinding of participants, personnel and outcome assessors. It is unclear whether blinding could have impacted behaviour or perceptions (e.g. activity risk-level, nocebo effect). Risk of ascertainment bias was high in one study[27] (i.e. no standardized falls definition was used), but all other studies used methods accepted to be low risk of bias (i.e. falls recorded daily on postcards or calendars). Risk of attrition bias was deemed high in three studies based on high or unbalanced lost to follow-up rates.[24,25,28]

Publication Bias

Since less than 10 eligible studies were found, a funnel plot was not constructed due to an inability to make meaningful conclusions about publication bias.

Subgroup Analyses and Exploration of Heterogeneity

Our pre-specified subgroup analyses did not adequately explain the statistical heterogeneity observed results for the rate and incidence of falls (Supplementary Figure S2). Deprescribing FRIDs appeared more effective when a preceding medication review was conducted by physicians compared to pharmacists (p=0.0004, I^2=91.9%, Analysis 1.5), while psychotropic withdrawal appeared more effective than strategies withdrawing any FRID (p=0.08, I^2=67.8%, Analysis 2.3). However, in both analyses, only 6 of 11 subgroup credibility criteria were met and each subgroup was limited to one trial with less than 100 participants (Supplementary Table S2). We, therefore, judged the credibility that these subgroup effects are real as poor and uncertain.

The available data did not permit subgroup analyses by place of residence or falls ascertainment method. The other subgroup analyses showed no evidence of difference beyond that due to chance.

Sensitivity Analyses

Our sensitivity analyses are shown in Supplementary Figure S3. The incorporation of trials with high risk of performance bias appeared to mask the potential benefit of deprescribing FRIDs on reducing the incidence and rate of falls, while the trials with high risk of attrition bias appeared to mask a potential increase in falls rate with deprescribing FRIDs. These results should be interpreted cautiously and definitive conclusions cannot be made. Data from trials with low risk of performance bias were limited to one trial with less than 100 participants, and data from trials with low risk of attrition bias were limited to two trials with less than 450 participants overall.

A post-hoc sensitivity analysis examining the impact of using a fixed vs. random effects model did not change conclusions regarding the effect of deprescribing FRIDs on the rate or incidence of falls.

Quality of Evidence

The GRADE evidence profile is shown in Table 2.

Table 2: GRADE Quality of Evidence Assessment

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**FRID deprescribing strategy**	**usual care**	**Relative (95% CI)**	**Absolute (95% CI)**		
Falls Rate												
4	randomised trials	serious [a]	serious [b]	not serious	serious [c]	none	353	340	**Rate ratio 0.98** (0.63 to 1.51)	-	⨁◯◯◯ VERY LOW	IMPORTANT
Falls Incidence												
4	randomised trials	serious [a]	serious [d]	not serious	serious [c]	none	190/499 (38.1%)	170/472 (36.0%)	**RR 1.04** (0.86 to 1.26)	**14 more per 1,000** (from 50 fewer to 94 more)	⨁◯◯◯ VERY LOW	IMPORTANT
								33.7%		**13 more per 1,000** (from 47 fewer to 88 more)		
Fall-Related Injuries												
1	randomised trials	serious [a]	not serious	not serious	serious [c]	none	93	93	**Rate ratio 0.89** (0.57 to 1.39)	-	⨁⨁◯◯ LOW	CRITICAL

We judged the quality of evidence to be low or very low for all outcomes (falls rates, falls incidence and fall-related injuries) after rating down for risk of bias, inconsistency and imprecision.

We believe the optimal information size (OIS) to make definitive conclusions on the effect of deprescribing FRIDs has not yet been met as the body of evidence is based on fewer than 2000 participants and less than 400 events.[33,34] This is based on the OIS calculation figure recommended by the GRADE guidelines using a well-established control falls event rate of 30% described in the literature and conservative relative risk reduction (RRR) of 20% (assuming $\alpha = 0.05$ and $\beta = 0.2$).[34,35]

DISCUSSION

This systematic review sought to determine whether deprescribing FRIDs decreased the risk of falls in older adults and found that there is a lack of robust high-quality evidence to support or refute the deprescribing of FRIDs alone as an effective fall prevention strategy. Incorporating data from 5 RCTs involving 1305 participants aged ≥65 years, our meta-analyses indicate that a FRID deprescribing strategy did not significantly change the rate of falls (RaR 0.98, 95% CI 0.63 to 1.51) nor the risk of falling (RD 0.01, 95% CI -0.06 to 0.09) over a 6 to 12-month follow-up period. Although this intervention focuses on those medications thought to be associated with falls, the uncertainty of its effect on falls and conclusions of current lack of evidence of effectiveness are similar to previous systematic reviews evaluating the effectiveness of medication reviews that had a broader focus on reducing polypharmacy and potentially inappropriate prescribing (i.e. not focused solely on FRIDs).[9,36]

There is also a significant absence of evidence for clinically- and patient-important outcomes such as fall-related injuries, fractures and hospitalizations. The only trial to date that

evaluated the rate of fall-related injuries did not demonstrate a statistically significant effect (RaR 0.89, 95% CI 0.57-1.39).[24] Our search found no trials measuring the impact on fall-related fractures, fall-related hospitalizations or adverse effects related to a FRID deprescribing strategy. Although this may be rooted in the difficulty of conducting RCTs powered for such outcomes, their measurement and reporting are still important to inform systematic review meta-analyses that could lead to more precise estimates.

Based on low-quality evidence, it is unclear whether deprescribing FRIDs as a single intervention leads to any appreciable clinically important benefit or harm. Our current best effect estimates for falls rate and incidence are centred around no appreciable difference (i.e. RaR ≈ 1, RR ≈ 1, RD ≈ 0). Although seemingly logical to assume, reducing isolated risk factors may not necessarily lead to a reduction in falls and fall-related complications. The absence of change in the incidence of hip fractures after statewide regulatory action on benzodiazepine prescribing in the United States that reduced benzodiazepine use by 60.3% is a real-world example of this phenomenon and the complexity of exposure-outcome relationships.[37]

Our findings likely reflect the multi-factorial nature of falls and the varying risk of different FRIDs. It is unclear as to what degree a particular risk factor or combination of risk factors (e.g. specific FRIDs) must be reduced to produce an appreciable change in falls. Medications may only have conditional or contributory causality to falls. It may be that medication-related interventions work best in combination with other interventions or only in specific contexts.

Only one trial[25] included in our review demonstrated a statistically significant benefit with deprescribing FRIDs. This was also the only trial to use study capsules to operationalize blinded deprescribing of FRIDs in participants, research personnel and outcome assessors. Its results might be more reflective of the true potential physiological effect of deprescribing FRIDs

because it minimized the risk of performance bias. However, the magnitude of benefit achievable in the non-research setting at this time may be closer to those seen in the unblinded trials due to the strong psychological and behavioural factors (e.g. nocebo effect) that may hinder successful deprescribing. Further advances in implementation science and behavioural change strategies are likely needed to facilitate medication optimization.

These results raise several questions about the presumed effectiveness of deprescribing FRIDs as an isolated falls prevention strategy. Given the amount of resources being invested into falls prevention initiatives around the world, clinicians and organizations should examine: (1) what is the strength of evidence supporting their current activities, (2) whether these activities are cost-effective, and (3) whether resources are being appropriately prioritized to those interventions shown to provide the most value. This should also be applied to what is being required of healthcare organizations in national accreditation standards (e.g. Joint Commission, Accreditation Canada) to help direct and encourage optimal use of limited healthcare resources.

Clinicians and policy-makers need to consider the current lack of strong evidence for deprescribing FRIDs as an isolated intervention for the specific purpose of reducing falls, particularly in patients who may be very reluctant or who have strong indications for specific FRIDs. FRID reduction is one out of many possible interventions that need to be considered. As with prescribing medications, deprescribing is a skill and comes with the potential for harm as well as benefit.[38] Thoughtful consideration of the goals, appropriateness and safety of deprescribing is important.[39] Our results highlight the need for a comprehensive and individualized approach to falls. Multi-component interventions are ideal, but interventions may need to be prioritized depending on time, resources and context.

Despite insufficient evidence to support or refute the deprescribing of FRIDs for falls prevention, our results do not mean that clinicians should avoid deprescribing FRIDs. There may be many other reasons to deprescribe these medications. These include avoidance of adverse drug events, improvements in cognition, increased medication adherence and drug costs savings. It is also unclear whether medication review and management with a broader focus on reducing polypharmacy and potentially inappropriate prescribing in older adults may be beneficial in preventing falls. Some RCTs with such interventions have shown a reduction of falls risk, while others have not demonstrated a significant difference.[40–46]

Our review highlights the need for future FRID deprescribing trials that evaluate patient-important outcomes (e.g. injuries, fractures and hospitalizations). Greater attention to optimal design and reporting is needed to minimize risk of bias and enhance our interpretation of the results. Examples include improved reporting of confounding baseline characteristics and intervention fidelity (e.g. number and types of FRIDs, degree and duration of dose reduction). Deprescribing is challenging and extra measures are likely needed to improve successful intervention adherence and follow-up.

STRENGTHS AND LIMITATIONS

Our review has limitations. There was variation in the operationalization of FRID deprescribing and degree of success achieved (e.g. dose reduction only, completion discontinuation, non-adherence). This presumably makes the detection of any potential benefit less likely and our conclusions more conservative. However, the effect estimates are likely more indicative of what might be expected outside of the research setting. These phenomena likely represent the real-life challenges of deprescribing (especially with certain types of FRIDs such as

psychotropics or opioids). Moreover, our ability to assess for confounders modifying falls risk was limited due to inconsistent reporting of relevant baseline characteristics and lack of patient-level data. Lastly, our ability to make definitive conclusions is limited because the total sample size across studies for each outcome did not yet meet our calculated estimate for the required optimal information size.

Our review has several strengths. First, our search was comprehensive and we included a rigorous grey literature search for unpublished studies. Second, we employed optimal analytical and interpretational approaches including duplicate assessment, subgroup credibility criteria and optimal information size considerations. Third, unlike previous medication-focused reviews, we applied the GRADE approach to assess the quality of evidence and our degree of confidence in the results.

CONCLUSIONS

Our systematic review found that deprescribing FRIDs as an isolated strategy results in little to no difference in the rate and risk of falls or falls-related injuries, but the evidence is still sparse and very low quality. Additional well-designed studies are needed to reach the optimal information size to reduce uncertainty about this intervention and establish its relative importance in the range of possible interventions that can be employed by clinicians and health systems to reduce falls.

Acknowledgements:

The authors would like to thank Lois Cottrell, medical librarian at St. Joseph's Healthcare Hamilton, Charlton Campus, Hamilton, Ontario, Canada and Andrea McLellan, Head of

Collection and Technical Services, School of Medicine liaison, at McMaster University, Hamilton, Ontario, Canada, for their assistance with the development of the search strategy.

Author Contributions:

JL conceptualized the study. JL and AH designed and developed the protocol. RP and EW assisted with citation review. RP and AN assisted with data extraction, risk of bias assessment and certainty of evidence grading. All authors contributed to the analysis and interpretation of results. JL drafted the initial manuscript and all authors contributed to its revision and final approval.

Funding:

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing Interests:

The authors have no potential conflicts of interest to declare.

Patient Consent for Publication:

None required.

Data Sharing Statement:

No unpublished data are available.

REFERENCES:

1 Hill KD, Wee R. Psychotropic drug-induced falls in older people: a review of interventions aimed at reducing the problem. *Drugs Aging* 2012;**29**:15–30. doi:10.2165/11598420-000000000-00000

2 Florence CS, Bergen G, Atherly A, *et al.* Medical Costs of Fatal and Nonfatal Falls in Older Adults. *J Am Geriatr Soc* 2018;**66**:693–8. doi:10.1111/jgs.15304

3 National Institute for Health and Care Excellence. Falls in older people: assessing risk and prevention. 2013.

4 Public Health Agency of Canada. Seniors' Falls in Canada. 2014.

5 Summary of the Updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons. *J Am Geriatr Soc* 2011;**59**:148–57. doi:10.1111/j.1532-5415.2010.03234.x

6 Guirguis-Blake JM, Michael YL, Perdue LA, *et al.* Interventions to Prevent Falls in Older Adults. *JAMA* 2018;**319**:1705. doi:10.1001/jama.2017.21962

7 Campbell AJ, Robertson MC. Fall Prevention: Single or Multiple Interventions? Single Interventions for Fall Prevention. *J Am Geriatr Soc* 2013;**61**:281–4. doi:10.1111/jgs.12095_2

8 Tricco AC, Thomas SM, Veroniki AA, *et al.* Comparisons of Interventions for Preventing Falls in Older Adults. *JAMA* 2017;**318**:1687. doi:10.1001/jama.2017.15006

9 Gillespie LD, Robertson MC, Gillespie WJ, *et al.* Interventions for preventing falls in older people living in the community. *Cochrane database Syst Rev* 2012;**9**:CD007146. doi:10.1002/14651858.CD007146.pub3

10 Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic

review and meta-analysis: I. Psychotropic drugs. *J Am Geriatr Soc* 1999;**47**:30–9.

11 Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: II. Cardiac and analgesic drugs. *J Am Geriatr Soc* 1999;**47**:40–50.

12 Woolcott JC, Richardson KJ, Wiens MO, *et al.* Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Arch Intern Med* 2009;**169**:1952–60. doi:10.1001/archinternmed.2009.357

13 de Vries M, Seppala LJ, Daams JG, *et al.* Fall-Risk-Increasing Drugs: A Systematic Review and Meta-Analysis: I. Cardiovascular Drugs. *J Am Med Dir Assoc* 2018;**19**:371.e1-371.e9. doi:10.1016/j.jamda.2017.12.013

14 Seppala LJ, Wermelink AMAT, de Vries M, *et al.* Fall-Risk-Increasing Drugs: A Systematic Review and Meta-Analysis: II. Psychotropics. *J Am Med Dir Assoc* 2018;**19**:371.e11-371.e17. doi:10.1016/j.jamda.2017.12.098

15 Seppala LJ, van de Glind EMM, Daams JG, *et al.* Fall-Risk-Increasing Drugs: A Systematic Review and Meta-analysis: III. Others. *J Am Med Dir Assoc* 2018;**19**:372.e1-372.e8. doi:10.1016/j.jamda.2017.12.099

16 The Cochrane Collaboration. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]*. 2011.

17 Moher D, Liberati A, Tetzlaff J, *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;**151**:264–9, W64.

18 Lee JY, Holbrook A. The efficacy of fall-risk-increasing drug (FRID) withdrawal for the prevention of falls and fall-related complications: protocol for a systematic review and meta-analysis. *Syst Rev* 2017;**6**:33.

19 Higgins JPT, Altman DG, Gøtzsche PC, *et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;**343**:d5928.

20 Akl EA, Sun X, Busse JW, *et al.* Specific instructions for estimating unclearly reported blinding status in randomized trials were reliable and valid. *J Clin Epidemiol* 2012;**65**:262–7. doi:10.1016/j.jclinepi.2011.04.015

21 Sun X, Briel M, Walter SD, *et al.* Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. *BMJ* 2010;**340**:c117.

22 Guyatt G, Oxman AD, Akl EA, *et al.* GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;**64**:383–94.

23 Streim JE, Filippo S, Have T, *et al.* Antidepressant discontinuation associated with cognitive decline in older adult residents of long-term care facilities. *Am J Geriatr psychiatry* 2012;**20**:S147–8. doi:10.1097/01.JGP.0000413064.91948.aa

24 Blalock SJ, Casteel C, Roth MT, *et al.* Impact of enhanced pharmacologic care on the prevention of falls: a randomized controlled trial. *Am J Geriatr Pharmacother* 2010;**8**:428–40. doi:10.1016/j.amjopharm.2010.09.002

25 Campbell AJ, Robertson MC, Gardner MM, *et al.* Psychotropic medication withdrawal and a home-based exercise program to prevent falls: a randomized, controlled trial. *J Am Geriatr Soc* 1999;**47**:850–3.

26 Mott DA, Martin B, Breslow R, *et al.* Impact of a medication therapy management intervention targeting medications associated with falling: Results of a pilot study. *J Am Pharm Assoc (2003)* 2016;**56**:22–8.

27 Patterson SM, Hughes CM, Crealey G, *et al.* An evaluation of an adapted U.S. model of pharmaceutical care to improve psychoactive prescribing for nursing home residents in

northern ireland (fleetwood northern ireland study). *J Am Geriatr Soc* 2010;**58**:44–53. doi:10.1111/j.1532-5415.2009.02617.x

28 Boyé NDA, van der Velde N, de Vries OJ, *et al.* Effectiveness of medication withdrawal in older fallers: results from the Improving Medication Prescribing to reduce Risk Of FALLs (IMPROveFALL) trial. *Age Ageing* 2017;**46**:142–6. doi:10.1093/ageing/afw161

29 Tinetti M, Kumar C. The Patient Who Falls. *JAMA J Am Med Assoc* 2010;**303**:273–4. doi:10.1001/jama.2009.2024

30 Chen Y, Zhu L-L, Zhou Q. Effects of drug pharmacokinetic/pharmacodynamic properties, characteristics of medication use, and relevant pharmacological interventions on fall risk in elderly patients. *Ther Clin Risk Manag* 2014;**10**:437–48. doi:10.2147/TCRM.S63756

31 Feinstein AR, Cicchetti D V. High agreement but low kappa: I. The problems of two paradoxes. *J Clin Epidemiol* 1990;**43**:543–9.

32 Tang W, Hu J, Zhang H, *et al.* Kappa coefficient: a popular measure of rater agreement. *Shanghai Arch psychiatry* 2015;**27**:62–7. doi:10.11919/j.issn.1002-0829.215010

33 Ioannidis J, Lau J. Evolution of treatment effects over time: empirical insight from recursive cumulative metaanalyses. *Proc Natl Acad Sci U S A* 2001;**98**:831–6. doi:10.1073/pnas.021529998

34 Guyatt GH, Oxman AD, Kunz R, *et al.* GRADE guidelines 6. Rating the quality of evidence--imprecision. *J Clin Epidemiol* 2011;**64**:1283–93. doi:10.1016/j.jclinepi.2011.01.012

35 O'Loughlin JL, Robitaille Y, Boivin JF, *et al.* Incidence of and risk factors for falls and injurious falls among the community-dwelling elderly. *Am J Epidemiol* 1993;**137**:342–54.

36 Guirguis-Blake JM, Michael YL, Perdue LA, *et al. Interventions to Prevent Falls in*

Community-Dwelling Older Adults: A Systematic Review for the U.S. Preventive Services Task Force. Agency for Healthcare Research and Quality (US) 2018.

37 Wagner AK, Ross-Degnan D, Gurwitz JH, *et al.* Effect of New York State regulatory action on benzodiazepine prescribing and hip fracture rates. *Ann Intern Med* 2007;**146**:96–103.

38 Reeve E, Moriarty F, Nahas R, *et al.* A narrative review of the safety concerns of deprescribing in older adults and strategies to mitigate potential harms. *Expert Opin Drug Saf* 2018;**17**:39–49. doi:10.1080/14740338.2018.1397625

39 Lee JY, Farrell B, Holbrook AM. De-prescribing benzodiazepine receptor agonists taken for insomnia: a review and key messages from practice guidelines. *Polish Arch Intern Med* 2018;**129**:839–45. doi:10.20452/pamw.4391

40 Pit SW, Byles JE, Henry DA, *et al.* A Quality Use of Medicines program for general practitioners and older people: a cluster randomised controlled trial. *Med J Aust* 2007;**187**:23–30.

41 Weber V, White A, McIlvried R. An electronic medical record (EMR)-based intervention to reduce polypharmacy and falls in an ambulatory rural elderly population. *J Gen Intern Med* 2008;**23**:399–404.

42 Zermansky AG, Alldred DP, Petty DR, *et al.* Clinical medication review by a pharmacist of elderly people living in care homes--randomised controlled trial. *Age Ageing* 2006;**35**:586–91. doi:10.1093/ageing/afl075

43 Frankenthal D, Lerman Y, Kalendaryev E, *et al.* Intervention with the screening tool of older persons potentially inappropriate prescriptions/screening tool to alert doctors to right treatment criteria in elderly residents of a chronic geriatric facility: a randomized clinical

trial. *J Am Geriatr Soc* 2014;**62**:1658–65. doi:10.1111/jgs.12993

44 Michalek C, Wehling M, Schlitzer J, *et al.* Effects of 'Fit fOR The Aged' (FORTA) on pharmacotherapy and clinical endpoints--a pilot randomized controlled study. *Eur J Clin Pharmacol* 2014;**70**:1261–7.

45 Meredith S, Feldman P, Frey D, *et al.* Improving medication use in newly admitted home healthcare patients: A randomized controlled trial. *J Am Geriatr Soc* 2002;**50**:1484–91. doi:10.1046/j.1532-5415.2002.50402.x

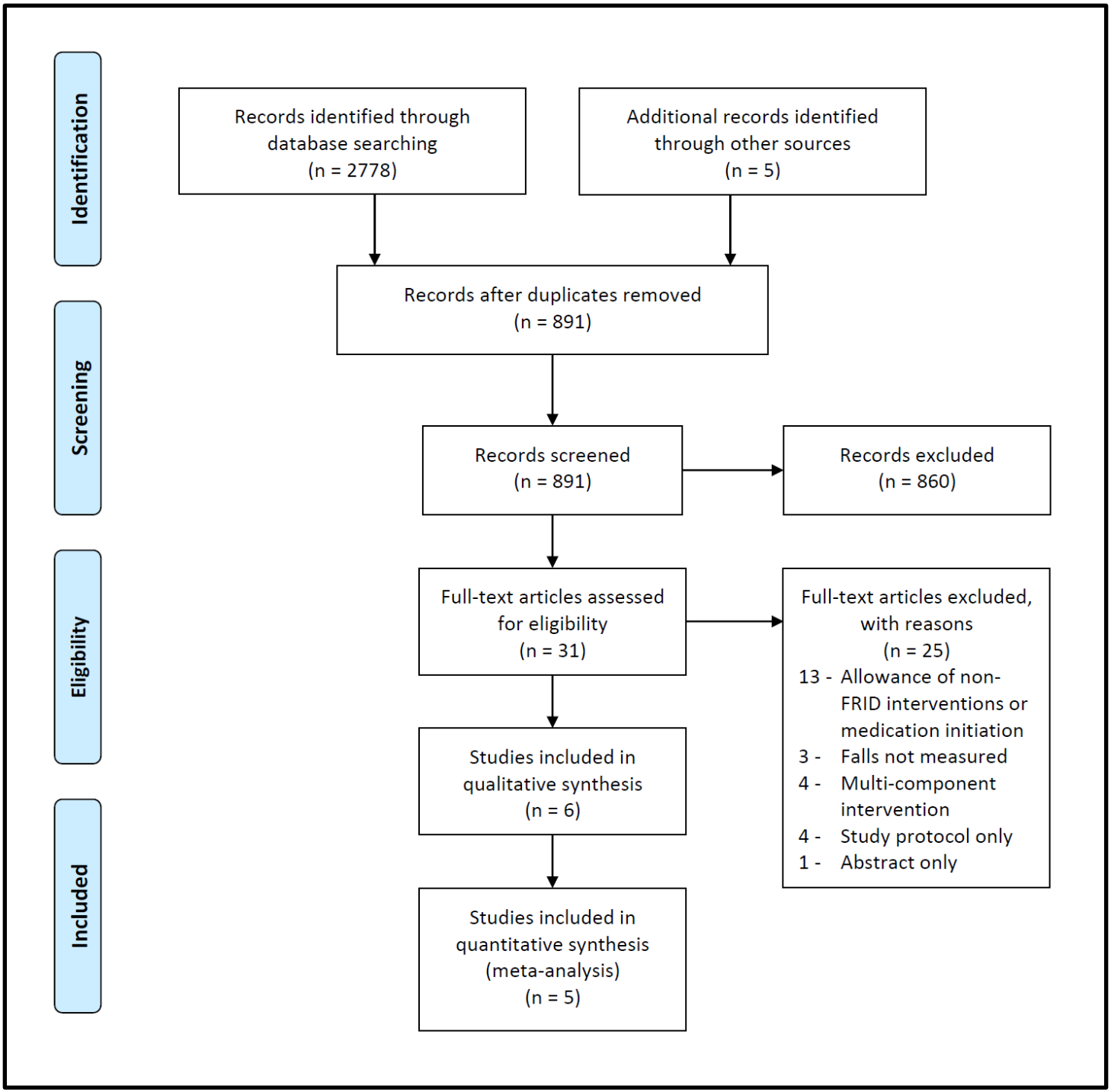
46 Sjoberg C, Wallerstedt SM. Effects of medication reviews performed by a physician on treatment with fracture-preventing and fall-risk-increasing drugs in older adults with hip fracture-a randomized controlled study. *J Am Geriatr Soc* 2013;**61**:1464–72.

FIGURES

Figure 1: PRISMA Flow Diagram of Study Selection Process

Figure 2: Forest Plots of FRID Withdrawal versus Usual Care

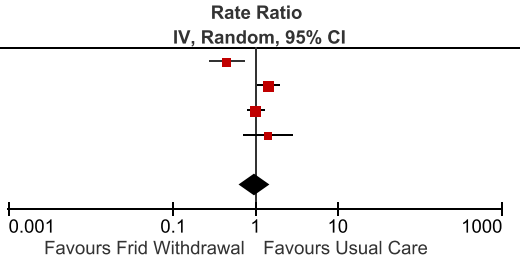
Figure 3: Risk of Bias Assessments


Identification
Screening
Eligibility
Included
Records identified through database searching (n = 2778)
Additional records identified through other sources (n = 5)
Records after duplicates removed (n = 891)
Records screened (n = 891)
Records excluded (n = 860)
Full-text articles assessed for eligibility (n = 31)
Full-text articles excluded, with reasons (n = 25)
13 - Allowance of non-FRID interventions or medication initiation
3 - Falls not measured
4 - Multi-component intervention
4 - Study protocol only
1 - Abstract only
Studies included in qualitative synthesis (n = 6)
Studies included in quantitative synthesis (meta-analysis) (n = 5)

1.1 Falls Rate

Study or Subgroup	log[Rate Ratio]	SE	FRID Withdrawal Total	Usual Care Total	Weight	Rate Ratio IV, Random, 95% CI	Year
Campbell 1999	-0.8023	0.2434	48	45	23.4%	0.45 [0.28, 0.72]	1999
Patterson 2010	0.3549	0.1465	173	161	28.4%	1.43 [1.07, 1.90]	2010
Blalock 2010	0.003	0.1117	93	93	29.9%	1.00 [0.81, 1.25]	2010
Mott 2016	0.3379	0.3416	39	41	18.4%	1.40 [0.72, 2.74]	2016
Total (95% CI)			**353**	**340**	**100.0%**	**0.98 [0.63, 1.51]**	

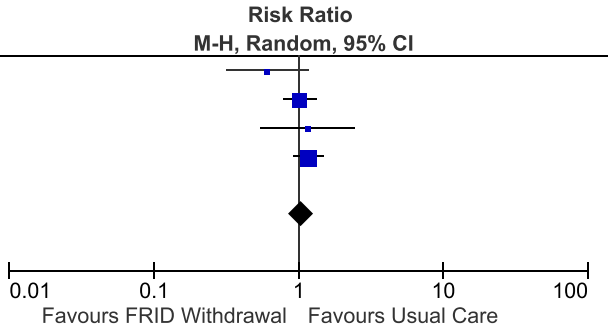
Heterogeneity: Tau² = 0.15; Chi² = 17.47, df = 3 (P = 0.0006); I² = 83%
Test for overall effect: Z = 0.11 (P = 0.92)



2.1 Falls Incidence – Risk Ratio

Study or Subgroup	FRID Withdrawal Events	FRID Withdrawal Total	Usual Care Events	Usual Care Total	Weight	Risk Ratio M-H, Random, 95% CI
Campbell 1999	11	48	17	45	8.4%	0.61 [0.32, 1.15]
Blalock 2010	53	93	52	93	39.3%	1.02 [0.79, 1.31]
Mott 2016	11	39	10	41	6.4%	1.16 [0.55, 2.41]
Boyé 2017	115	319	91	293	45.9%	1.16 [0.93, 1.45]
Total (95% CI)		**499**		**472**	**100.0%**	**1.04 [0.86, 1.26]**
Total events	190		170			

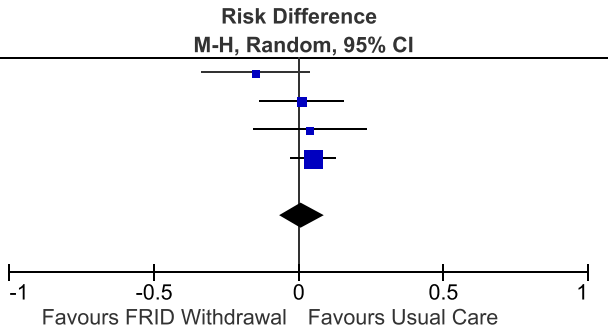
Heterogeneity: Tau² = 0.01; Chi² = 3.70, df = 3 (P = 0.30); I² = 19%
Test for overall effect: Z = 0.44 (P = 0.66)



2.2 Falls Incidence – Risk Difference

Study or Subgroup	FRID Withdrawal Events	FRID Withdrawal Total	Usual Care Events	Usual Care Total	Weight	Risk Difference M-H, Random, 95% CI
Campbell 1999	11	48	17	45	14.2%	-0.15 [-0.33, 0.04]
Blalock 2010	53	93	52	93	21.8%	0.01 [-0.13, 0.15]
Mott 2016	11	39	10	41	13.2%	0.04 [-0.15, 0.23]
Boyé 2017	115	319	91	293	50.9%	0.05 [-0.02, 0.12]
Total (95% CI)		**499**		**472**	**100.0%**	**0.01 [-0.06, 0.09]**
Total events	190		170			

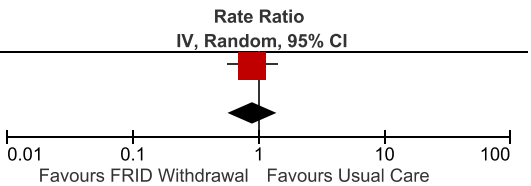
Heterogeneity: Tau² = 0.00; Chi² = 3.86, df = 3 (P = 0.28); I² = 22%
Test for overall effect: Z = 0.31 (P = 0.76)

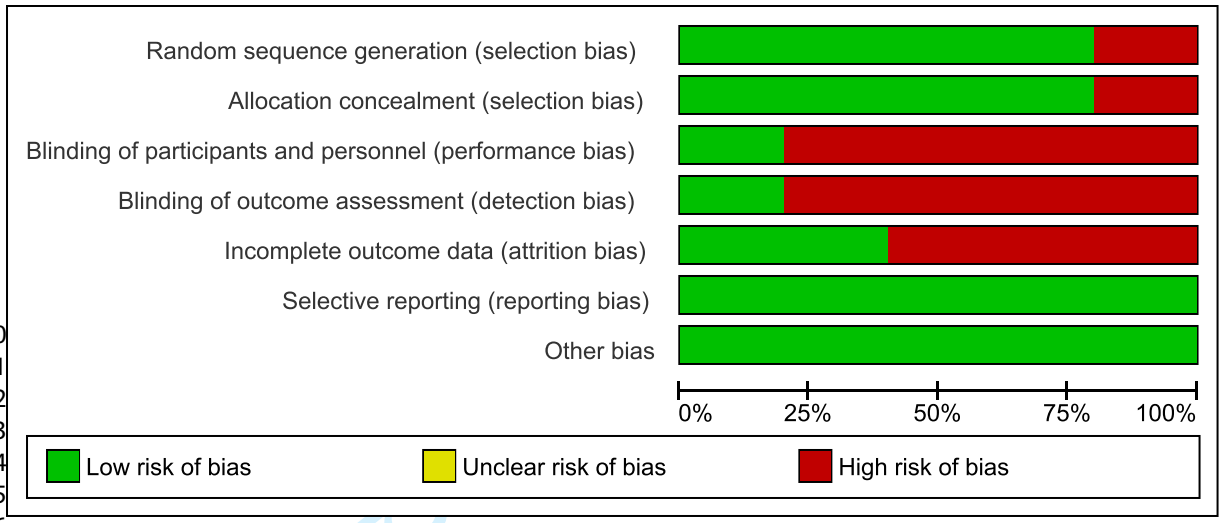


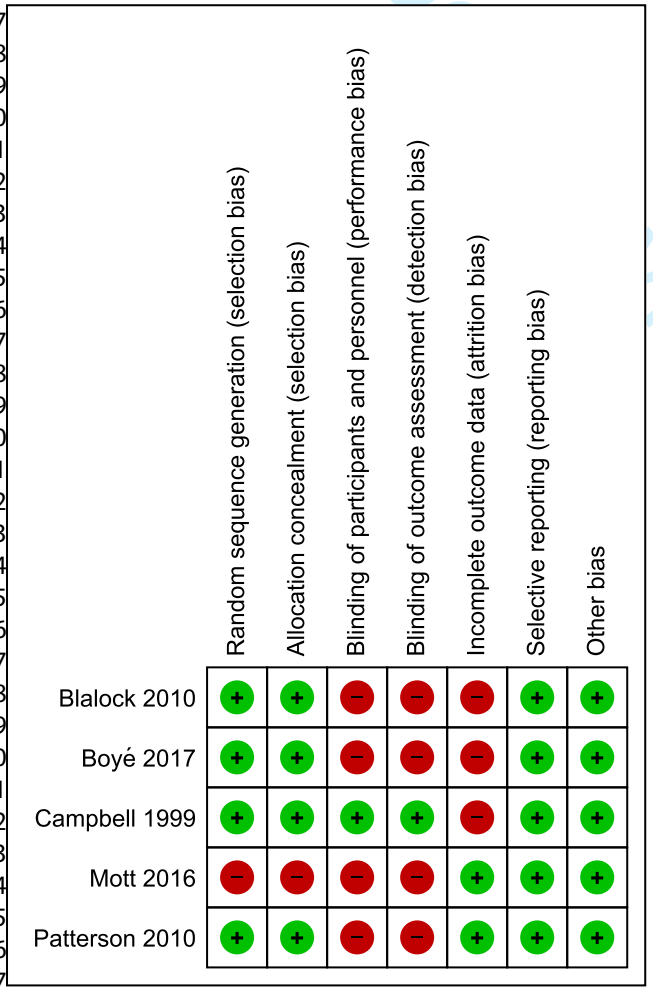
3.1 Fall-Related Injuries

Study or Subgroup	log[Rate Ratio]	SE	FRID Withdrawal Total	Usual Care Total	Weight	Rate Ratio IV, Random, 95% CI	Year
Blalock 2010	-0.1165	0.2273	93	93	100.0%	0.89 [0.57, 1.39]	2010
Total (95% CI)			**93**	**93**	**100.0%**	**0.89 [0.57, 1.39]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.51 (P = 0.61)







Supplementary Figure S1: OVID Medline Search Strategy

Database(s): OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

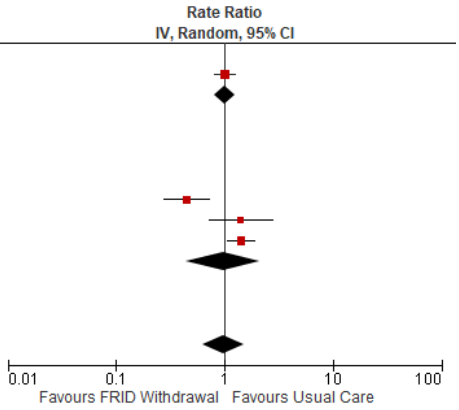
Search Strategy:

#	Searches
1	exp Accidental Falls/pc [Prevention & Control]
2	fall.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
3	falls.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
4	exp Deprescriptions/
5	((medicat* or drug*) adj3 (deprescrib* or withdraw* or cessat* or stop* or discontin*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
6	((antihypertensive* or diuretic* or beta-blocker* or sedative* or hypnotic* or neuroleptic* or antipsychotic* or antidepressant* or benzodiazepine* or narcotic* or opioid* or narcotic* or NSAID*) adj3 (deprescrib* or withdraw* or cessat* or stop* or discontin*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
7	fall-risk increasing drugs.mp.
8	FRID.mp.
9	((medicat* or drug*) adj3 (review* or improv* or program*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
10	exp "Drug-Related Side Effects and Adverse Reactions"/pc [Prevention & Control]
11	exp Medication Therapy Management/ or exp "Drug Utilization Review"/
12	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13	1 or 2 or 3
14	12 and 13
15	remove duplicates from 14
16	exp Clinical Trial/
17	(randomized or randomised).ab,ti.
18	placebo.ab,ti.
19	randomly.ab,ti.
20	groups.ab,ti.
21	randomized controlled trial.pt.
22	controlled clinical trial.pt.
23	16 or 17 or 18 or 19 or 20 or 21 or 22
24	15 and 23

Supplementary Figure S2: Subgroup Analyses

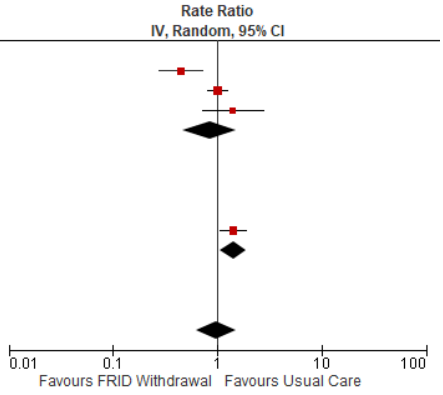
1.2 Falls Rate - Known vs. Unknown Faller

Study or Subgroup	log[Rate Ratio]	SE	FRID Withdrawal Total	Usual Care Total	Weight	Rate Ratio IV, Random, 95% CI
1.2.1 Known Faller						
Blalock 2010	0.003	0.1117	93	93	29.9%	1.00 [0.81, 1.25]
Subtotal (95% CI)			**93**	**93**	**29.9%**	**1.00 [0.81, 1.25]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.03 (P = 0.98)						
1.2.2 Unknown Faller						
Campbell 1999	-0.8023	0.2434	48	45	23.4%	0.45 [0.28, 0.72]
Mott 2016	0.3379	0.3416	39	41	18.4%	1.40 [0.72, 2.74]
Patterson 2010	0.3549	0.1465	173	161	28.4%	1.43 [1.07, 1.90]
Subtotal (95% CI)			**260**	**247**	**70.1%**	**0.96 [0.44, 2.10]**
Heterogeneity: Tau² = 0.41; Chi² = 17.23, df = 2 (P = 0.0002); I² = 88%						
Test for overall effect: Z = 0.10 (P = 0.92)						
Total (95% CI)			**353**	**340**	**100.0%**	**0.98 [0.63, 1.51]**
Heterogeneity: Tau² = 0.15; Chi² = 17.47, df = 3 (P = 0.0006); I² = 83%						
Test for overall effect: Z = 0.11 (P = 0.92)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.92), I² = 0%						



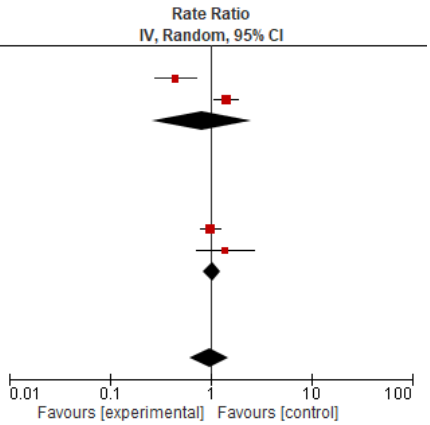
1.3 Falls Rate - Community vs. Institutionalized

Study or Subgroup	log[Rate Ratio]	SE	FRID Withdrawal Total	Usual Care Total	Weight	Rate Ratio IV, Random, 95% CI	Year
1.3.1 Community							
Campbell 1999	-0.8023	0.2434	48	45	23.4%	0.45 [0.28, 0.72]	1999
Blalock 2010	0.003	0.1117	93	93	29.9%	1.00 [0.81, 1.25]	2010
Mott 2016	0.3379	0.3416	39	41	18.4%	1.40 [0.72, 2.74]	2016
Subtotal (95% CI)			**180**	**179**	**71.6%**	**0.84 [0.47, 1.52]**	
Heterogeneity: Tau² = 0.21; Chi² = 10.82, df = 2 (P = 0.004); I² = 82%							
Test for overall effect: Z = 0.57 (P = 0.57)							
1.3.2 Institutionalized							
Patterson 2010	0.3549	0.1465	173	161	28.4%	1.43 [1.07, 1.90]	2010
Subtotal (95% CI)			**173**	**161**	**28.4%**	**1.43 [1.07, 1.90]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.42 (P = 0.02)							
Total (95% CI)			**353**	**340**	**100.0%**	**0.98 [0.63, 1.51]**	
Heterogeneity: Tau² = 0.15; Chi² = 17.47, df = 3 (P = 0.0006); I² = 83%							
Test for overall effect: Z = 0.11 (P = 0.92)							
Test for subgroup differences: Chi² = 2.49, df = 1 (P = 0.11), I² = 59.8%							



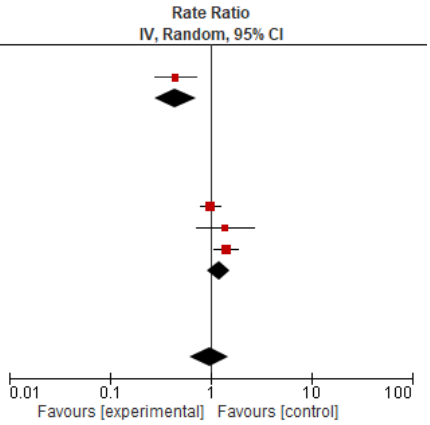
1.4 Falls Rate - Psychotropic Withdrawal vs. Any FRID Withdrawal

Study or Subgroup	log[Rate Ratio]	SE	FRID Withdrawal Total	Usual Care Total	Weight	Rate Ratio IV, Random, 95% CI
1.4.1 Psychotropic Withdrawal (Antipsychotic, Anxiolytic, Sedative, Hyponotic)						
Campbell 1999	-0.8023	0.2434	48	45	23.4%	0.45 [0.28, 0.72]
Patterson 2010	0.3549	0.1465	173	161	28.4%	1.43 [1.07, 1.90]
Subtotal (95% CI)			**221**	**206**	**51.7%**	**0.81 [0.26, 2.52]**
Heterogeneity: Tau² = 0.63; Chi² = 16.59, df = 1 (P < 0.0001); I² = 94%						
Test for overall effect: Z = 0.36 (P = 0.72)						
1.4.2 Any FRID						
Blalock 2010	0.003	0.1117	93	93	29.9%	1.00 [0.81, 1.25]
Mott 2016	0.3379	0.3416	39	41	18.4%	1.40 [0.72, 2.74]
Subtotal (95% CI)			**132**	**134**	**48.3%**	**1.04 [0.84, 1.28]**
Heterogeneity: Tau² = 0.00; Chi² = 0.87, df = 1 (P = 0.35); I² = 0%						
Test for overall effect: Z = 0.33 (P = 0.74)						
Total (95% CI)			**353**	**340**	**100.0%**	**0.98 [0.63, 1.51]**
Heterogeneity: Tau² = 0.15; Chi² = 17.47, df = 3 (P = 0.0006); I² = 83%						
Test for overall effect: Z = 0.11 (P = 0.92)						
Test for subgroup differences: Chi² = 0.17, df = 1 (P = 0.68), I² = 0%						



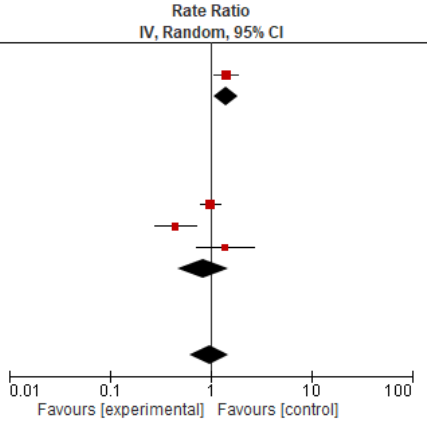
1.5 Falls Rate - Physician vs. Pharmacist Medication Review

Study or Subgroup	log[Rate Ratio]	SE	FRID Withdrawal Total	Usual Care Total	Weight	Rate Ratio IV, Random, 95% CI
1.5.1 Physician Medication Review						
Campbell 1999	-0.8023	0.2434	48	45	23.4%	0.45 [0.28, 0.72]
Subtotal (95% CI)			**48**	**45**	**23.4%**	**0.45 [0.28, 0.72]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.30 (P = 0.0010)						
1.5.2 Pharmacist Medication Review						
Blalock 2010	0.003	0.1117	93	93	29.9%	1.00 [0.81, 1.25]
Mott 2016	0.3379	0.3416	39	41	18.4%	1.40 [0.72, 2.74]
Patterson 2010	0.3549	0.1465	173	161	28.4%	1.43 [1.07, 1.90]
Subtotal (95% CI)			**305**	**295**	**76.6%**	**1.20 [0.92, 1.58]**
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 3.99$, df = 2 (P = 0.14); $I^2 = 50\%$						
Test for overall effect: Z = 1.33 (P = 0.18)						
Total (95% CI)			**353**	**340**	**100.0%**	**0.98 [0.63, 1.51]**
Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 17.47$, df = 3 (P = 0.0006); $I^2 = 83\%$						
Test for overall effect: Z = 0.11 (P = 0.92)						
Test for subgroup differences: $Chi^2 = 12.41$, df = 1 (P = 0.0004), $I^2 = 91.9\%$						

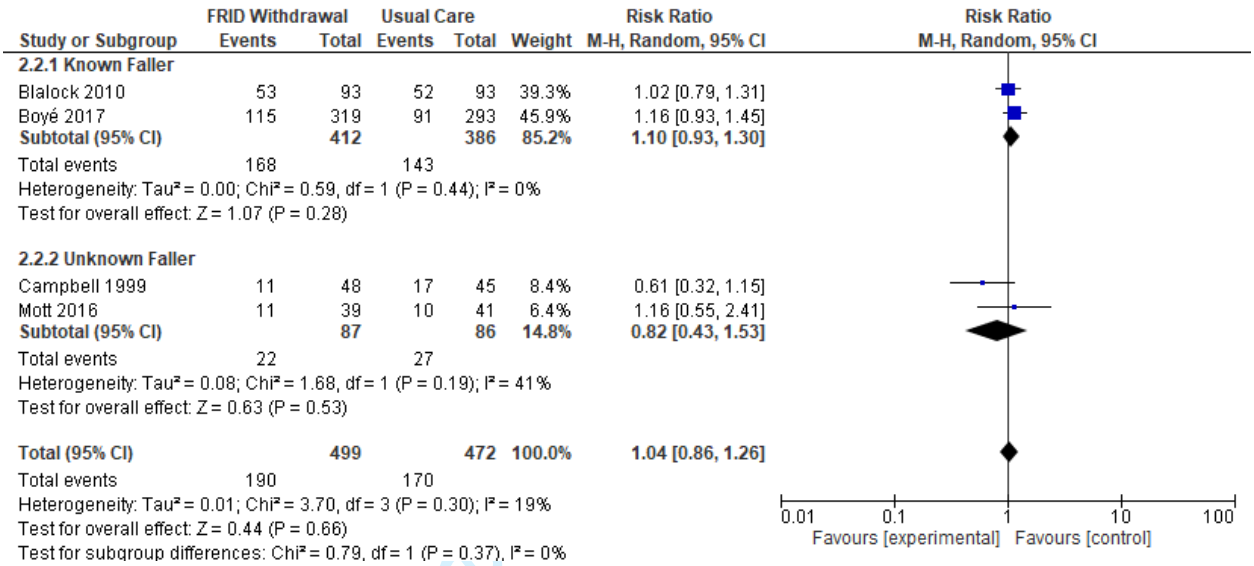


1.6 Falls Rate - Observed vs. Self-Reported Falls

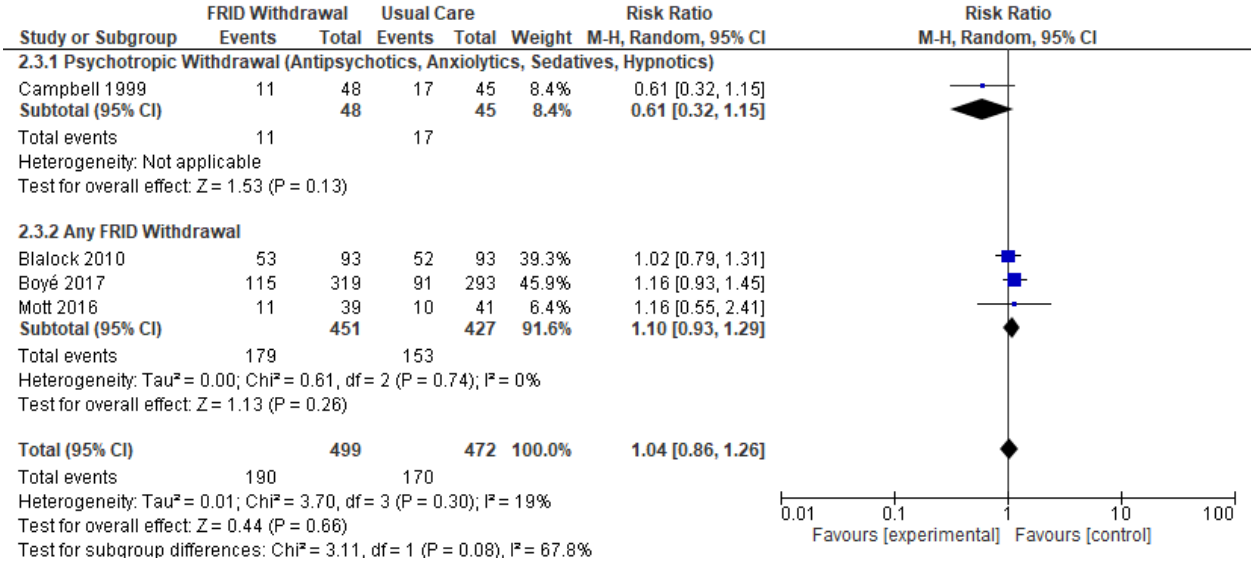
Study or Subgroup	log[Rate Ratio]	SE	FRID Withdrawal Total	Usual Care Total	Weight	Rate Ratio IV, Random, 95% CI
1.6.1 Observed Falls						
Patterson 2010	0.3549	0.1465	173	161	28.4%	1.43 [1.07, 1.90]
Subtotal (95% CI)			**173**	**161**	**28.4%**	**1.43 [1.07, 1.90]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.42 (P = 0.02)						
1.6.2 Self-Reported Falls						
Blalock 2010	0.003	0.1117	93	93	29.9%	1.00 [0.81, 1.25]
Campbell 1999	-0.8023	0.2434	48	45	23.4%	0.45 [0.28, 0.72]
Mott 2016	0.3379	0.3416	39	41	18.4%	1.40 [0.72, 2.74]
Subtotal (95% CI)			**180**	**179**	**71.6%**	**0.84 [0.47, 1.52]**
Heterogeneity: $Tau^2 = 0.21$; $Chi^2 = 10.82$, df = 2 (P = 0.004); $I^2 = 82\%$						
Test for overall effect: Z = 0.57 (P = 0.57)						
Total (95% CI)			**353**	**340**	**100.0%**	**0.98 [0.63, 1.51]**
Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 17.47$, df = 3 (P = 0.0006); $I^2 = 83\%$						
Test for overall effect: Z = 0.11 (P = 0.92)						
Test for subgroup differences: $Chi^2 = 2.49$, df = 1 (P = 0.11), $I^2 = 59.8\%$						



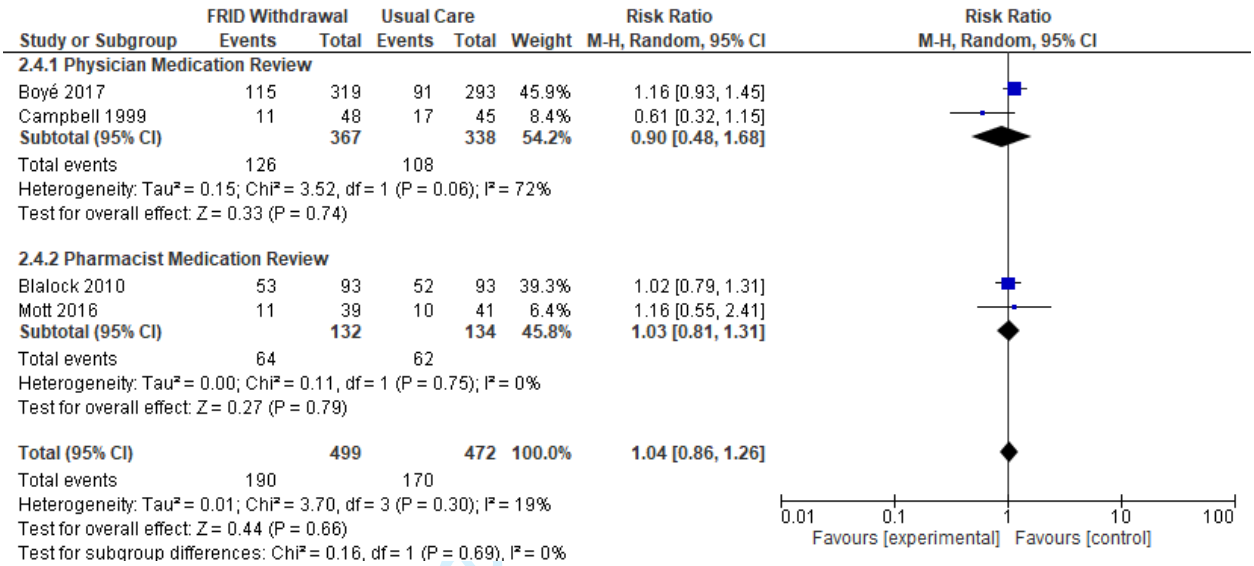
2.2 Falls Incidence - Known vs. Unknown Faller



2.3 Falls Incidence - Psychotropic Withdrawal vs. Any FRID Withdrawal



2.4 Falls Incidence - Physician vs. Pharmacist Medication Review



Supplementary Table S1: Subgroup Credibility Assessment – Clinician Medication Review

Physician vs. Pharmacist Medication Review Subgroup for Falls Rate

Design	**Criteria Met?**
Is the subgroup variable a characteristic measured at baseline or after randomization?	Yes – Variable determined at baseline
Is the effect suggested by comparisons within rather between studies?	No – Comparison between studies
Was the hypothesis specified a priori?	Yes
Was the direction of the subgroup effect specified a priori?	No
Was the subgroup effect one of a small number of hypothesized effects tested?	Yes – 1 of 5 analyses
Analysis	
Does the interaction test suggest a low likelihood that chance explains the apparent subgroup effect?	Yes – p =0.0004
Is the significant subgroup effect independent?	Yes
Context	
Is the size of the subgroup effect large?	Yes – RaR 0.45 vs. 1.20
Is the interaction consistent across studies?	No
Is the interaction consistent across closely related outcomes within the study?	No – Subgroup interaction was not seen for incidence of falls
Is there indirect evidence that supports the hypothesized interaction (biological rationale)?	No - No compelling external evidence supporting subgroup hypothesis

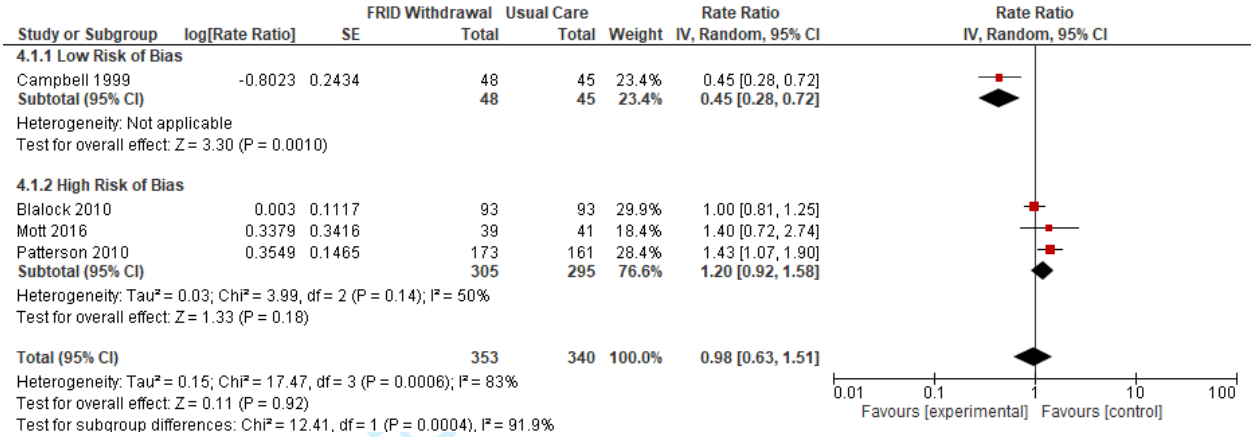
Supplementary Table S2: Subgroup Credibility Assessment – FRID Withdrawal Type

Antipsychotic vs. Any FRID Withdrawal for Falls Incidence

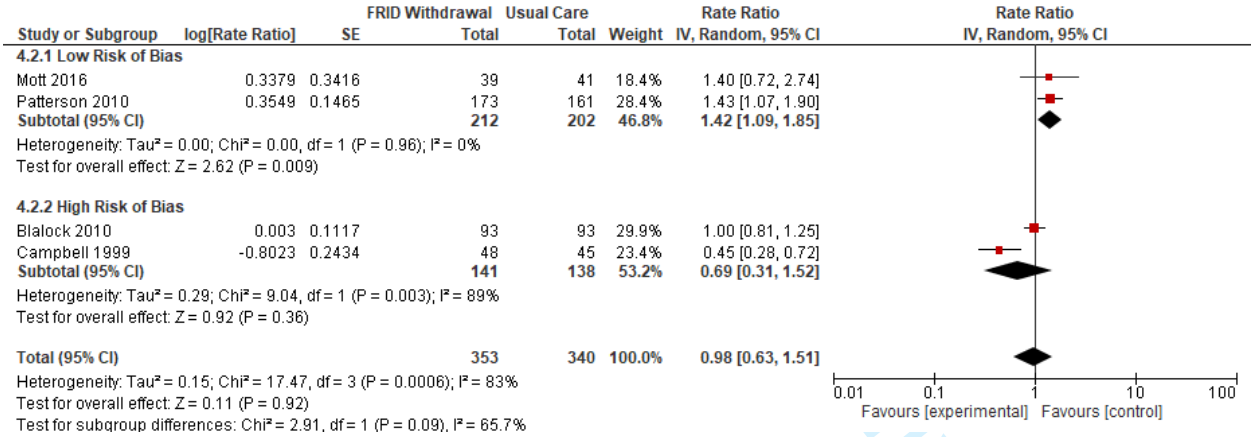
Design	**Criteria Met?**
Is the subgroup variable a characteristic measured at baseline or after randomization?	Yes – Variable determined at baseline
Is the effect suggested by comparisons within rather between studies?	No – Comparison between studies
Was the hypothesis specified a priori?	Yes
Was the direction of the subgroup effect specified a priori?	No
Was the subgroup effect one of a small number of hypothesized effects tested?	Yes – 1 of 3 analyses
Analysis	
Does the interaction test suggest a low likelihood that chance explains the apparent subgroup effect?	Yes – p=0.06
Is the significant subgroup effect independent?	No
Context	
Is the size of the subgroup effect large?	Yes – RR 0.61 vs. 1.14
Is the interaction consistent across studies?	No
Is the interaction consistent across closely related outcomes within the study?	No – Subgroup interaction was not seen for rate of falls
Is there indirect evidence that supports the hypothesized interaction (biological rationale)?	Yes – Antipsychotics associated with one of highest risks of falls. The withdrawal of any FRID may involve withdrawal of those with lower risks and limit potential benefit.

Supplementary Figure S3: Sensitivity Analyses

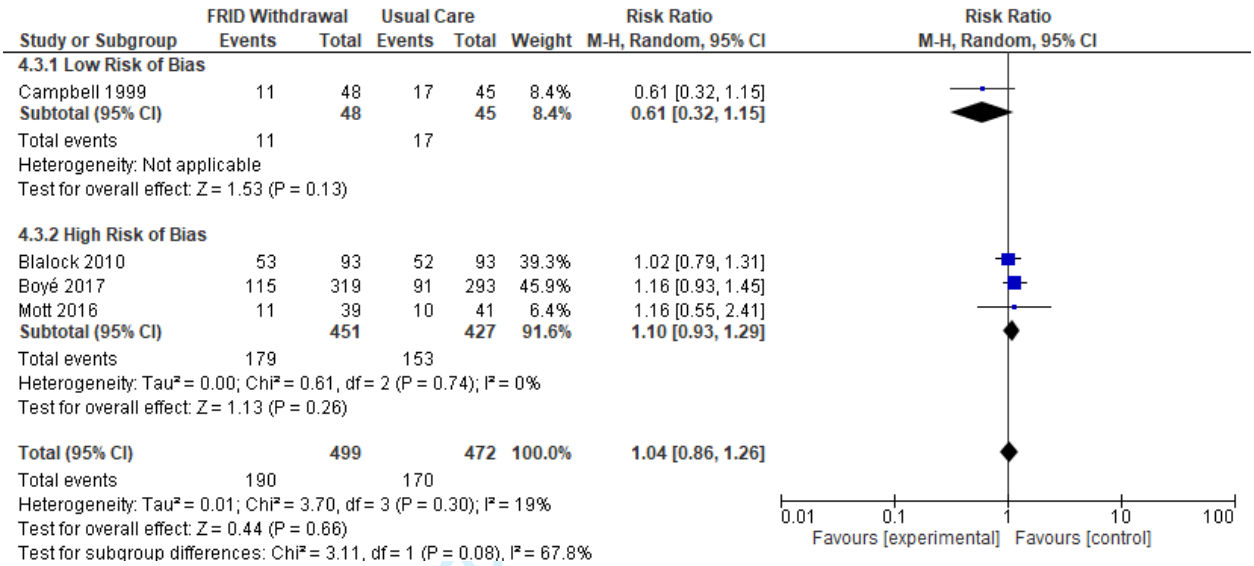
4.1 Falls Rate - Low vs. High Risk of Bias due to Blinding



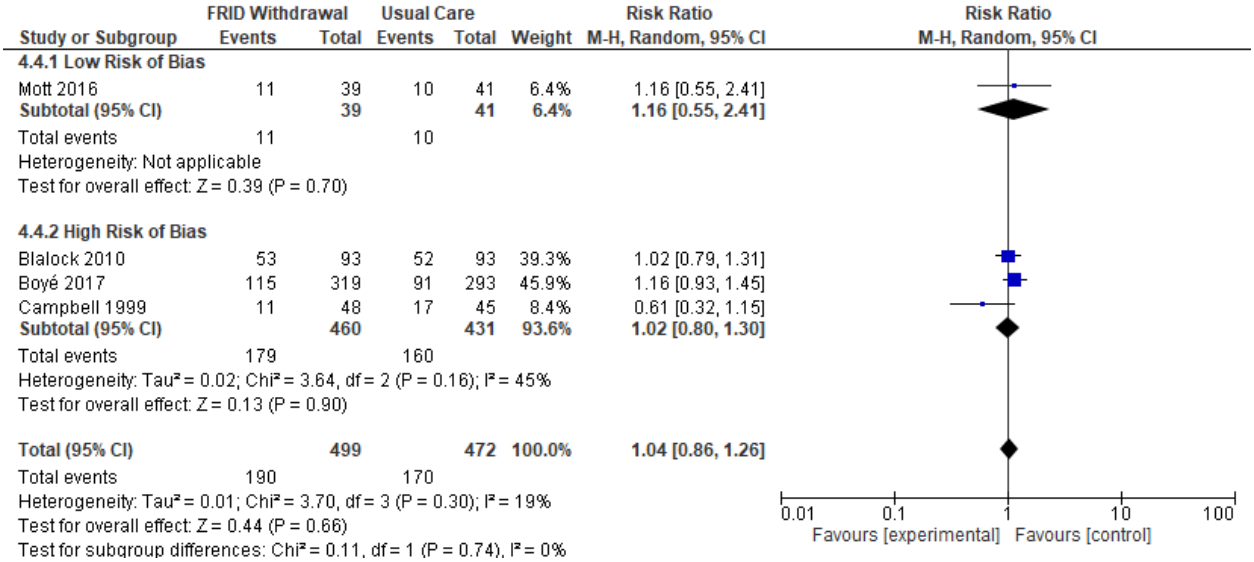
4.2 Falls Rate - Low vs. High Risk of Bias due to Attritional Bias



4.3 Falls Incidence - Low vs. High Risk of Bias due to Blinding



4.4 Falls Incidence - Low vs. High Risk of Bias due to Attrition Bias

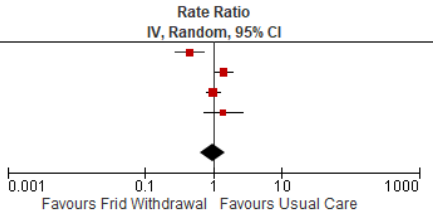


4.5 Falls Rate – Random vs. Effects Model

Random Effects Model

Study or Subgroup	log[Rate Ratio]	SE	FRID Withdrawal Total	Usual Care Total	Weight	Rate Ratio IV, Random, 95% CI	Year
Campbell 1999	-0.8023	0.2434	48	45	23.4%	0.45 [0.28, 0.72]	1999
Patterson 2010	0.3549	0.1465	173	161	28.4%	1.43 [1.07, 1.90]	2010
Blalock 2010	0.003	0.1117	93	93	29.9%	1.00 [0.81, 1.25]	2010
Mott 2016	0.3379	0.3416	39	41	18.4%	1.40 [0.72, 2.74]	2016
Total (95% CI)			**353**	**340**	**100.0%**	**0.98 [0.63, 1.51]**	

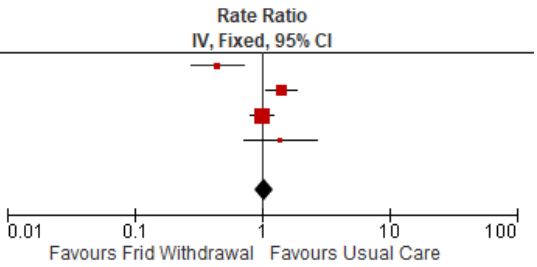
Heterogeneity: Tau² = 0.15; Chi² = 17.47, df = 3 (P = 0.0006); I² = 83%
Test for overall effect: Z = 0.11 (P = 0.92)



Fixed Effects Model

Study or Subgroup	log[Rate Ratio]	SE	Weight	Rate Ratio IV, Fixed, 95% CI	Year
Campbell 1999	-0.8023	0.2434	11.1%	0.45 [0.28, 0.72]	1999
Patterson 2010	0.3549	0.1465	30.6%	1.43 [1.07, 1.90]	2010
Blalock 2010	0.003	0.1117	52.7%	1.00 [0.81, 1.25]	2010
Mott 2016	0.3379	0.3416	5.6%	1.40 [0.72, 2.74]	2016
Total (95% CI)			**100.0%**	**1.04 [0.89, 1.22]**	

Heterogeneity: Chi² = 17.47, df = 3 (P = 0.0006); I² = 83%
Test for overall effect: Z = 0.50 (P = 0.62)

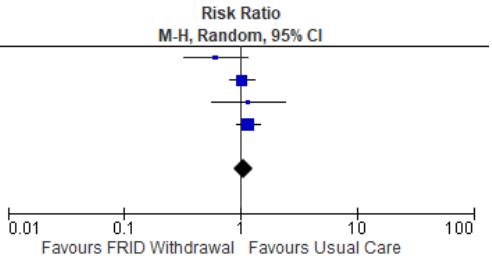


4.6 Falls Incidence – Random vs. Fixed Effects Model

Random Effects Model

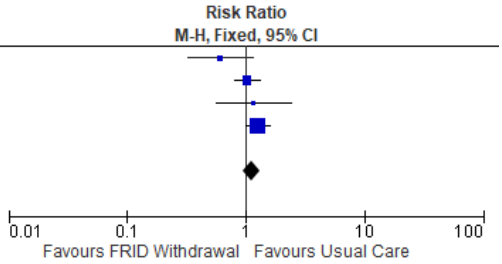
Study or Subgroup	FRID Withdrawal Events	FRID Withdrawal Total	Usual Care Events	Usual Care Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Campbell 1999	11	48	17	45	8.4%	0.61 [0.32, 1.15]	1999
Blalock 2010	53	93	52	93	39.3%	1.02 [0.79, 1.31]	2010
Mott 2016	11	39	10	41	6.4%	1.16 [0.55, 2.41]	2016
Boyé 2017	115	319	91	293	45.9%	1.16 [0.93, 1.45]	2017
Total (95% CI)		**499**		**472**	**100.0%**	**1.04 [0.86, 1.26]**	
Total events	190		170				

Heterogeneity: Tau² = 0.01; Chi² = 3.70, df = 3 (P = 0.30); I² = 19%
Test for overall effect: Z = 0.44 (P = 0.66)



Study or Subgroup	FRID Withdrawal Events	FRID Withdrawal Total	Usual Care Events	Usual Care Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Campbell 1999	11	48	17	45	10.3%	0.61 [0.32, 1.15]	1999
Blalock 2010	53	93	52	93	30.5%	1.02 [0.79, 1.31]	2010
Mott 2016	11	39	10	41	5.7%	1.16 [0.55, 2.41]	2016
Boyé 2017	115	308	91	308	53.4%	1.26 [1.01, 1.58]	2017
Total (95% CI)		**488**		**487**	**100.0%**	**1.12 [0.95, 1.31]**	
Total events	190		170				

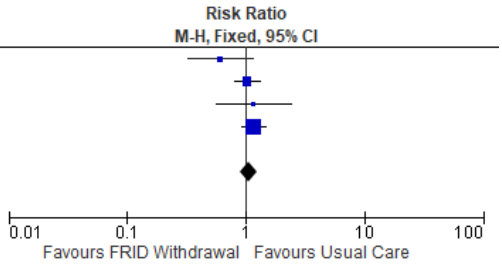
Heterogeneity: Chi² = 5.16, df = 3 (P = 0.16); I² = 42%
Test for overall effect: Z = 1.32 (P = 0.19)



Fixed Effects Model

Study or Subgroup	FRID Withdrawal Events	FRID Withdrawal Total	Usual Care Events	Usual Care Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Campbell 1999	11	48	17	45	10.1%	0.61 [0.32, 1.15]	1999
Blalock 2010	53	93	52	93	29.9%	1.02 [0.79, 1.31]	2010
Mott 2016	11	39	10	41	5.6%	1.16 [0.55, 2.41]	2016
Boyé 2017	115	319	91	293	54.5%	1.16 [0.93, 1.45]	2017
Total (95% CI)		**499**		**472**	**100.0%**	**1.06 [0.90, 1.25]**	
Total events	190		170				

Heterogeneity: Chi² = 3.70, df = 3 (P = 0.30); I² = 19%
Test for overall effect: Z = 0.74 (P = 0.46)



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary Figure S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8-9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8-9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9-10

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9-10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9-10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10 Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10-11 Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13-14 Figure 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12-13, Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12-13 Figure 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	15-16 Table 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	14-15
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	17-20
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	20-21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	21
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	22

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

BMJ Open

Deprescribing Fall-Risk-Increasing Drugs (FRIDs) for the Prevention of Falls and Fall-related Complications: A Systematic Review and Meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-035978.R3
Article Type:	Original research
Date Submitted by the Author:	20-Nov-2020
Complete List of Authors:	Lee, Justin; McMaster University, Division of Geriatric Medicine, Department of Medicine; McMaster University, Department of Health Research Methods, Evidence and Impact Negm, AM; McMaster University Faculty of Health Sciences, School of Rehabilitation Sciences; Hamilton Health Sciences, Geriatric Education and Research in Aging Sciences Centre Peters, Ryan; Queen's University, Department of Medicine Wong, Eric; University of Toronto, Division of Geriatric Medicine, Department of Medicine Holbrook, Anne; McMaster University, Division of Clinical Pharmacology and Toxicology, Department of Medicine; McMaster University Faculty of Health Sciences, Department of Health Research Methods, Evidence and Impact
Primary Subject Heading:	Geriatric medicine
Secondary Subject Heading:	Pharmacology and therapeutics, General practice / Family practice, Evidence based practice
Keywords:	INTERNAL MEDICINE, CLINICAL PHARMACOLOGY, GERIATRIC MEDICINE, PRIMARY CARE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

TITLE: Deprescribing Fall-Risk-Increasing Drugs (FRIDs) for the Prevention of Falls and Fall-related Complications: A Systematic Review and Meta-analysis

AUTHORS: Justin Lee, BScPhm, ACPR, MD[1,2,3]

Ahmed Negm, MD, MSc, PhD[3,4]

Ryan Peters, BSc, MD[5]

Eric Wong, BSc, MD[6]

Anne Holbrook, MD, PharmD, MSc[2,7]

[1]Division of Geriatric Medicine, Department of Medicine, McMaster University, Hamilton, Ontario, Canada
[2]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton,
Ontario, Canada
[3]Geriatric Education and Research in Aging Sciences (GERAS) Centre, Hamilton, Ontario, Canada
[4]School of Rehabilitation Sciences, Faculty of Health Sciences, McMaster University, Hamilton Ontario, Canada;
[5]Department of Medicine, Queen's University, Kingston, Ontario, Canada
[6]Division of Geriatric Medicine, Department of Medicine, University of Toronto, Toronto, Ontario, Canada
[7]Division of Clinical Pharmacology and Toxicology, Department of Medicine, McMaster University, Hamilton, Ontario, Canada

CORRESPONDING AUTHOR: Justin Lee
Geriatric Education and Research in Aging Sciences Centre
88 Maplewood Avenue, Room 158
Hamilton, Ontario, Canada L8M 1W9
Email: justin.lee@medportal.ca
Telephone: (905) 521-2100

MAIN TEXT WORD COUNT: 3724 (excluding title page, abstract, references, tables)

ABSTRACT:

Objectives: Prevention of falls and fall-related injuries is a priority due to the substantial health and financial burden of falls on patients and healthcare systems. Deprescribing medications known as "fall-risk increasing drugs" (FRIDs) is a common strategy to prevent falls. We conducted a systematic review to determine its efficacy for the prevention of falls and fall-related complications.

Design: Systematic review and meta-analysis

Data sources: MEDLINE, EMBASE, CENTRAL, CINAHL and grey literature from inception to August 1, 2020.

Eligibility criteria for selecting studies: Randomized controlled trials of FRID withdrawal compared to usual care evaluating the rate of falls, incidence of falls, fall-related injuries, fall-related fractures, fall-related hospitalizations or adverse effects related to the intervention in adults aged ≥65 years.

Data extraction and synthesis: Two reviewers independently performed citation screening, data abstraction, risk of bias assessment and certainty of evidence grading. Random-effects models were used for meta-analyses.

Results: Five trials involving 1305 participants met eligibility criteria. Deprescribing FRIDs did not change the rate of falls (rate ratio [RaR] 0.98, 95% CI 0.63 to 1.51), the incidence of falls (risk difference [RD] 0.01, 95% CI -0.06 to 0.09; relative risk [RR] 1.04, 95% CI 0.86 to 1.26) or rate

of fall-related injuries (RaR 0.89, 95% CI 0.57 to 1.39) over a 6 to 12 month follow-up period. No trials evaluated the impact of deprescribing FRIDs on fall-related fractures or hospitalizations.

Conclusion: There is a paucity of robust high-quality evidence to support or refute that a FRID deprescribing strategy alone is effective at preventing falls or falls-related injury in older adults. Although there may be other reasons to deprescribe FRIDs, our systematic review found that it may result in little to no difference in the rate or risk of falls as an sole falls reduction strategy.

Registration: PROSPERO CRD42016040203

Key Words: Falls, Falls prevention, Fall-risk increasing drug (FRID), Deprescribing, Medication withdrawal, Seniors, Older Adults, Systematic review

Word Count: 295

ARTICLE SUMMARY

Strengths and Limitations of this Study:

- This study's results are based on a systematic review and meta-analysis of randomised controlled trials
- We employed rigorous analytic methods and interpretational approaches including duplicate assessment, subgroup credibility criteria and optimal information size considerations.
- We assessed the certainty in evidence (i.e. quality of evidence) using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Framework.
- Additional studies are needed to reach the optimal information size to reduce uncertainty about this intervention and establish its relative importance in the range of possible fall prevention interventions

INTRODUCTION

Falls and fall-related injuries are significant public health concerns. Every year, 1 in 3 older adults aged ≥65 years falls and 10% of these falls cause serious injury or hospitalization.[1] Falls are estimated to annually cost $50 billion in the United States, $2 billion in Canada, and £2.3 billion in the United Kingdom.[2–4] All jurisdictional levels are making significant investments to implement falls prevention quality improvement initiatives. These include Public Health England's National Falls Prevention Coordinating Group (NFPRCG), the Centers for Disease Control and Prevention (CDC) Stopping Elderly Accidents, Deaths, & Injuries (STEADI) Initiative, and Health Canada's Canadian Patient Safety Institute "Reducing Falls and Injuries from Falls" initiative. National accreditation bodies such as the United States Joint Commission and Accreditation Canada also mandate specific falls prevention activities of healthcare organizations through their required organizational practices and standards.

Since the majority of falls result from multiple factors (e.g. poor strength and balance, visual and cognitive impairment), current practice guidelines and accreditation standards focus on multi-factorial assessment and intervention strategies.[5] These strategies involve the combination of two or more interventions (e.g. exercise, home or environmental modification, vision assessment, education, medication management, vitamin D supplementation). However, the 2018 United States Preventive Services Task Force evidence report recommends that multifactorial interventions only be offered to select patients because the overall net benefit is small.[6] In fact, there is ongoing debate on the relative merits of focusing on single versus multifactorial interventions, and many clinicians and institutions focus on single interventions due to limited resources.[7]

As an individual intervention, only exercise has robust evidence demonstrating reductions in the incidence of fallers and rate of injurious falls.[6,8] It is unclear if other parts of the multi-component strategy are effective, how large is their individual treatment effect, and which components should be prioritized when resources are limited.

Although there is limited evidence of effectiveness, deprescribing medications known as "fall-risk increasing drugs" (FRIDs) is common practice and typically included in both multifactorial and single intervention strategies. The justification is based on observational studies that suggest certain medications are associated with increased falls risk as well as some randomized controlled trials (RCTs) that have shown that medication management interventions (including those with a broader focus of reducing polypharmacy and/or potentially inappropriate prescribing) may reduce the risk of falls.[9] FRIDs include anti-hypertensives, anti-arrhythmics, anti-cholinergics, anti-histamines, sedatives-hypnotics, anti-psychotics, anti-depressants, opioids and NSAIDs.[10–15]. Although the mechanisms are not fully understood, these drugs may influence falls risk by adversely affecting the cardiovascular or central nervous system (e.g. orthostatic hypotension, bradycardia, sedation, sleep disturbance, confusion, dizziness).

Key issues affecting the quality of this observational evidence and certainty of a causal relationship include: (1) variable adjustment for confounders, dosage or duration of therapy, (2) medication use confirmed only at baseline (but not throughout follow-up), and (3) potential prescribing bias associated with specific medication classes. Most meta-analyses have also been based on the pooling of unadjusted estimates and thus susceptible to bias including confounding by indication. As a result, it is unclear whether the observed increase in falls is causally related to such drug use versus the underlying conditions or patients for which the drugs are treating.

With the aim of evaluating its effectiveness as a single falls prevention strategy, we conducted this systematic review to answer the following: "In older adults aged 65 years or older, does deprescribing and the withdrawal of fall-risk increasing drugs (FRIDs) decrease the risk of falls compared to usual care and continuation of these drugs?" To the best of our knowledge, no previous systematic review has addressed this specific research question.

METHODS

This review was developed using the Cochrane Handbook and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[16,17] The protocol was registered in PROSPERO (CRD42016040203) and previously published and described in detail.[18]

Search Strategy

MEDLINE, EMBASE, CINAHL and the Cochrane Central Register of Controlled Trials (CENTRAL) electronic databases were searched from inception to August 1, 2020 using a combination of Medical Subject Headings, controlled and free-text terms synonymous for the intervention. The MEDLINE search strategy is shown in Supplementary Figure S1. This strategy was modified for use in other databases.

Reference lists of relevant studies, reviews and guidelines were reviewed to identify additional studies. Trial registries and geriatric medicine conference abstracts were also reviewed.

Study Eligibility Criteria

After pilot testing the eligibility criteria, pairs of reviewers independently conducted screening. A third reviewer resolved disagreements.

Studies were included if they were RCTs evaluating FRID deprescribing or withdrawal with the intent of reducing falls. FRID deprescribing was defined as the planned and supervised discontinuation or dose reduction of single or multiple medications thought to independently increase falls risk.[10–12]

The comparator could be usual care (i.e. no change in usual activities and/or no FRID withdrawal) or a control intervention not thought to reduce falls. Studies focused on adults aged ≥65 years from all settings were included. Studies involving FRID withdrawal within multi-component interventions were excluded if the effect of FRID withdrawal could not be isolated.

The primary outcomes of this review were the (1) rate of falls (defined as the total number of falls per unit of person time that falls were monitored) and (2) incidence of falls (i.e. number of fallers). Secondary outcomes included the incidence of (1) fall-related fractures, (2) fall-related injuries, (3) fall-related hospitalization, (4) adverse effects related to the withdrawal intervention (e.g. disease relapse, symptomatic withdrawal).

Data Extraction and Quality Assessment

Two reviewers independently abstracted data on study characteristics, participants, interventions, comparisons, and outcomes using standardized electronic data extraction forms. Disagreements were resolved through consensus.

Two reviewed independently conducted risk of bias (RoB) assessments using the Cochrane Risk of Bias tool.[19] A previously published modification to the RoB assessment was employed to estimate unclearly reported study methods and allow for sensitivity analysis.[20] This

modification involved a structured approach where a score of "definitely low risk", "probably low risk", "probably high risk", or "definitely high risk" was assigned to each RoB criterion. "Definitely" and "probably" scores were collapsed for both low and high RoB scores. Disagreements were resolved through consensus.

Data Synthesis and Analysis

The rate of falls was reported as a rate ratio (RaR) with a 95% confidence interval (CI). Dichotomous outcomes (i.e. incidences of falls, fall-related fracture, fall-related injury, fall-related hospitalization and adverse effects related to the withdrawal intervention) have been reported as risk ratios (RR) with 95% CIs.

We used RevMan 5.3 and the intention-to-treat principle for all statistical analyses. We conducted meta-analyses using the generic inverse variance method to allow pooling of effect estimates. A random effects model was used given expected between-trial variations in methodological, participant and medication characteristics between studies. We had originally planned to pool data at various pre-specified time intervals, but all included studies had follow-up between 6 to 12 months.

We assessed heterogeneity through visual inspection of forest plots and statistical tests. A two-tailed test with p-value <0.10 was considered significant for all Chi-square analyses as per recommendations from the Cochrane Handbook and the I^2 was interpreted using the Cochrane Collaboration thresholds.[16]

Heterogeneity was explored in subgroup analyses based on five a priori hypotheses (Supplementary Table S1).[18] These included differences in baseline propensity for falls as influenced by (1) a history of recurrent falls (e.g. known faller or not) or (2) place of residence or

care (e.g. community, long-term care); differences in the intervention as influenced by (3) specific medication class(es) chosen for withdrawal and (4) preceding medication review by a clinician for FRID withdrawal appropriateness; as well as differences in methodology based on (5) definitions used for "falls" (e.g., observed vs. self-reported). We assessed the credibility of any apparent subgroup effects using eleven previously published criteria recommended by the Cochrane Handbook.[21]

A priori sensitivity analyses were conducted to explore the impact of low vs. high RoB based on blinding and attrition. Studies did not report per-protocol results that would allow for our planned intention-to-treat vs. per-protocol sensitivity analysis. The impact of using a fixed vs. random effects model was explored in a post hoc sensitivity analysis.

The confidence in effect estimates for each reported outcome was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.[22]

Patient and Public Involvement

Patients and the public were not involved in this review.

RESULTS

Of 891 citations identified, 31 were relevant for full text review and 6 met eligibility criteria (κ=0.79, 95% CI 0.51-1.00, substantial agreement). One study was available as an abstract, but it did not report its falls data.[23] Data were requested from the authors, but we did not receive a response. The PRISMA flow diagram summarizing our search results is shown in Figure 1.

Study Characteristics

The included trials in our review are described in Table 1.

Table 1: Characteristics of Included Studies

Author, Year	Study Design	Population	Sample Size	Age Mean (SD)	Targeted FRIDs	Intervention	Control	Study Outcomes
Blalock 2010 [24]	RCT	1) Community setting 2) Age ≥ 65 3) Speak, read English 4) ≥ 4 prescription medications 5) ≥ 1 high falls-risk medication 6) ≥ 1 fall not attributable to syncope within previous year	186 (93 I/93 C)	74.8 (6.9)	Benzodiazepines, antidepressants, anticonvulsants, sedative hypnotics, opioid analgesics, antipsychotics, and skeletal muscle relaxants	1) Pharmacist medication review 2) Physician coordinated medication changes 3) Fall brochure, home safety checklist	1) Fall brochure, home safety checklist	1) Rate of falls 2) Incidence of falls
Campbell 1999 [25]	RCT	1) Community setting 2) Age ≥ 65 3) Using benzodiazepine, other hypnotic, anti-depressant or major tranquilizer 4) Ambulatory 5) No physiotherapy 6) General practitioner thought psychotropic medication withdrawal beneficial	93 Arm 1: 24 (I) Arm 2: 24 (I) Arm 3: 21 (C)* Arm 4: 24 (C)*	74.7 (7.2)	Psychotropic medications (e.g. benzodiazepines, hypnotics, antidepressants, tranquilizers)	<u>Arm 1</u> 1) Withdrawal of psychotropic medication over 14 weeks 2) Placebo substitution 3) Home exercise programme <u>Arm 2</u> 1) Psychotropic medication withdrawal 2) Placebo substitution 3) No home exercise programme	<u>Arm 3</u> 1) No change in psychotropic medication 2) Home exercise programme <u>Arm 4</u> 1) No change in psychotropic medication 2) No exercise programme	1) Rate of falls 2) Incidence of falls
Mott 2016 [26]	Cluster RCT	1) Community setting 2) Age ≥ 65 3) English-speaking 4) Fall in last 12 months/fear of falling 5) Workshop participation 6) Capable of consent	80 (39 I/41 C)	75.6 (6.5)	Neuroleptics, benzodiazepines, anti-depressants, sedative-hypnotics, anti-hypertensives, cyclobenzaprine, carisoprodol, sedating antihistamines, oxybutynin, carbamazepine, methocarbamol, prochlorperazine, benztropine, trihexiphenidyl	1) FRID pharmacist review 2) Medication-related action plan (MAP) developed by pharmacist for patient 3) Pharmacist follow-up 4) Patient given pamphlet 5) describing the role of medications in falls and monthly falls calendars	1) Medications in falls pamphlet	1) Rate of falls 2) Incidence of falls
Patterson 2010 [27]	Cluster RCT	1) Nursing home setting with ≥ 30 beds; not exclusive care of terminally ill 2) Age ≥ 65	334 (173 I/161 C)	82.7 (8.4)	Psychoactive medications (i.e. hypnotics, anxiolytics, antipsychotics)	1) Monthly medication review via pharmacist for appropriateness 2) Nurse and prescriber collaboration to improve medications	1) Usual care	1) Rate of falls
Boyé 2017 [28]	RCT	1) Acute care emergency department setting; attended due to fall incident 2) Age ≥ 65 3) ≥ 1 FRID for ≥ 2 weeks prior to the fall 4) MMSE ≥ 21/30 5) Ambulates independently 6) Community dwelling 7) Informed consent by patient	612 (319 I/293 C)	80.2 (7.3)	Anxiolytics/hypnotics, antidepressants, neuroleptics, anti-hypertensives, anti-arrhythmics, NSAIDs, H2 receptor antagonists, opioids, sympathomimetics, anti-histaminics, diuretics	1) Investigator conducted FRID assessment, proposed changes 2) Changes discussed with geriatrician and general practitioner/prescribing doctor 3) If consensus, FRID discontinued, reduced dosage, substituted for potentially safer option	1) Usual care	1) Rate of falls 2) Incidence of falls

Abbreviations: FRID = Fall-risk-increasing drug, I = Intervention, C = Control

* Arm 3 and Arm 4 classified as controls due to lack of FRID withdrawal in these arms of the factorial design

Three studies were individually randomized, while two studies were cluster randomized by either nursing home or health centre. Studies ranged in size from 80 to 612 participants. With exception of one study[26], studies were multi-centre involving 144 sites and 4 countries. All were conducted in the community setting except for one conducted in long-term care.[27] Follow-up periods ranged from 6 to 12 months.

Overall, there were 1305 participants across all trials. Most were female (>70%) and had a falls history (78.9%). Several key confounders were not reported in the studies including: (1) baseline number and types of FRIDs, (2) baseline number of medications, and (3) baseline number and types of co-morbidities. All these factors are thought to potentially modify falls risk.[29,30]

All interventions included a preceding assessment for FRID deprescribing appropriateness. This was conducted by physicians in 2 trials and pharmacists in 3 trials. Three trials tried to withdraw any FRID, while others focused on sedative-hypnotics, antipsychotics, or antidepressants. Successful discontinuation and adherence to deprescribing protocols were low in all studies. Rates of complete discontinuation of at least one FRID ranged from 10 to 40%.

In terms of our study outcomes, 4 trials measured the rate of falls and 4 measured falls incidence. One trial reported fall-related injuries.[24] Fall-related fractures, fall-related hospitalization or deprescribing-related adverse effects were not measured by any of the trials.

Summary of Findings

Rate and Incidence of Falls

Four studies reported the effect of deprescribing FRIDs on the rate of falls. Deprescribing FRIDs did not reduce the rate of falling (RaR 0.98, 95% CI 0.63 to 1.51; Figure 2 – Analysis 1.1).

Considerable statistical heterogeneity was present (χ^2=17.47, p=0.0006, I^2=83%) and subsequently explored in subgroup analysis.

Four studies reported the effect of deprescribing FRIDs on the risk of falls as measured by falls incidence. Deprescribing FRIDs did not reduce the incidence of falls (RR 1.04, 95% CI 0.86 to 1.26, I^2 = 19%, χ^2=3.70, p = 0.30; Figure 2 – Analysis 2.1). In absolute terms, there was a non-significant risk difference increase of 0.01 (95% CI -0.06 to 0.09, I^2 = 22%, p=0.76; Figure 2 – Analysis 2.2)

Rate of Injurious Falls

One trial reported the effect of deprescribing FRIDs on fall-related injuries.[24] Deprescribing FRIDs did not reduce the rate of fall-related injuries (RaR 0.89, 95% CI 0.57 to 1.39; Figure 2 – Analysis 3.1). This trial did not report data that would allow for any of our pre-planned subgroup analyses.

Risk of Bias Assessment

Figure 3 summarizes our RoB assessments. All studies were deemed at high risk of bias in at least one domain. The overall mean weighted kappa across all assessments was 0.67 (moderate agreement). For individual RoB assessments, kappa ranged from 0 to 0.85. Inter-rater agreement is actually higher than indicated by the calculated scores due to the "kappa co-efficient paradox".[31,32] Low kappas (e.g. κ=0) occurred despite high levels of observed agreement (e.g. $\geq$ 80% agreement) for two RoB assessments. True agreement is falsely attributed to chance agreement by the kappa calculation when there is substantial imbalance in marginal ratings.

For falls rate and incidence, all studies except one[25] were judged at high risk of bias for lack of blinding of participants, personnel and outcome assessors. It is unclear whether blinding could have impacted behaviour or perceptions (e.g. activity risk-level, nocebo effect). Risk of ascertainment bias was high in one study[27] (i.e. no standardized falls definition was used), but all other studies used methods accepted to be low risk of bias (i.e. falls recorded daily on postcards or calendars). Risk of attrition bias was deemed high in three studies based on high or unbalanced lost to follow-up rates.[24,25,28]

Publication Bias

Since less than 10 eligible studies were found, a funnel plot was not constructed due to an inability to make meaningful conclusions about publication bias.

Subgroup Analyses and Exploration of Heterogeneity

Our pre-specified subgroup analyses did not adequately explain the statistical heterogeneity observed results for the rate and incidence of falls (Supplementary Figure S2). Deprescribing FRIDs appeared more effective when a preceding medication review was conducted by physicians compared to pharmacists (p=0.0004, I^2=91.9%, Analysis 1.5), while psychotropic withdrawal appeared more effective than strategies withdrawing any FRID (p=0.08, I^2=67.8%, Analysis 2.3). However, in both analyses, only 6 of 11 subgroup credibility criteria were met and each subgroup was limited to one trial with less than 100 participants (Supplementary Table S2). We, therefore, judged the credibility that these subgroup effects are real as poor and uncertain.

The available data did not permit subgroup analyses by place of residence or falls ascertainment method. The other subgroup analyses showed no evidence of difference beyond that due to chance.

Sensitivity Analyses

Our sensitivity analyses are shown in Supplementary Figure S3. The incorporation of trials with high risk of performance bias appeared to mask the potential benefit of deprescribing FRIDs on reducing the incidence and rate of falls, while the trials with high risk of attrition bias appeared to mask a potential increase in falls rate with deprescribing FRIDs. These results should be interpreted cautiously and definitive conclusions cannot be made. Data from trials with low risk of performance bias were limited to one trial with less than 100 participants, and data from trials with low risk of attrition bias were limited to two trials with less than 450 participants overall.

A post-hoc sensitivity analysis examining the impact of using a fixed vs. random effects model did not change conclusions regarding the effect of deprescribing FRIDs on the rate or incidence of falls.

Quality of Evidence

The GRADE evidence profile is shown in Table 2.

Table 2: GRADE Quality of Evidence Assessment

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**FRID deprescribing strategy**	**usual care**	**Relative (95% CI)**	**Absolute (95% CI)**		
Falls Rate												
4	randomised trials	serious [a]	serious [b]	not serious	serious [c]	none	353	340	**Rate ratio 0.98** (0.63 to 1.51)	-	⨁◯◯◯ VERY LOW	IMPORTANT
Falls Incidence												
4	randomised trials	serious [a]	serious [d]	not serious	serious [c]	none	190/499 (38.1%)	170/472 (36.0%)	**RR 1.04** (0.86 to 1.26)	**14 more per 1,000** (from 50 fewer to 94 more)	⨁◯◯◯ VERY LOW	IMPORTANT
								33.7%		**13 more per 1,000** (from 47 fewer to 88 more)		
Fall-Related Injuries												
1	randomised trials	serious [a]	not serious	not serious	serious [c]	none	93	93	**Rate ratio 0.89** (0.57 to 1.39)	-	⨁⨁◯◯ LOW	CRITICAL

We judged the quality of evidence to be low or very low for all outcomes (falls rates, falls incidence and fall-related injuries) after rating down for risk of bias, inconsistency and imprecision.

We believe the optimal information size (OIS) to make definitive conclusions on the effect of deprescribing FRIDs has not yet been met as the body of evidence is based on fewer than 2000 participants and less than 400 events.[33,34] This is based on the OIS calculation figure recommended by the GRADE guidelines using a well-established control falls event rate of 30% described in the literature and conservative relative risk reduction (RRR) of 20% (assuming $\alpha = 0.05$ and $\beta = 0.2$).[34,35]

DISCUSSION

This systematic review sought to determine whether deprescribing FRIDs decreased the risk of falls in older adults and found that there is a lack of robust high-quality evidence to support or refute the deprescribing of FRIDs alone as an effective fall prevention strategy. Incorporating data from 5 RCTs involving 1305 participants aged ≥65 years, our meta-analyses indicate that a FRID deprescribing strategy did not significantly change the rate of falls (RaR 0.98, 95% CI 0.63 to 1.51) nor the risk of falling (RD 0.01, 95% CI -0.06 to 0.09) over a 6 to 12-month follow-up period. Although this intervention focuses on those medications thought to be associated with falls, the uncertainty of its effect on falls and conclusions of current lack of evidence of effectiveness are similar to previous systematic reviews evaluating the effectiveness of medication reviews that had a broader focus on reducing polypharmacy and potentially inappropriate prescribing (i.e. not focused solely on FRIDs).[9,36]

There is also a significant absence of evidence for clinically- and patient-important outcomes such as fall-related injuries, fractures and hospitalizations. The only trial to date that

evaluated the rate of fall-related injuries did not demonstrate a statistically significant effect (RaR 0.89, 95% CI 0.57-1.39).[24] Our search found no trials measuring the impact on fall-related fractures, fall-related hospitalizations or adverse effects related to a FRID deprescribing strategy. Although this may be rooted in the difficulty of conducting RCTs powered for such outcomes, their measurement and reporting are still important to inform systematic review meta-analyses that could lead to more precise estimates.

Based on low-quality evidence, it is unclear whether deprescribing FRIDs as a single intervention leads to any appreciable clinically important benefit or harm. Our current best effect estimates for falls rate and incidence are centred around no appreciable difference (i.e. RaR ≈ 1, RR ≈ 1, RD ≈ 0). Although seemingly logical to assume, reducing isolated risk factors may not necessarily lead to a reduction in falls and fall-related complications. The absence of change in the incidence of hip fractures after statewide regulatory action on benzodiazepine prescribing in the United States that reduced benzodiazepine use by 60.3% is a real-world example of this phenomenon and the complexity of exposure-outcome relationships.[37]

Our findings likely reflect the multi-factorial nature of falls and the varying risk of different FRIDs. It is unclear as to what degree a particular risk factor or combination of risk factors (e.g. specific FRIDs) must be reduced to produce an appreciable change in falls. Medications may only have conditional or contributory causality to falls. It may be that medication-related interventions work best in combination with other interventions or only in specific contexts.

Only one trial[25] included in our review demonstrated a statistically significant benefit with deprescribing FRIDs. This was also the only trial to use study capsules to operationalize blinded deprescribing of FRIDs in participants, research personnel and outcome assessors. Its results might be more reflective of the true potential physiological effect of deprescribing FRIDs

because it minimized the risk of performance bias. However, the magnitude of benefit achievable in the non-research setting at this time may be closer to those seen in the unblinded trials due to the strong psychological and behavioural factors (e.g. nocebo effect) that may hinder successful deprescribing. Further advances in implementation science and behavioural change strategies are likely needed to facilitate medication optimization.

These results raise several questions about the presumed effectiveness of deprescribing FRIDs as an isolated falls prevention strategy. Given the amount of resources being invested into falls prevention initiatives around the world, clinicians and organizations should examine: (1) what is the strength of evidence supporting their current activities, (2) whether these activities are cost-effective, and (3) whether resources are being appropriately prioritized to those interventions shown to provide the most value. This should also be applied to what is being required of healthcare organizations in national accreditation standards (e.g. Joint Commission, Accreditation Canada) to help direct and encourage optimal use of limited healthcare resources.

Clinicians and policy-makers need to consider the current lack of strong evidence for deprescribing FRIDs as an isolated intervention for the specific purpose of reducing falls, particularly in patients who may be very reluctant or who have strong indications for specific FRIDs. FRID reduction is one out of many possible interventions that need to be considered. As with prescribing medications, deprescribing is a skill and comes with the potential for harm as well as benefit.[38] Thoughtful consideration of the goals, appropriateness and safety of deprescribing is important.[39] Our results highlight the need for a comprehensive and individualized approach to falls. Multi-component interventions are ideal, but interventions may need to be prioritized depending on time, resources and context.

Despite insufficient evidence to support or refute the deprescribing of FRIDs for falls prevention, our results do not mean that clinicians should avoid deprescribing FRIDs. There may be many other reasons to deprescribe these medications. These include avoidance of adverse drug events, improvements in cognition, increased medication adherence and drug costs savings. It is also unclear whether medication review and management with a broader focus on reducing polypharmacy and potentially inappropriate prescribing in older adults may be beneficial in preventing falls. Some RCTs with such interventions have shown a reduction of falls risk, while others have not demonstrated a significant difference.[40–46]

Our review highlights the need for future FRID deprescribing trials that evaluate patient-important outcomes (e.g. injuries, fractures and hospitalizations). Greater attention to optimal design and reporting is needed to minimize risk of bias and enhance our interpretation of the results. Examples include improved reporting of confounding baseline characteristics and intervention fidelity (e.g. number and types of FRIDs, degree and duration of dose reduction). Deprescribing is challenging and extra measures are likely needed to improve successful intervention adherence and follow-up.

STRENGTHS AND LIMITATIONS

Our review has limitations. There was variation in the operationalization of FRID deprescribing and degree of success achieved (e.g. dose reduction only, completion discontinuation, non-adherence). This presumably makes the detection of any potential benefit less likely and our conclusions more conservative. However, the effect estimates are likely more indicative of what might be expected outside of the research setting. These phenomena likely represent the real-life challenges of deprescribing (especially with certain types of FRIDs such as

psychotropics or opioids). Moreover, our ability to assess for confounders modifying falls risk was limited due to inconsistent reporting of relevant baseline characteristics and lack of patient-level data. Lastly, our ability to make definitive conclusions is limited because the total sample size across studies for each outcome did not yet meet our calculated estimate for the required optimal information size.

Our review has several strengths. First, our search was comprehensive and we included a rigorous grey literature search for unpublished studies. Second, we employed optimal analytical and interpretational approaches including duplicate assessment, subgroup credibility criteria and optimal information size considerations. Third, unlike previous medication-focused reviews, we applied the GRADE approach to assess the quality of evidence and our degree of confidence in the results.

CONCLUSIONS

Our systematic review found that deprescribing FRIDs as an isolated strategy results in little to no difference in the rate and risk of falls or falls-related injuries, but the evidence is still sparse and very low quality. Additional well-designed studies are needed to reach the optimal information size to reduce uncertainty about this intervention and establish its relative importance in the range of possible interventions that can be employed by clinicians and health systems to reduce falls.

Acknowledgements:

The authors would like to thank Lois Cottrell, medical librarian at St. Joseph's Healthcare Hamilton, Charlton Campus, Hamilton, Ontario, Canada and Andrea McLellan, Head of

Collection and Technical Services, School of Medicine liaison, at McMaster University, Hamilton, Ontario, Canada, for their assistance with the development of the search strategy.

Author Contributions:

JL conceptualized the study. JL and AH designed and developed the protocol. RP and EW assisted with citation review. RP and AN assisted with data extraction, risk of bias assessment and certainty of evidence grading. All authors contributed to the analysis and interpretation of results. JL drafted the initial manuscript and all authors contributed to its revision and final approval.

Funding:

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing Interests:

The authors have no potential conflicts of interest to declare.

Patient Consent for Publication:

None required.

Data Sharing Statement:

No unpublished data are available.

REFERENCES:

1 Hill KD, Wee R. Psychotropic drug-induced falls in older people: a review of interventions aimed at reducing the problem. *Drugs Aging* 2012;**29**:15–30. doi:10.2165/11598420-000000000-00000

2 Florence CS, Bergen G, Atherly A, *et al.* Medical Costs of Fatal and Nonfatal Falls in Older Adults. *J Am Geriatr Soc* 2018;**66**:693–8. doi:10.1111/jgs.15304

3 National Institute for Health and Care Excellence. Falls in older people: assessing risk and prevention. 2013.

4 Public Health Agency of Canada. Seniors' Falls in Canada. 2014.

5 Summary of the Updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons. *J Am Geriatr Soc* 2011;**59**:148–57. doi:10.1111/j.1532-5415.2010.03234.x

6 Guirguis-Blake JM, Michael YL, Perdue LA, *et al.* Interventions to Prevent Falls in Older Adults. *JAMA* 2018;**319**:1705. doi:10.1001/jama.2017.21962

7 Campbell AJ, Robertson MC. Fall Prevention: Single or Multiple Interventions? Single Interventions for Fall Prevention. *J Am Geriatr Soc* 2013;**61**:281–4. doi:10.1111/jgs.12095_2

8 Tricco AC, Thomas SM, Veroniki AA, *et al.* Comparisons of Interventions for Preventing Falls in Older Adults. *JAMA* 2017;**318**:1687. doi:10.1001/jama.2017.15006

9 Gillespie LD, Robertson MC, Gillespie WJ, *et al.* Interventions for preventing falls in older people living in the community. *Cochrane database Syst Rev* 2012;**9**:CD007146. doi:10.1002/14651858.CD007146.pub3

10 Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic

review and meta-analysis: I. Psychotropic drugs. *J Am Geriatr Soc* 1999;**47**:30–9.

11 Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: II. Cardiac and analgesic drugs. *J Am Geriatr Soc* 1999;**47**:40–50.

12 Woolcott JC, Richardson KJ, Wiens MO, *et al.* Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Arch Intern Med* 2009;**169**:1952–60. doi:10.1001/archinternmed.2009.357

13 de Vries M, Seppala LJ, Daams JG, *et al.* Fall-Risk-Increasing Drugs: A Systematic Review and Meta-Analysis: I. Cardiovascular Drugs. *J Am Med Dir Assoc* 2018;**19**:371.e1-371.e9. doi:10.1016/j.jamda.2017.12.013

14 Seppala LJ, Wermelink AMAT, de Vries M, *et al.* Fall-Risk-Increasing Drugs: A Systematic Review and Meta-Analysis: II. Psychotropics. *J Am Med Dir Assoc* 2018;**19**:371.e11-371.e17. doi:10.1016/j.jamda.2017.12.098

15 Seppala LJ, van de Glind EMM, Daams JG, *et al.* Fall-Risk-Increasing Drugs: A Systematic Review and Meta-analysis: III. Others. *J Am Med Dir Assoc* 2018;**19**:372.e1-372.e8. doi:10.1016/j.jamda.2017.12.099

16 The Cochrane Collaboration. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]*. 2011.

17 Moher D, Liberati A, Tetzlaff J, *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;**151**:264–9, W64.

18 Lee JY, Holbrook A. The efficacy of fall-risk-increasing drug (FRID) withdrawal for the prevention of falls and fall-related complications: protocol for a systematic review and meta-analysis. *Syst Rev* 2017;**6**:33.

19 Higgins JPT, Altman DG, Gøtzsche PC, *et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;**343**:d5928.

20 Akl EA, Sun X, Busse JW, *et al.* Specific instructions for estimating unclearly reported blinding status in randomized trials were reliable and valid. *J Clin Epidemiol* 2012;**65**:262–7. doi:10.1016/j.jclinepi.2011.04.015

21 Sun X, Briel M, Walter SD, *et al.* Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. *BMJ* 2010;**340**:c117.

22 Guyatt G, Oxman AD, Akl EA, *et al.* GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;**64**:383–94.

23 Streim JE, Filippo S, Have T, *et al.* Antidepressant discontinuation associated with cognitive decline in older adult residents of long-term care facilities. *Am J Geriatr psychiatry* 2012;**20**:S147–8. doi:10.1097/01.JGP.0000413064.91948.aa

24 Blalock SJ, Casteel C, Roth MT, *et al.* Impact of enhanced pharmacologic care on the prevention of falls: a randomized controlled trial. *Am J Geriatr Pharmacother* 2010;**8**:428–40. doi:10.1016/j.amjopharm.2010.09.002

25 Campbell AJ, Robertson MC, Gardner MM, *et al.* Psychotropic medication withdrawal and a home-based exercise program to prevent falls: a randomized, controlled trial. *J Am Geriatr Soc* 1999;**47**:850–3.

26 Mott DA, Martin B, Breslow R, *et al.* Impact of a medication therapy management intervention targeting medications associated with falling: Results of a pilot study. *J Am Pharm Assoc (2003)* 2016;**56**:22–8.

27 Patterson SM, Hughes CM, Crealey G, *et al.* An evaluation of an adapted U.S. model of pharmaceutical care to improve psychoactive prescribing for nursing home residents in

northern ireland (fleetwood northern ireland study). *J Am Geriatr Soc* 2010;**58**:44–53. doi:10.1111/j.1532-5415.2009.02617.x

28 Boyé NDA, van der Velde N, de Vries OJ, *et al.* Effectiveness of medication withdrawal in older fallers: results from the Improving Medication Prescribing to reduce Risk Of FALLs (IMPROveFALL) trial. *Age Ageing* 2017;**46**:142–6. doi:10.1093/ageing/afw161

29 Tinetti M, Kumar C. The Patient Who Falls. *JAMA J Am Med Assoc* 2010;**303**:273–4. doi:10.1001/jama.2009.2024

30 Chen Y, Zhu L-L, Zhou Q. Effects of drug pharmacokinetic/pharmacodynamic properties, characteristics of medication use, and relevant pharmacological interventions on fall risk in elderly patients. *Ther Clin Risk Manag* 2014;**10**:437–48. doi:10.2147/TCRM.S63756

31 Feinstein AR, Cicchetti D V. High agreement but low kappa: I. The problems of two paradoxes. *J Clin Epidemiol* 1990;**43**:543–9.

32 Tang W, Hu J, Zhang H, *et al.* Kappa coefficient: a popular measure of rater agreement. *Shanghai Arch psychiatry* 2015;**27**:62–7. doi:10.11919/j.issn.1002-0829.215010

33 Ioannidis J, Lau J. Evolution of treatment effects over time: empirical insight from recursive cumulative metaanalyses. *Proc Natl Acad Sci U S A* 2001;**98**:831–6. doi:10.1073/pnas.021529998

34 Guyatt GH, Oxman AD, Kunz R, *et al.* GRADE guidelines 6. Rating the quality of evidence--imprecision. *J Clin Epidemiol* 2011;**64**:1283–93. doi:10.1016/j.jclinepi.2011.01.012

35 O'Loughlin JL, Robitaille Y, Boivin JF, *et al.* Incidence of and risk factors for falls and injurious falls among the community-dwelling elderly. *Am J Epidemiol* 1993;**137**:342–54.

36 Guirguis-Blake JM, Michael YL, Perdue LA, *et al. Interventions to Prevent Falls in*

Community-Dwelling Older Adults: A Systematic Review for the U.S. Preventive Services Task Force. Agency for Healthcare Research and Quality (US) 2018.

37 Wagner AK, Ross-Degnan D, Gurwitz JH, *et al.* Effect of New York State regulatory action on benzodiazepine prescribing and hip fracture rates. *Ann Intern Med* 2007;**146**:96–103.

38 Reeve E, Moriarty F, Nahas R, *et al.* A narrative review of the safety concerns of deprescribing in older adults and strategies to mitigate potential harms. *Expert Opin Drug Saf* 2018;**17**:39–49. doi:10.1080/14740338.2018.1397625

39 Lee JY, Farrell B, Holbrook AM. De-prescribing benzodiazepine receptor agonists taken for insomnia: a review and key messages from practice guidelines. *Polish Arch Intern Med* 2018;**129**:839–45. doi:10.20452/pamw.4391

40 Pit SW, Byles JE, Henry DA, *et al.* A Quality Use of Medicines program for general practitioners and older people: a cluster randomised controlled trial. *Med J Aust* 2007;**187**:23–30.

41 Weber V, White A, McIlvried R. An electronic medical record (EMR)-based intervention to reduce polypharmacy and falls in an ambulatory rural elderly population. *J Gen Intern Med* 2008;**23**:399–404.

42 Zermansky AG, Alldred DP, Petty DR, *et al.* Clinical medication review by a pharmacist of elderly people living in care homes--randomised controlled trial. *Age Ageing* 2006;**35**:586–91. doi:10.1093/ageing/afl075

43 Frankenthal D, Lerman Y, Kalendaryev E, *et al.* Intervention with the screening tool of older persons potentially inappropriate prescriptions/screening tool to alert doctors to right treatment criteria in elderly residents of a chronic geriatric facility: a randomized clinical

trial. *J Am Geriatr Soc* 2014;**62**:1658–65. doi:10.1111/jgs.12993

44 Michalek C, Wehling M, Schlitzer J, *et al.* Effects of 'Fit fOR The Aged' (FORTA) on pharmacotherapy and clinical endpoints--a pilot randomized controlled study. *Eur J Clin Pharmacol* 2014;**70**:1261–7.

45 Meredith S, Feldman P, Frey D, *et al.* Improving medication use in newly admitted home healthcare patients: A randomized controlled trial. *J Am Geriatr Soc* 2002;**50**:1484–91. doi:10.1046/j.1532-5415.2002.50402.x

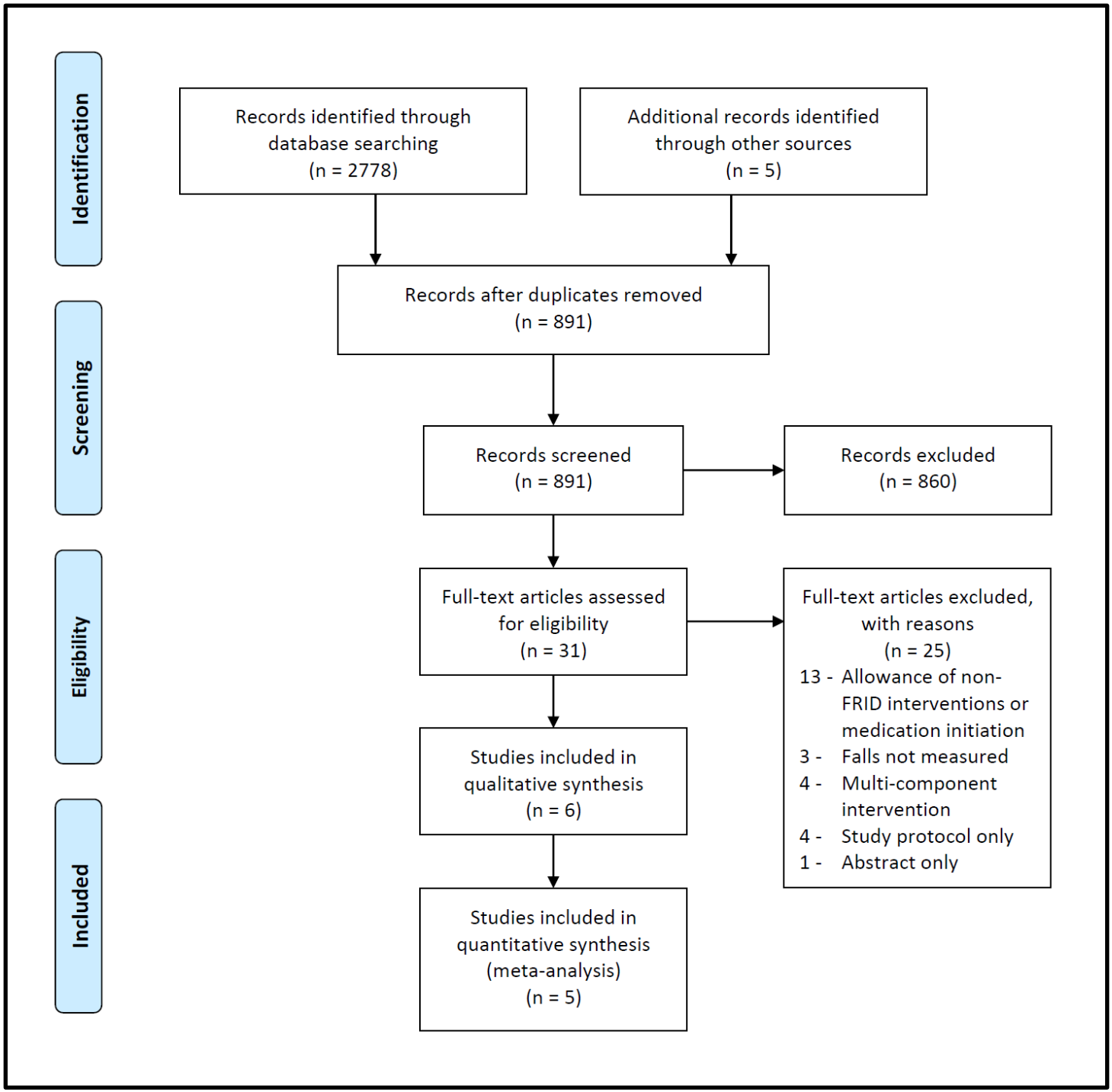
46 Sjoberg C, Wallerstedt SM. Effects of medication reviews performed by a physician on treatment with fracture-preventing and fall-risk-increasing drugs in older adults with hip fracture-a randomized controlled study. *J Am Geriatr Soc* 2013;**61**:1464–72.

FIGURES

Figure 1: PRISMA Flow Diagram of Study Selection Process

Figure 2: Forest Plots of FRID Withdrawal versus Usual Care

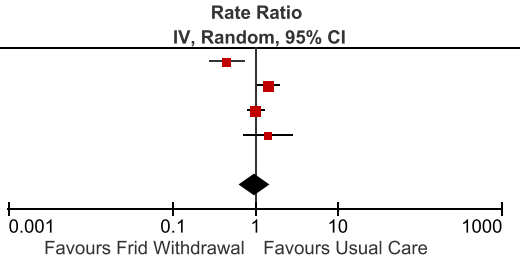
Figure 3: Risk of Bias Assessments


Identification
Screening
Eligibility
Included
Records identified through database searching (n = 2778)
Additional records identified through other sources (n = 5)
Records after duplicates removed (n = 891)
Records screened (n = 891)
Records excluded (n = 860)
Full-text articles assessed for eligibility (n = 31)
Full-text articles excluded, with reasons (n = 25)
13 - Allowance of non-FRID interventions or medication initiation
3 - Falls not measured
4 - Multi-component intervention
4 - Study protocol only
1 - Abstract only
Studies included in qualitative synthesis (n = 6)
Studies included in quantitative synthesis (meta-analysis) (n = 5)

1.1 Falls Rate

Study or Subgroup	log[Rate Ratio]	SE	FRID Withdrawal Total	Usual Care Total	Weight	Rate Ratio IV, Random, 95% CI	Year
Campbell 1999	-0.8023	0.2434	48	45	23.4%	0.45 [0.28, 0.72]	1999
Patterson 2010	0.3549	0.1465	173	161	28.4%	1.43 [1.07, 1.90]	2010
Blalock 2010	0.003	0.1117	93	93	29.9%	1.00 [0.81, 1.25]	2010
Mott 2016	0.3379	0.3416	39	41	18.4%	1.40 [0.72, 2.74]	2016
Total (95% CI)			**353**	**340**	**100.0%**	**0.98 [0.63, 1.51]**	

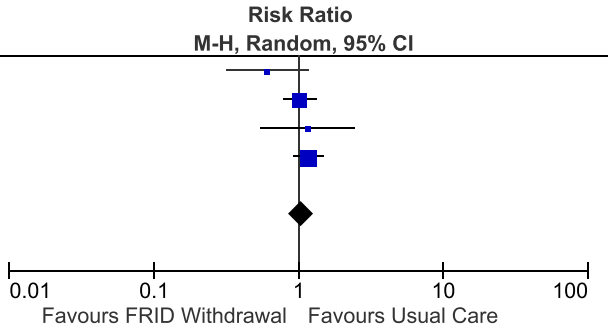
Heterogeneity: Tau² = 0.15; Chi² = 17.47, df = 3 (P = 0.0006); I² = 83%
Test for overall effect: Z = 0.11 (P = 0.92)



2.1 Falls Incidence – Risk Ratio

Study or Subgroup	FRID Withdrawal Events	FRID Withdrawal Total	Usual Care Events	Usual Care Total	Weight	Risk Ratio M-H, Random, 95% CI
Campbell 1999	11	48	17	45	8.4%	0.61 [0.32, 1.15]
Blalock 2010	53	93	52	93	39.3%	1.02 [0.79, 1.31]
Mott 2016	11	39	10	41	6.4%	1.16 [0.55, 2.41]
Boyé 2017	115	319	91	293	45.9%	1.16 [0.93, 1.45]
Total (95% CI)		**499**		**472**	**100.0%**	**1.04 [0.86, 1.26]**
Total events	190		170			

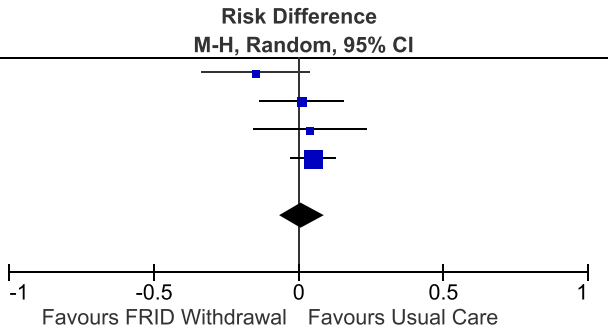
Heterogeneity: Tau² = 0.01; Chi² = 3.70, df = 3 (P = 0.30); I² = 19%
Test for overall effect: Z = 0.44 (P = 0.66)



2.2 Falls Incidence – Risk Difference

Study or Subgroup	FRID Withdrawal Events	FRID Withdrawal Total	Usual Care Events	Usual Care Total	Weight	Risk Difference M-H, Random, 95% CI
Campbell 1999	11	48	17	45	14.2%	-0.15 [-0.33, 0.04]
Blalock 2010	53	93	52	93	21.8%	0.01 [-0.13, 0.15]
Mott 2016	11	39	10	41	13.2%	0.04 [-0.15, 0.23]
Boyé 2017	115	319	91	293	50.9%	0.05 [-0.02, 0.12]
Total (95% CI)		**499**		**472**	**100.0%**	**0.01 [-0.06, 0.09]**
Total events	190		170			

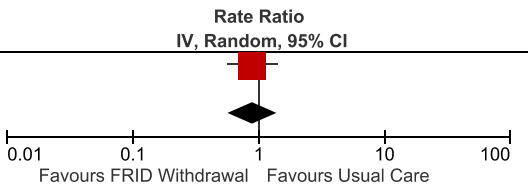
Heterogeneity: Tau² = 0.00; Chi² = 3.86, df = 3 (P = 0.28); I² = 22%
Test for overall effect: Z = 0.31 (P = 0.76)

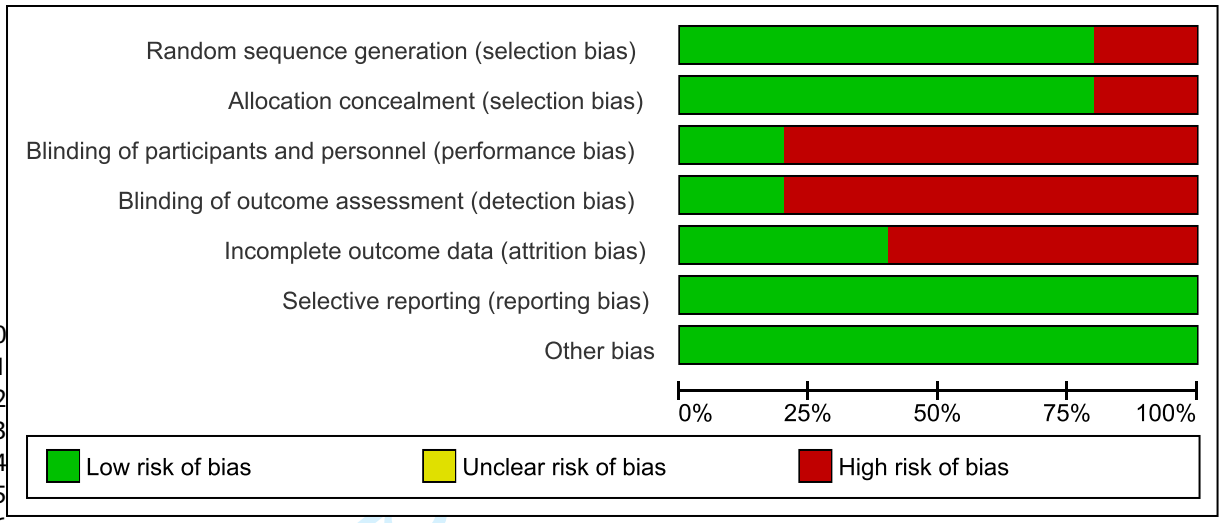


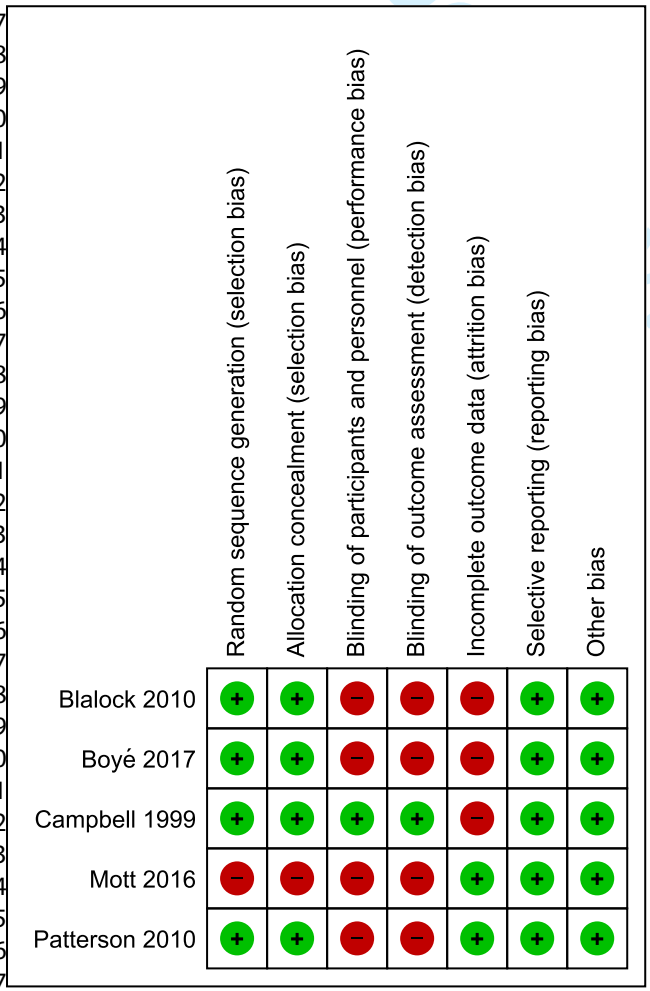
3.1 Fall-Related Injuries

Study or Subgroup	log[Rate Ratio]	SE	FRID Withdrawal Total	Usual Care Total	Weight	Rate Ratio IV, Random, 95% CI	Year
Blalock 2010	-0.1165	0.2273	93	93	100.0%	0.89 [0.57, 1.39]	2010
Total (95% CI)			**93**	**93**	**100.0%**	**0.89 [0.57, 1.39]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.51 (P = 0.61)







Supplementary Figure S1: OVID Medline Search Strategy

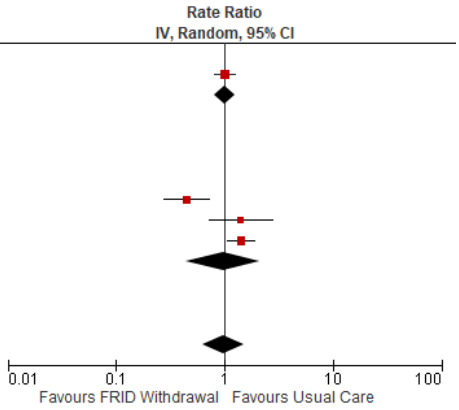
Database(s): OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Search Strategy:

#	Searches
1	exp Accidental Falls/pc [Prevention & Control]
2	fall.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
3	falls.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
4	exp Deprescriptions/
5	((medicat* or drug*) adj3 (deprescrib* or withdraw* or cessat* or stop* or discontin*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
6	((antihypertensive* or diuretic* or beta-blocker* or sedative* or hypnotic* or neuroleptic* or antipsychotic* or antidepressant* or benzodiazepine* or narcotic* or opioid* or narcotic* or NSAID*) adj3 (deprescrib* or withdraw* or cessat* or stop* or discontin*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
7	fall-risk increasing drugs.mp.
8	FRID.mp.
9	((medicat* or drug*) adj3 (review* or improv* or program*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
10	exp "Drug-Related Side Effects and Adverse Reactions"/pc [Prevention & Control]
11	exp Medication Therapy Management/ or exp "Drug Utilization Review"/
12	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13	1 or 2 or 3
14	12 and 13
15	remove duplicates from 14
16	exp Clinical Trial/
17	(randomized or randomised).ab,ti.
18	placebo.ab,ti.
19	randomly.ab,ti.
20	groups.ab,ti.
21	randomized controlled trial.pt.
22	controlled clinical trial.pt.
23	16 or 17 or 18 or 19 or 20 or 21 or 22
24	15 and 23

Supplementary Figure S2: Subgroup Analyses

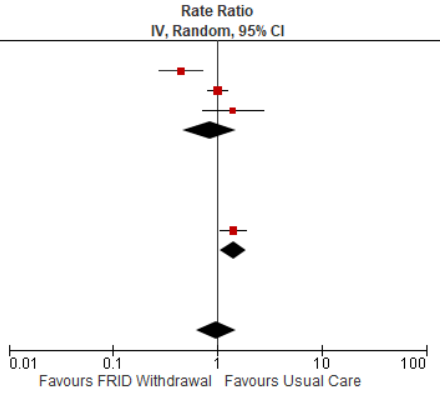
1.2 Falls Rate - Known vs. Unknown Faller

Study or Subgroup	log[Rate Ratio]	SE	FRID Withdrawal Total	Usual Care Total	Weight	Rate Ratio IV, Random, 95% CI
1.2.1 Known Faller						
Blalock 2010	0.003	0.1117	93	93	29.9%	1.00 [0.81, 1.25]
Subtotal (95% CI)			**93**	**93**	**29.9%**	**1.00 [0.81, 1.25]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.03 (P = 0.98)						
1.2.2 Unknown Faller						
Campbell 1999	-0.8023	0.2434	48	45	23.4%	0.45 [0.28, 0.72]
Mott 2016	0.3379	0.3416	39	41	18.4%	1.40 [0.72, 2.74]
Patterson 2010	0.3549	0.1465	173	161	28.4%	1.43 [1.07, 1.90]
Subtotal (95% CI)			**260**	**247**	**70.1%**	**0.96 [0.44, 2.10]**
Heterogeneity: Tau² = 0.41; Chi² = 17.23, df = 2 (P = 0.0002); I² = 88%						
Test for overall effect: Z = 0.10 (P = 0.92)						
Total (95% CI)			**353**	**340**	**100.0%**	**0.98 [0.63, 1.51]**
Heterogeneity: Tau² = 0.15; Chi² = 17.47, df = 3 (P = 0.0006); I² = 83%						
Test for overall effect: Z = 0.11 (P = 0.92)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.92), I² = 0%						



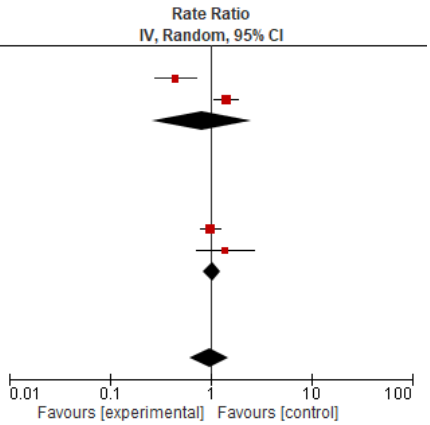
1.3 Falls Rate - Community vs. Institutionalized

Study or Subgroup	log[Rate Ratio]	SE	FRID Withdrawal Total	Usual Care Total	Weight	Rate Ratio IV, Random, 95% CI	Year
1.3.1 Community							
Campbell 1999	-0.8023	0.2434	48	45	23.4%	0.45 [0.28, 0.72]	1999
Blalock 2010	0.003	0.1117	93	93	29.9%	1.00 [0.81, 1.25]	2010
Mott 2016	0.3379	0.3416	39	41	18.4%	1.40 [0.72, 2.74]	2016
Subtotal (95% CI)			**180**	**179**	**71.6%**	**0.84 [0.47, 1.52]**	
Heterogeneity: Tau² = 0.21; Chi² = 10.82, df = 2 (P = 0.004); I² = 82%							
Test for overall effect: Z = 0.57 (P = 0.57)							
1.3.2 Institutionalized							
Patterson 2010	0.3549	0.1465	173	161	28.4%	1.43 [1.07, 1.90]	2010
Subtotal (95% CI)			**173**	**161**	**28.4%**	**1.43 [1.07, 1.90]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.42 (P = 0.02)							
Total (95% CI)			**353**	**340**	**100.0%**	**0.98 [0.63, 1.51]**	
Heterogeneity: Tau² = 0.15; Chi² = 17.47, df = 3 (P = 0.0006); I² = 83%							
Test for overall effect: Z = 0.11 (P = 0.92)							
Test for subgroup differences: Chi² = 2.49, df = 1 (P = 0.11), I² = 59.8%							



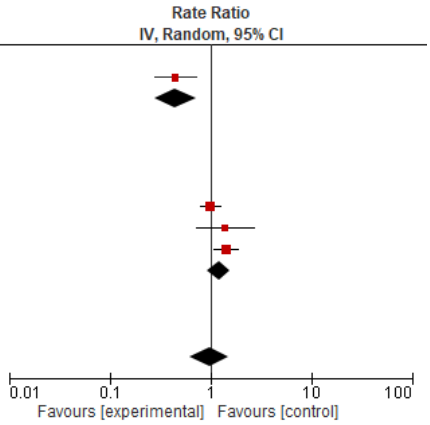
1.4 Falls Rate - Psychotropic Withdrawal vs. Any FRID Withdrawal

Study or Subgroup	log[Rate Ratio]	SE	FRID Withdrawal Total	Usual Care Total	Weight	Rate Ratio IV, Random, 95% CI
1.4.1 Psychotropic Withdrawal (Antipsychotic, Anxiolytic, Sedative, Hyponotic)						
Campbell 1999	-0.8023	0.2434	48	45	23.4%	0.45 [0.28, 0.72]
Patterson 2010	0.3549	0.1465	173	161	28.4%	1.43 [1.07, 1.90]
Subtotal (95% CI)			**221**	**206**	**51.7%**	**0.81 [0.26, 2.52]**
Heterogeneity: Tau² = 0.63; Chi² = 16.59, df = 1 (P < 0.0001); I² = 94%						
Test for overall effect: Z = 0.36 (P = 0.72)						
1.4.2 Any FRID						
Blalock 2010	0.003	0.1117	93	93	29.9%	1.00 [0.81, 1.25]
Mott 2016	0.3379	0.3416	39	41	18.4%	1.40 [0.72, 2.74]
Subtotal (95% CI)			**132**	**134**	**48.3%**	**1.04 [0.84, 1.28]**
Heterogeneity: Tau² = 0.00; Chi² = 0.87, df = 1 (P = 0.35); I² = 0%						
Test for overall effect: Z = 0.33 (P = 0.74)						
Total (95% CI)			**353**	**340**	**100.0%**	**0.98 [0.63, 1.51]**
Heterogeneity: Tau² = 0.15; Chi² = 17.47, df = 3 (P = 0.0006); I² = 83%						
Test for overall effect: Z = 0.11 (P = 0.92)						
Test for subgroup differences: Chi² = 0.17, df = 1 (P = 0.68), I² = 0%						



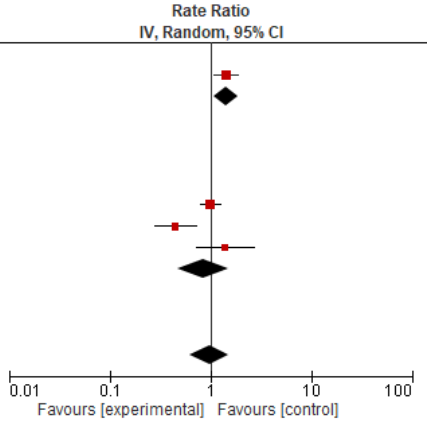
1.5 Falls Rate - Physician vs. Pharmacist Medication Review

Study or Subgroup	log[Rate Ratio]	SE	FRID Withdrawal Total	Usual Care Total	Weight	Rate Ratio IV, Random, 95% CI
1.5.1 Physician Medication Review						
Campbell 1999	-0.8023	0.2434	48	45	23.4%	0.45 [0.28, 0.72]
Subtotal (95% CI)			**48**	**45**	**23.4%**	**0.45 [0.28, 0.72]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.30 (P = 0.0010)						
1.5.2 Pharmacist Medication Review						
Blalock 2010	0.003	0.1117	93	93	29.9%	1.00 [0.81, 1.25]
Mott 2016	0.3379	0.3416	39	41	18.4%	1.40 [0.72, 2.74]
Patterson 2010	0.3549	0.1465	173	161	28.4%	1.43 [1.07, 1.90]
Subtotal (95% CI)			**305**	**295**	**76.6%**	**1.20 [0.92, 1.58]**
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 3.99$, df = 2 (P = 0.14); $I^2 = 50\%$						
Test for overall effect: Z = 1.33 (P = 0.18)						
Total (95% CI)			**353**	**340**	**100.0%**	**0.98 [0.63, 1.51]**
Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 17.47$, df = 3 (P = 0.0006); $I^2 = 83\%$						
Test for overall effect: Z = 0.11 (P = 0.92)						
Test for subgroup differences: $Chi^2 = 12.41$, df = 1 (P = 0.0004), $I^2 = 91.9\%$						

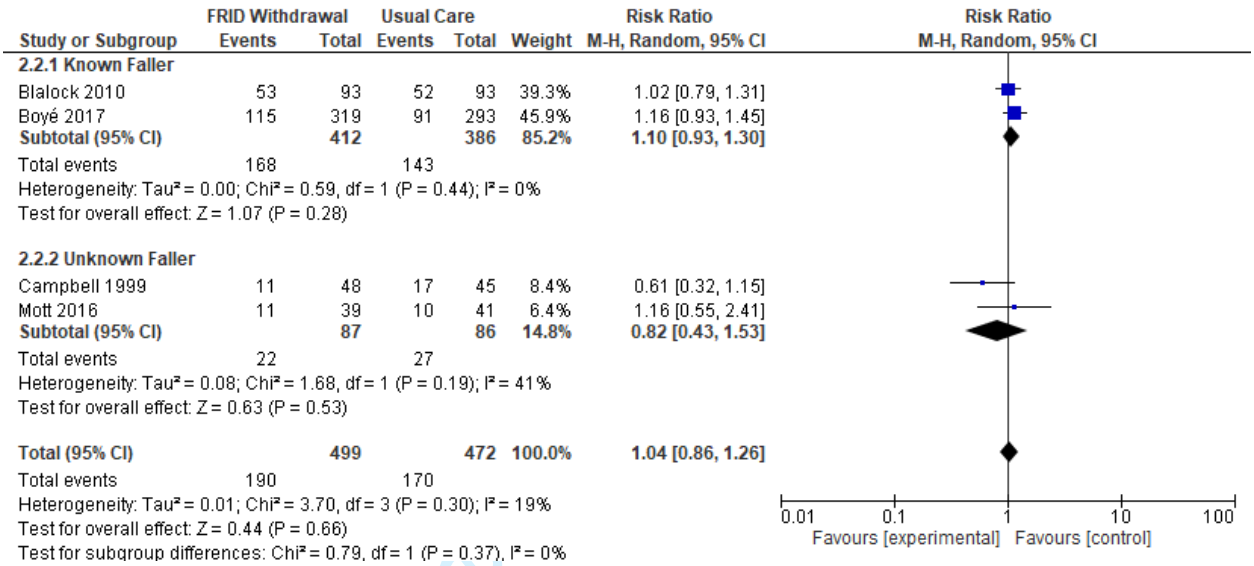


1.6 Falls Rate - Observed vs. Self-Reported Falls

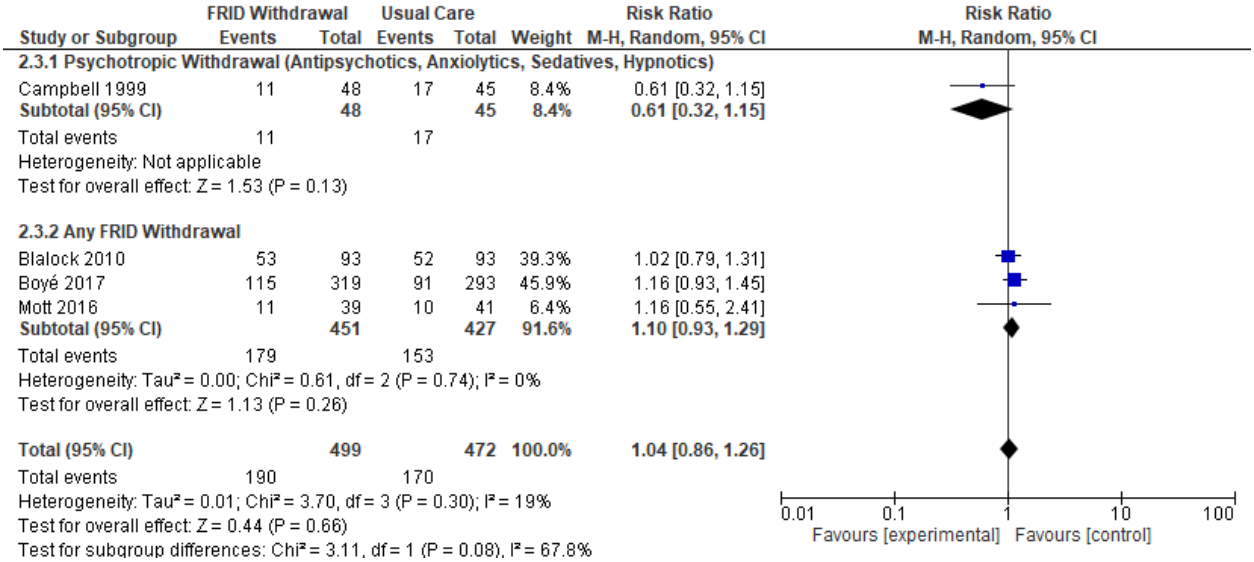
Study or Subgroup	log[Rate Ratio]	SE	FRID Withdrawal Total	Usual Care Total	Weight	Rate Ratio IV, Random, 95% CI
1.6.1 Observed Falls						
Patterson 2010	0.3549	0.1465	173	161	28.4%	1.43 [1.07, 1.90]
Subtotal (95% CI)			**173**	**161**	**28.4%**	**1.43 [1.07, 1.90]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.42 (P = 0.02)						
1.6.2 Self-Reported Falls						
Blalock 2010	0.003	0.1117	93	93	29.9%	1.00 [0.81, 1.25]
Campbell 1999	-0.8023	0.2434	48	45	23.4%	0.45 [0.28, 0.72]
Mott 2016	0.3379	0.3416	39	41	18.4%	1.40 [0.72, 2.74]
Subtotal (95% CI)			**180**	**179**	**71.6%**	**0.84 [0.47, 1.52]**
Heterogeneity: $Tau^2 = 0.21$; $Chi^2 = 10.82$, df = 2 (P = 0.004); $I^2 = 82\%$						
Test for overall effect: Z = 0.57 (P = 0.57)						
Total (95% CI)			**353**	**340**	**100.0%**	**0.98 [0.63, 1.51]**
Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 17.47$, df = 3 (P = 0.0006); $I^2 = 83\%$						
Test for overall effect: Z = 0.11 (P = 0.92)						
Test for subgroup differences: $Chi^2 = 2.49$, df = 1 (P = 0.11), $I^2 = 59.8\%$						



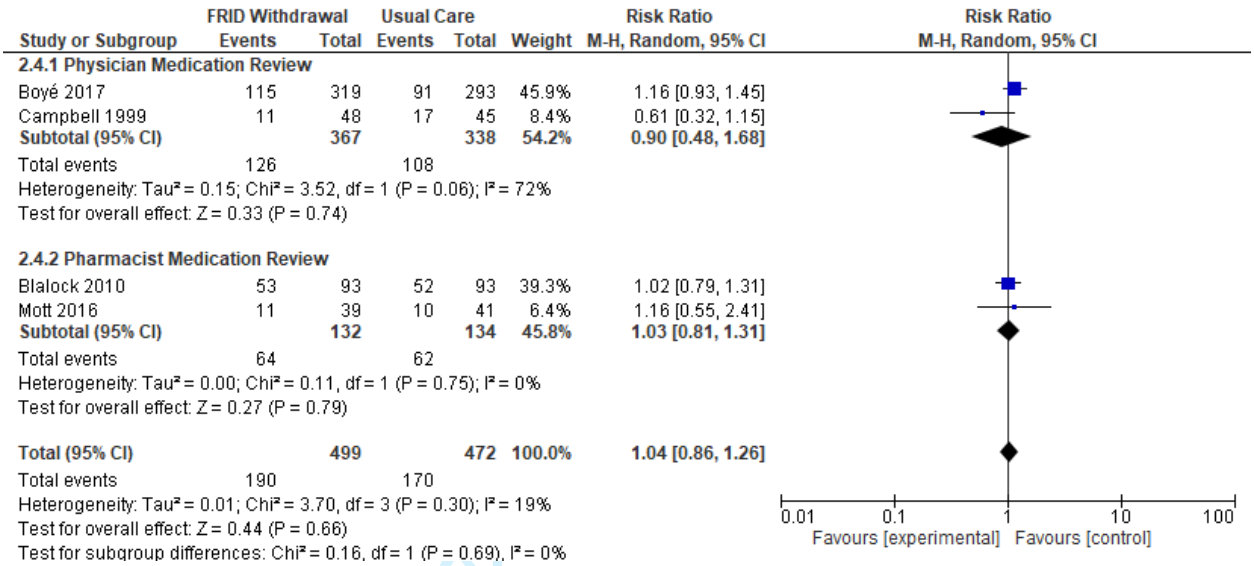
2.2 Falls Incidence - Known vs. Unknown Faller



2.3 Falls Incidence - Psychotropic Withdrawal vs. Any FRID Withdrawal



2.4 Falls Incidence - Physician vs. Pharmacist Medication Review



Supplementary Table S1: Subgroup Credibility Assessment – Clinician Medication Review

Physician vs. Pharmacist Medication Review Subgroup for Falls Rate

Design	**Criteria Met?**
Is the subgroup variable a characteristic measured at baseline or after randomization?	Yes – Variable determined at baseline
Is the effect suggested by comparisons within rather between studies?	No – Comparison between studies
Was the hypothesis specified a priori?	Yes
Was the direction of the subgroup effect specified a priori?	No
Was the subgroup effect one of a small number of hypothesized effects tested?	Yes – 1 of 5 analyses
Analysis	
Does the interaction test suggest a low likelihood that chance explains the apparent subgroup effect?	Yes – p =0.0004
Is the significant subgroup effect independent?	Yes
Context	
Is the size of the subgroup effect large?	Yes – RaR 0.45 vs. 1.20
Is the interaction consistent across studies?	No
Is the interaction consistent across closely related outcomes within the study?	No – Subgroup interaction was not seen for incidence of falls
Is there indirect evidence that supports the hypothesized interaction (biological rationale)?	No - No compelling external evidence supporting subgroup hypothesis

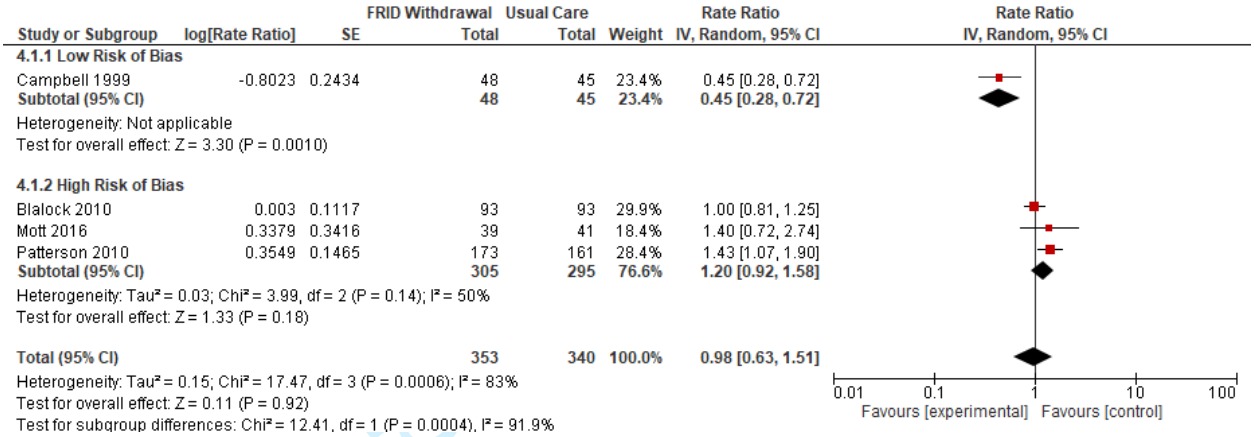
Supplementary Table S2: Subgroup Credibility Assessment – FRID Withdrawal Type

Antipsychotic vs. Any FRID Withdrawal for Falls Incidence

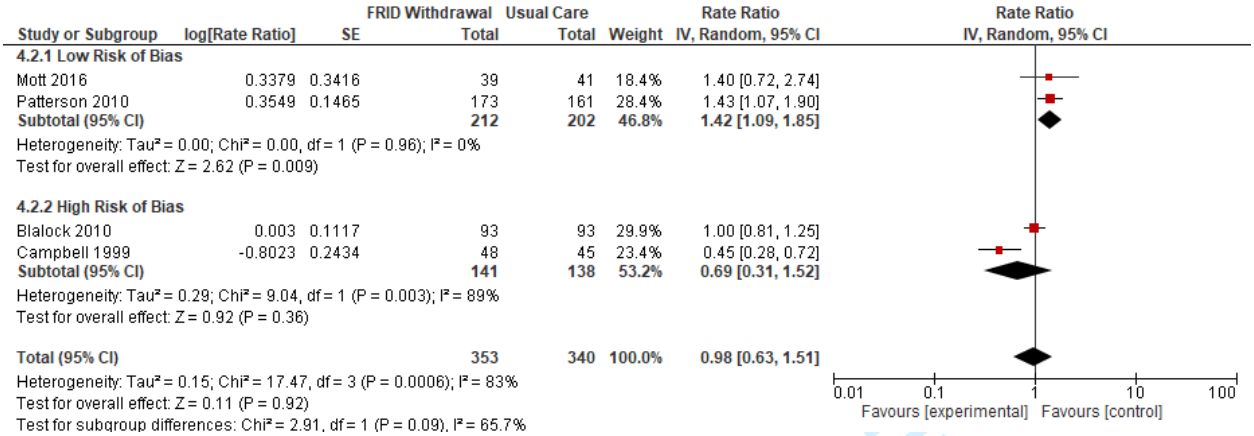
Design	Criteria Met?
Is the subgroup variable a characteristic measured at baseline or after randomization?	Yes – Variable determined at baseline
Is the effect suggested by comparisons within rather between studies?	No – Comparison between studies
Was the hypothesis specified a priori?	Yes
Was the direction of the subgroup effect specified a priori?	No
Was the subgroup effect one of a small number of hypothesized effects tested?	Yes – 1 of 3 analyses
Analysis	
Does the interaction test suggest a low likelihood that chance explains the apparent subgroup effect?	Yes – p=0.06
Is the significant subgroup effect independent?	No
Context	
Is the size of the subgroup effect large?	Yes – RR 0.61 vs. 1.14
Is the interaction consistent across studies?	No
Is the interaction consistent across closely related outcomes within the study?	No – Subgroup interaction was not seen for rate of falls
Is there indirect evidence that supports the hypothesized interaction (biological rationale)?	Yes – Antipsychotics associated with one of highest risks of falls. The withdrawal of any FRID may involve withdrawal of those with lower risks and limit potential benefit.

Supplementary Figure S3: Sensitivity Analyses

4.1 Falls Rate - Low vs. High Risk of Bias due to Blinding

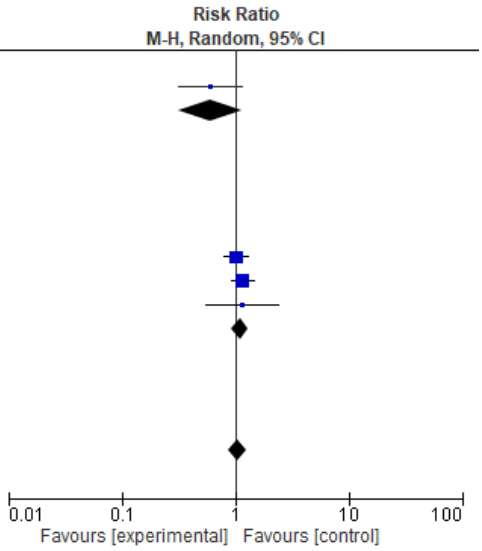


4.2 Falls Rate - Low vs. High Risk of Bias due to Attritional Bias



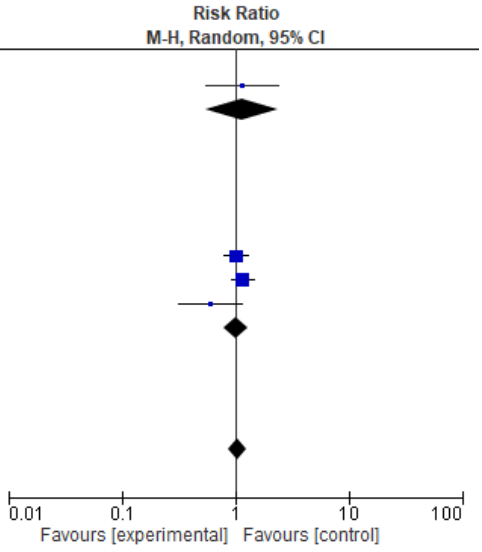
4.3 Falls Incidence - Low vs. High Risk of Bias due to Blinding

Study or Subgroup	FRID Withdrawal Events	Total	Usual Care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4.3.1 Low Risk of Bias						
Campbell 1999	11	48	17	45	8.4%	0.61 [0.32, 1.15]
Subtotal (95% CI)		**48**		**45**	**8.4%**	**0.61 [0.32, 1.15]**
Total events	11		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.53 (P = 0.13)						
4.3.2 High Risk of Bias						
Blalock 2010	53	93	52	93	39.3%	1.02 [0.79, 1.31]
Boyé 2017	115	319	91	293	45.9%	1.16 [0.93, 1.45]
Mott 2016	11	39	10	41	6.4%	1.16 [0.55, 2.41]
Subtotal (95% CI)		**451**		**427**	**91.6%**	**1.10 [0.93, 1.29]**
Total events	179		153			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.61$, df = 2 (P = 0.74); $I^2 = 0\%$						
Test for overall effect: Z = 1.13 (P = 0.26)						
Total (95% CI)		**499**		**472**	**100.0%**	**1.04 [0.86, 1.26]**
Total events	190		170			
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 3.70$, df = 3 (P = 0.30); $I^2 = 19\%$						
Test for overall effect: Z = 0.44 (P = 0.66)						
Test for subgroup differences: $Chi^2 = 3.11$, df = 1 (P = 0.08), $I^2 = 67.8\%$						



4.4 Falls Incidence - Low vs. High Risk of Bias due to Attrition Bias

Study or Subgroup	FRID Withdrawal Events	Total	Usual Care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4.4.1 Low Risk of Bias						
Mott 2016	11	39	10	41	6.4%	1.16 [0.55, 2.41]
Subtotal (95% CI)		**39**		**41**	**6.4%**	**1.16 [0.55, 2.41]**
Total events	11		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.39 (P = 0.70)						
4.4.2 High Risk of Bias						
Blalock 2010	53	93	52	93	39.3%	1.02 [0.79, 1.31]
Boyé 2017	115	319	91	293	45.9%	1.16 [0.93, 1.45]
Campbell 1999	11	48	17	45	8.4%	0.61 [0.32, 1.15]
Subtotal (95% CI)		**460**		**431**	**93.6%**	**1.02 [0.80, 1.30]**
Total events	179		160			
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 3.64$, df = 2 (P = 0.16); $I^2 = 45\%$						
Test for overall effect: Z = 0.13 (P = 0.90)						
Total (95% CI)		**499**		**472**	**100.0%**	**1.04 [0.86, 1.26]**
Total events	190		170			
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 3.70$, df = 3 (P = 0.30); $I^2 = 19\%$						
Test for overall effect: Z = 0.44 (P = 0.66)						
Test for subgroup differences: $Chi^2 = 0.11$, df = 1 (P = 0.74), $I^2 = 0\%$						

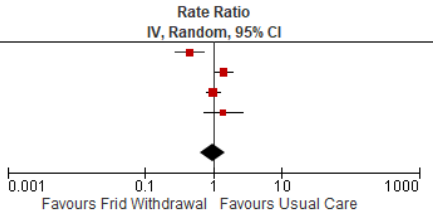


4.5 Falls Rate – Random vs. Effects Model

Random Effects Model

Study or Subgroup	log[Rate Ratio]	SE	FRID Withdrawal Total	Usual Care Total	Weight	Rate Ratio IV, Random, 95% CI	Year
Campbell 1999	-0.8023	0.2434	48	45	23.4%	0.45 [0.28, 0.72]	1999
Patterson 2010	0.3549	0.1465	173	161	28.4%	1.43 [1.07, 1.90]	2010
Blalock 2010	0.003	0.1117	93	93	29.9%	1.00 [0.81, 1.25]	2010
Mott 2016	0.3379	0.3416	39	41	18.4%	1.40 [0.72, 2.74]	2016
Total (95% CI)			**353**	**340**	**100.0%**	**0.98 [0.63, 1.51]**	

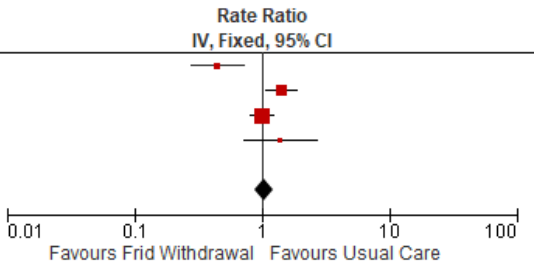
Heterogeneity: Tau² = 0.15; Chi² = 17.47, df = 3 (P = 0.0006); I² = 83%
Test for overall effect: Z = 0.11 (P = 0.92)



Fixed Effects Model

Study or Subgroup	log[Rate Ratio]	SE	Weight	Rate Ratio IV, Fixed, 95% CI	Year
Campbell 1999	-0.8023	0.2434	11.1%	0.45 [0.28, 0.72]	1999
Patterson 2010	0.3549	0.1465	30.6%	1.43 [1.07, 1.90]	2010
Blalock 2010	0.003	0.1117	52.7%	1.00 [0.81, 1.25]	2010
Mott 2016	0.3379	0.3416	5.6%	1.40 [0.72, 2.74]	2016
Total (95% CI)			**100.0%**	**1.04 [0.89, 1.22]**	

Heterogeneity: Chi² = 17.47, df = 3 (P = 0.0006); I² = 83%
Test for overall effect: Z = 0.50 (P = 0.62)

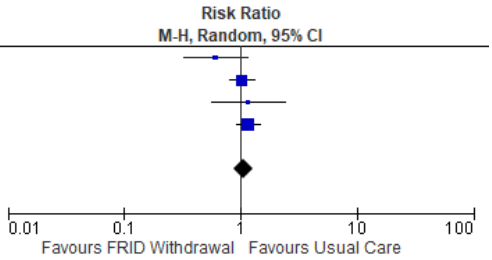


4.6 Falls Incidence – Random vs. Fixed Effects Model

Random Effects Model

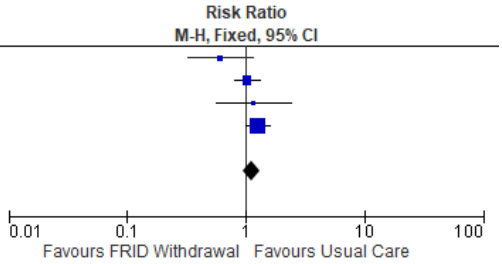
Study or Subgroup	FRID Withdrawal Events	Total	Usual Care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Campbell 1999	11	48	17	45	8.4%	0.61 [0.32, 1.15]	1999
Blalock 2010	53	93	52	93	39.3%	1.02 [0.79, 1.31]	2010
Mott 2016	11	39	10	41	6.4%	1.16 [0.55, 2.41]	2016
Boyé 2017	115	319	91	293	45.9%	1.16 [0.93, 1.45]	2017
Total (95% CI)		**499**		**472**	**100.0%**	**1.04 [0.86, 1.26]**	
Total events	190		170				

Heterogeneity: Tau² = 0.01; Chi² = 3.70, df = 3 (P = 0.30); I² = 19%
Test for overall effect: Z = 0.44 (P = 0.66)



Study or Subgroup	FRID Withdrawal Events	Total	Usual Care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Campbell 1999	11	48	17	45	10.3%	0.61 [0.32, 1.15]	1999
Blalock 2010	53	93	52	93	30.5%	1.02 [0.79, 1.31]	2010
Mott 2016	11	39	10	41	5.7%	1.16 [0.55, 2.41]	2016
Boyé 2017	115	308	91	308	53.4%	1.26 [1.01, 1.58]	2017
Total (95% CI)		**488**		**487**	**100.0%**	**1.12 [0.95, 1.31]**	
Total events	190		170				

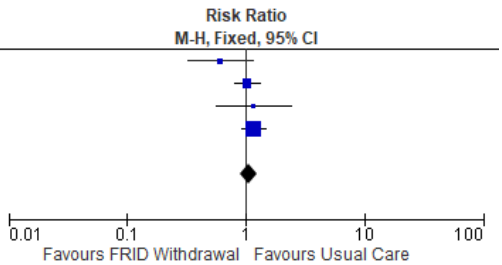
Heterogeneity: Chi² = 5.16, df = 3 (P = 0.16); I² = 42%
Test for overall effect: Z = 1.32 (P = 0.19)



Fixed Effects Model

Study or Subgroup	FRID Withdrawal Events	Total	Usual Care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Campbell 1999	11	48	17	45	10.1%	0.61 [0.32, 1.15]	1999
Blalock 2010	53	93	52	93	29.9%	1.02 [0.79, 1.31]	2010
Mott 2016	11	39	10	41	5.6%	1.16 [0.55, 2.41]	2016
Boyé 2017	115	319	91	293	54.5%	1.16 [0.93, 1.45]	2017
Total (95% CI)		**499**		**472**	**100.0%**	**1.06 [0.90, 1.25]**	
Total events	190		170				

Heterogeneity: Chi² = 3.70, df = 3 (P = 0.30); I² = 19%
Test for overall effect: Z = 0.74 (P = 0.46)



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary Figure S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8-9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8-9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9-10

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9-10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9-10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10 Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10-11 Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13-14 Figure 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12-13, Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12-13 Figure 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	15-16 Table 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	14-15
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	17-20
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	20-21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	21
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	22

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097