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

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3 **TITLE:** Deprescribing Fall-Risk-Increasing Drugs (FRIDs) for the Prevention of Falls and
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5 Fall-related Complications: A Systematic Review and Meta-analysis
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10 **AUTHORS:** Justin Lee, BScPhm, ACPR, MD^{1,2,3}

11
12 Ahmed Negm, MD, MSc, PhD^{3,4}

13
14 Ryan Peters, BSc, MD⁵

15
16 Eric Wong, BSc, MD⁶

17
18 Anne Holbrook, MD, PharmD, MSc^{2,7}
19
20
21
22
23

24 ¹Division of Geriatric Medicine, Department of Medicine, McMaster University, Hamilton,
25 Ontario, Canada

26 ²Department of Health Research Methods, Evidence, and Impact, McMaster University,
27 Hamilton,
28 Ontario, Canada

29 ³Geriatric Education and Research in Aging Sciences (GERAS) Centre, Hamilton, Ontario,
30 Canada

31 ⁴School of Rehabilitation Sciences, Faculty of Health Sciences, McMaster University, Hamilton
32 Ontario, Canada;

33 ⁵Michael DeGroote School of Medicine, McMaster University, Hamilton, Ontario, Canada

34 ⁶Division of Geriatric Medicine, Department of Medicine, University of Toronto, Toronto,
35 Ontario, Canada

36 ⁷Division of Clinical Pharmacology and Toxicology, Department of Medicine, McMaster
37 University, Hamilton, Ontario, Canada
38
39
40

41 **CORRESPONDING AUTHOR:** Justin Lee
42 Geriatric Education and Research in Aging Sciences Centre
43 88 Maplewood Avenue, Room 158
44 Hamilton, Ontario, Canada L8M 1W9
45 Email: justin.lee@medportal.ca
46 Telephone: (905) 521-2100
47
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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

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3 of falls (risk difference [RD] 0.01, 95% CI -0.06 to 0.09; relative risk [RR] 1.04, 95% CI 0.86 to
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5 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-
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7 up period. No trials evaluated the impact of deprescribing FRIDs on fall-related fractures or
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9 hospitalizations.
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14 **Conclusion:** There is a paucity of robust high-quality evidence to support or refute that a FRID
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16 deprescribing strategy is effective at preventing falls or falls-related injury in older adults.
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18 Although there may be other reasons to deprescribe FRIDs, our systematic review found that it
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20 may result in little to no difference in the rate or risk of falls.
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26 **Registration:** PROSPERO CRD42016040203
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33 withdrawal, Seniors, Older Adults, Systematic review
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38 **Word Count: 298**
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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.

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3 Despite limited evidence of effectiveness, deprescribing medications known as “fall-risk
4 increasing drugs” (FRIDs) is common practice and typically included in both multifactorial and
5 single intervention strategies. The justification is based on the belief that certain medications
6 increase the risk for falls. These include anti-hypertensives, anti-arrhythmics, anti-cholinergics,
7 anti-histamines, sedatives-hypnotics, anti-psychotics, anti-depressants, opioids and NSAIDs.[9–
8 11] This evidence is based primarily on retrospective observational data with limited adjustment
9 for confounders, dosage or duration of therapy. It is therefore unclear whether the associated
10 increase in falls is truly related to such drug use versus the underlying conditions or patients for
11 which the drugs are treating.
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24 To justify the common practice of deprescribing FRIDs, confirmation of its effectiveness
25 as a fall prevention strategy in older adults is needed. To the best of our knowledge, no previous
26 systematic review has addressed this specific question nor incorporated new data from the largest
27 RCT of FRID withdrawal to date.[12] We therefore conducted this systematic review to evaluate
28 the deprescribing of FRIDs to prevent falls and clarify its evidence base.
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38 **METHODS**

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

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3 MEDLINE, EMBASE, CINAHL and the Cochrane Central Register of Controlled Trials
4 (CENTRAL) electronic databases were searched from inception to March 31, 2019 using a
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6 combination of Medical Subject Headings, controlled and free-text terms synonymous for the
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8 intervention. The MEDLINE search strategy is shown in Supplementary Figure S1. This strategy
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10 was modified for use in other databases.
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15 Reference lists of relevant studies, reviews and guidelines were reviewed to identify
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17 additional studies. Trial registries and geriatric medicine conference abstracts were also reviewed.
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21 **Study Eligibility Criteria**

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24 After pilot testing the eligibility criteria, pairs of reviewers independently conducted
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26 screening. A third reviewer resolved disagreements.
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29 Studies were included if they were RCTs evaluating FRID deprescribing or withdrawal
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31 with the intent of reducing falls. FRID deprescribing was defined as the planned and supervised
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33 discontinuation or dose reduction of single or multiple medications thought to independently
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35 increase falls risk.[9–11]
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38 The comparator could be usual care (i.e. no change in usual activities and/or no FRID
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40 withdrawal) or a control intervention not thought to reduce falls. Studies focused on adults aged
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42 ≥ 65 years from all settings were included. Studies involving FRID withdrawal within multi-
43
44 component interventions were excluded if the effect of FRID withdrawal could not be isolated.
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47 The primary outcomes of this review were the (1) rate of falls (defined as the total number
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49 of falls per unit of person time that falls were monitored) and (2) incidence of falls (i.e. number of
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51 fallers). Secondary outcomes included the incidence of (1) fall-related fractures, (2) fall-related
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3 injuries, (3) fall-related hospitalization, (4) adverse effects related to the withdrawal intervention
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5 (e.g. disease relapse, symptomatic withdrawal).
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10 **Data Extraction and Quality Assessment**

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12 Two reviewers independently abstracted data on general study characteristics, study
13 participants, interventions, comparisons, and outcomes using standardized electronic data
14 extraction forms. Disagreements were resolved through consensus.
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19 Two reviewed independently conducted risk of bias (RoB) assessments using the Cochrane
20 Risk of Bias tool.[16] A previously published modification to the RoB assessment was employed
21 to estimate unclearly reported study methods and allow for sensitivity analysis.[17] This
22 modification involved a structured approach where a score of “definitely low risk”, “probably low
23 risk”, “probably high risk”, or “definitely high risk” was assigned to each RoB criterion.
24 “Definitely” and “probably” scores were collapsed for both low- and high-risk of bias score.
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33 Disagreements were resolved through consensus.
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38 **Data Synthesis and Analysis**

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40 The rate of falls was reported as a rate ratio (RaR) with a 95% confidence interval (CI).
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42 Dichotomous outcomes (i.e. incidences of falls, fall-related fracture, fall-related injury, fall-related
43 hospitalization and adverse effects related to the withdrawal intervention) have been reported as
44 risk ratios (RR) with 95% CIs.
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49 We used RevMan 5.3 and the intention-to-treat principle for all statistical analyses. We
50 conducted meta-analyses using the generic inverse variance method to allow pooling of effect
51 estimates. A random effects model was used given expected between-trial variations in
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3 methodological, participant and medication characteristics between studies. We had originally
4 planned to pool data at various pre-specified time intervals, but all included studies had follow-up
5 between 6 to 12 months.
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10 We assessed heterogeneity through visual inspection of forest plots and statistical tests. A
11 two-tailed test with p-value <0.10 was considered significant for all Chi-square analyses as per
12 recommendations from the Cochrane Handbook and the I^2 was interpreted using the Cochrane
13 Collaboration thresholds.[13]
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19 Heterogeneity was explored in subgroup analyses based on five a priori hypotheses
20 (Supplementary Table S1).[15] These included differences in baseline propensity for falls as
21 influenced by (1) a history of recurrent falls (e.g., known faller or not) or (2) place of residence or
22 care (e.g., community, long-term care); differences in the intervention as influenced by (3) specific
23 medication class(es) chosen for withdrawal and (4) preceding medication review by clinician for
24 FRID withdrawal appropriateness; as well as differences in methodology based on (5) definitions
25 used for “falls” (e.g., observed vs. self-reported). We assessed the credibility of any apparent
26 subgroup effects using eleven previously published criteria recommended by the Cochrane
27 Handbook.[18]
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40 A priori sensitivity analyses were conducted to explore the impact of low vs. high RoB
41 based on blinding and attrition. Studies did not report per-protocol results that would allow for our
42 planned intention-to-treat vs. per-protocol sensitivity analysis. The impact of using a fixed vs.
43 random effects model was explored in a post hoc sensitivity analysis.
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49 The confidence in effect estimates for each reported outcome was assessed using the
50 Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.[19]
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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 ($\kappa=0.79$, 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	<ol style="list-style-type: none"> 1) Community setting 2) Age \geq 65 3) Speak, read English 4) \geq 4 prescription medications 5) \geq 1 high falls-risk medication 6) \geq 1 fall not attributable to syncope within 1 year preceding randomization 	186 (93 I/93 C)	74.8 (6.9)	<ol style="list-style-type: none"> 1) Pharmacist medication review 2) Physician coordinated medication changes 3) Fall brochure, home safety checklist 	<ol style="list-style-type: none"> 1) Fall brochure, home safety checklist 	<ol style="list-style-type: none"> 1) Rate of falls 2) Incidence of falls
Campbell et al, 1999 [22]	RCT	<ol style="list-style-type: none"> 1) Community setting 2) Age \geq 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)	<u>Arm 1</u> <ol style="list-style-type: none"> 1) Withdrawal of psychotropic medication over 14 weeks 2) Placebo substitution 3) Home exercise programme <u>Arm 2</u> <ol style="list-style-type: none"> 1) Psychotropic medication withdrawal 2) Placebo substitution 3) No home exercise programme 	<u>Arm 3</u> <ol style="list-style-type: none"> 1) No change in psychotropic medication 2) Home exercise programme <u>Arm 4</u> <ol style="list-style-type: none"> 1) No change in psychotropic medication 2) No exercise programme 	<ol style="list-style-type: none"> 1) Rate of falls 2) Incidence of falls
Mott et al, 2016 [23]	Cluster RCT	<ol style="list-style-type: none"> 1) Community setting 2) Age \geq 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)	<ol style="list-style-type: none"> 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 	<ol style="list-style-type: none"> 1) Medications in falls pamphlet 	<ol style="list-style-type: none"> 1) Rate of falls 2) Incidence of falls
Patterson et al, 2010 [24]	Cluster RCT	<ol style="list-style-type: none"> 1) Nursing home setting with \geq 30 beds; not exclusive care of terminally ill 2) Age \geq 65 	334 (173 I/161 C)	82.7 (8.4)	<ol style="list-style-type: none"> 1) Monthly medication review via pharmacist for appropriateness 2) Nurse and prescriber collaboration to improve medications 	<ol style="list-style-type: none"> 1) Usual care 	<ol style="list-style-type: none"> 1) Rate of falls
Boyé et al, 2017 [12]	RCT	<ol style="list-style-type: none"> 1) Acute care emergency department setting; attended due to fall incident 2) Age \geq 65 3) \geq 1 FRID for \geq 2 weeks prior to the fall 4) MMSE \geq 21/30 5) Ambulates independently 6) Community dwelling 7) Informed consent by patient 	612 (319 I/293 C)	80.2 (7.3)	<ol style="list-style-type: none"> 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 	<ol style="list-style-type: none"> 1) Usual care 	<ol style="list-style-type: none"> 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

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3 Three studies were individually randomized, while two studies were cluster randomized by either
4 nursing home or health centre. Studies ranged in size from 80 to 612 participants. With exception
5 of one study[23], studies were multi-centre involving 144 sites and 4 countries. All were conducted
6 in the community setting except for one conducted in long-term care.[24] Follow-up periods
7 ranged from 6 to 12 months.
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11 Overall, there were 1305 participants across all trials. Most were female (>70%) and had a
12 falls history (78.9%). Several key confounders were not reported in the studies including: (1)
13 baseline number and types of FRIDs, (2) baseline number of medications, and (3) baseline number
14 and types of co-morbidities. All these factors are thought to potentially modify falls risk.[25,26]
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17 All interventions included a preceding assessment for FRID deprescribing appropriateness.
18 This was conducted by physicians in 2 trials and pharmacists in 3 trials. Three trials tried to
19 withdraw any FRID, while others focused on sedative-hypnotics, antipsychotics, or
20 antidepressants. Successful discontinuation and adherence to deprescribing protocols were low in
21 all studies. Rates of complete discontinuation of at least one FRID ranged from 10 to 40%.
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24 In terms of our study outcomes, 4 trials measured the rate of falls and 4 measured falls
25 incidence. One trial reported fall-related injuries.[21] Fall-related fractures, fall-related
26 hospitalization or deprescribing-related adverse effects were not measured by any of the trials.
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33 34 35 36 37 38 39 40 41 42 43 44 **Summary of Findings**

45 46 47 **Rate and Incidence of Falls**

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49 Four studies reported the effect of deprescribing FRIDs on the rate of falls. Deprescribing
50 FRIDs did not reduce the rate of falling (RaR 0.98, 95% CI 0.63 to 1.51; Figure 2 – Analysis 1.1).
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3 Considerable statistical heterogeneity was present ($\chi^2=17.47$, $p=0.0006$, $I^2=83\%$) and subsequently
4 explored in subgroup analysis.
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8 Four studies reported the effect of deprescribing FRIDs on the risk of falls as measured by
9 falls incidence. Deprescribing FRIDs did not reduce the incidence of falls (RR 1.04, 95% CI 0.86
10 to 1.26, $I^2 = 19\%$, $\chi^2=3.70$, $p = 0.30$; Figure 2 – Analysis 2.1). In absolute terms, there was a non-
11 significant risk difference increase of 0.01 (95% CI -0.06 to 0.09, $I^2 = 22\%$, $p=0.76$; Figure 2 –
12 Analysis 2.2)
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19 20 21 ***Rate of Injurious Falls*** 22

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24 One trial reported the effect of deprescribing FRIDs on fall-related injuries.[21]
25 Deprescribing FRIDs did not reduce the rate of fall-related injuries (RaR 0.89, 95% CI 0.57 to
26 1.39; Figure 2 – Analysis 3.1). This trial did not report data that would allow for any of our pre-
27 planned subgroup analyses.
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33 34 35 **Risk of Bias Assessment** 36

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38 Figure 3 summarizes our RoB assessments. All studies were deemed high risk of bias in at
39 least one domain. The overall mean weighted kappa across all assessments was 0.67 (moderate
40 agreement). For individual RoB assessments, kappa ranged from 0 to 0.85. Inter-rater agreement
41 is actually higher than indicated by the calculated scores due the “kappa co-efficient
42 paradox”. [27,28] Low kappas (e.g. $\kappa=0$) occurred despite high levels of observed agreement (e.g.
43 $\geq 80\%$ agreement) for two RoB assessments. True agreement is falsely attributed to chance
44 agreement by the kappa calculation when there is substantial imbalance in marginal ratings.
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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

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3 of performance bias were limited to one trial with less than 100 participants, and data from trials with
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5 low risk of attrition bias were limited to two trials with less than 450 participants overall.
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8 A post-hoc sensitivity analysis examining the impact of using a fixed vs. random effects
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10 model did not change conclusions regarding the effect of de-prescribing FRIDs on the rate or
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12 incidence of falls.
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14 15 16 17 **Quality of Evidence**

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19 The GRADE evidence profile is shown in Table 2.
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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)	-	⊕○○○ VERY LOW	IMPORTANT
								33.7%				
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

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3 We judged the quality of evidence to be low or very low for all outcomes (falls rates, falls incidence
4 and fall-related injuries) after rating down for risk of bias, inconsistency and imprecision.
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8 We believe the optimal information size (OIS) to make definitive conclusions on the effect
9
10 of deprescribing FRIDs has not yet been met as the body of evidence is based on fewer than 2000
11 participants and less than 400 events.[29,30] This is based on the OIS calculation figure
12 recommended by the GRADE guidelines using a well-established control falls event rate of 30%
13 described in the literature and conservative relative risk reduction (RRR) of 20% (assuming $\alpha =$
14 0.05 and $\beta = 0.2$).[30,31]
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24 **DISCUSSION**

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26 This systematic review found that there is a lack of robust high-quality evidence to support
27 or refute the deprescribing of FRIDs as an effective fall prevention strategy. Incorporating data
28 from 5 RCTs involving 1305 participants aged ≥ 65 years, our meta-analyses indicate that a FRID
29 deprescribing strategy did not significantly change the rate of falls (RaR 0.98, 95% CI 0.63 to
30 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.
31 Although the intervention focused on those medications thought to be associated with falls, the
32 results and conclusions are similar to previous systematic reviews evaluating the effect of generic
33 (non-FRID focused) medication reviews.[32]
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45 There is also a significant absence of evidence for clinically- and patient-important
46 outcomes such as fall-related injuries, fractures and hospitalizations. The only trial to date that
47 evaluated the rate of fall-related injuries did not demonstrate a statistically significant effect (RaR
48 0.89, 95% CI 0.57-1.39).[21] Our search found no trials measuring the impact on fall-related
49 fractures, fall-related hospitalizations or adverse effects related to a FRID deprescribing strategy.
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3 Based on low-quality evidence, it is unclear whether deprescribing FRIDs leads to any
4 appreciable clinically important benefit or harm. In fact, our current best effect estimates for falls
5 rate and incidence are centred around no appreciable difference (i.e. $RaR \approx 1$, $RR \approx 1$, $RD \approx 0$).
6
7 Although seemingly logical to assume, reducing risk factors may not necessarily lead to reduction
8 in falls and fall-related complications. The absence of change in the incidence of hip fractures after
9
10 statewide regulatory action on benzodiazepine prescribing in the United States that reduced
11 benzodiazepine use by 60.3% is a real-world example of this phenomena and the complexity of
12 exposure-outcome relationships.[33] Furthermore, it is unclear as to what degree a particular risk
13 factor or combination of risk factors (e.g. specific FRIDs) must be reduced to produce an
14 appreciable change in falls. This likely reflects the multi-factorial nature of falls and the varying
15 risk of different FRIDs.
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28 Only one trial[22] included in our review demonstrated a statistically significant benefit
29 with deprescribing FRIDs. This was also the only trial to use study capsules to operationalize
30 blinded deprescribing of FRIDs in participants, research personnel and outcome assessors. Its
31 results might be more reflective of the potential effect of deprescribing FRIDs. However, the
32 magnitude of benefit achievable in the “real world” setting may be closer to those seen in the
33 unblinded trials due to the strong mitigating factors preventing successful deprescribing.
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42 These results raise several questions about current practice and the presumed effectiveness
43 of deprescribing FRIDs as a falls prevention strategy. Given the amount of resources being
44 invested into falls prevention initiatives around the world, clinicians and organizations should re-
45 examine: (1) what is the strength of evidence supporting their current activities, (2) whether these
46 activities are cost-effective, and (3) whether resources are being appropriately prioritized to those
47 interventions shown to provide the most value. This should also be applied to what is being
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3 required of healthcare organizations in national accreditation standards (e.g. Joint Commission,
4 Accreditation Canada) to help direct and encourage optimal use of limited healthcare resources.
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8 Clinicians and policy-makers should acknowledge the lack of strong evidence for this
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10 intervention for the specific purpose of reducing falls, particularly in patients who may be very
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12 reluctant or who have strong indications for specific FRIDs. As with prescribing medications,
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14 deprescribing is a skill and comes with the potential for harm as well as benefit.[34] Thoughtful
15
16 consideration of the goals, appropriateness and safety of deprescribing is important. Despite
17
18 insufficient evidence to support or refute the deprescribing of FRIDs for falls prevention, it should
19
20 be noted that there may be other reasons to deprescribe these medications. These include avoidance
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22 of adverse drug events, improvements in cognition, increased medication adherence and drug costs
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24 savings.
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28 Our review highlights the need for future FRID deprescribing trials that evaluate patient-
29
30 important outcomes (e.g. injuries, fractures and hospitalizations). Greater attention to optimal
31
32 design and reporting is needed to minimize risk of bias. Examples include improved reporting of
33
34 confounding baseline characteristics and intervention fidelity (e.g. number and types of FRIDs,
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36 degree and duration of dose reduction). Deprescribing is challenging and extra measures are likely
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38 needed to improve successful intervention adherence and follow-up.
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44 **STRENGTHS AND LIMITATIONS**

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47 Our review has limitations. There was variation in the operationalization of FRID
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49 deprescribing and degree of success achieved (e.g. dose reduction only, completion
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51 discontinuation, non-adherence). This presumably makes the detection of any potential benefit less
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53 likely and our conclusions more conservative. However, the effect estimates are likely more
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3 indicative of what might be expected outside of the research setting. These phenomena likely
4 represent the real-life challenges of deprescribing (especially with certain types of FRIDs such as
5 psychotropics or opioids). Moreover, our ability to assess for confounders modifying falls risk was
6 limited due to inconsistent reporting of relevant baseline characteristics and lack of patient-level
7 data. Lastly, our ability to make definitive conclusions is limited because the total sample size
8 across studies for each outcome did not yet meet our calculated estimate for the required optimal
9 information size.
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19 Our review has several strengths. First, our search was comprehensive and we included a
20 rigorous grey literature search for unpublished studies. Second, we employed optimal analytical
21 and interpretational approaches including duplicate assessment, subgroup credibility criteria and
22 optimal information size considerations. Third, unlike previous medication-focused reviews, we
23 applied the GRADE approach to assess the quality of evidence and our degree of confidence in
24 the results.
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35 CONCLUSIONS

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37 Our systematic review found that deprescribing FRIDs results in little to no difference in
38 the rate and risk of falls or falls-related injuries, but the evidence is still sparse and very low quality.
39 Additional well-designed studies are needed to reach the optimal information size to reduce
40 uncertainty about this intervention and establish its relative importance in the range of possible
41 interventions that can be employed by clinicians and health systems to reduce falls.
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16
17 JL conceptualized the study. JL and AH designed and developed the protocol. RP and EW assisted
18 with citation review. RP and AN assisted with data extraction, risk of bias assessment and certainty
19 of evidence grading. All authors contributed to the analysis and interpretation of results. JL drafted
20 the initial manuscript and all authors contributed to its revision and final approval.
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38 **Competing Interests:**

39
40 The authors have no potential conflicts of interest to declare.
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44 **Patient Consent for Publication:**

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46 None required.
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51 **Data Sharing Statement:**

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53 No unpublished data are available.
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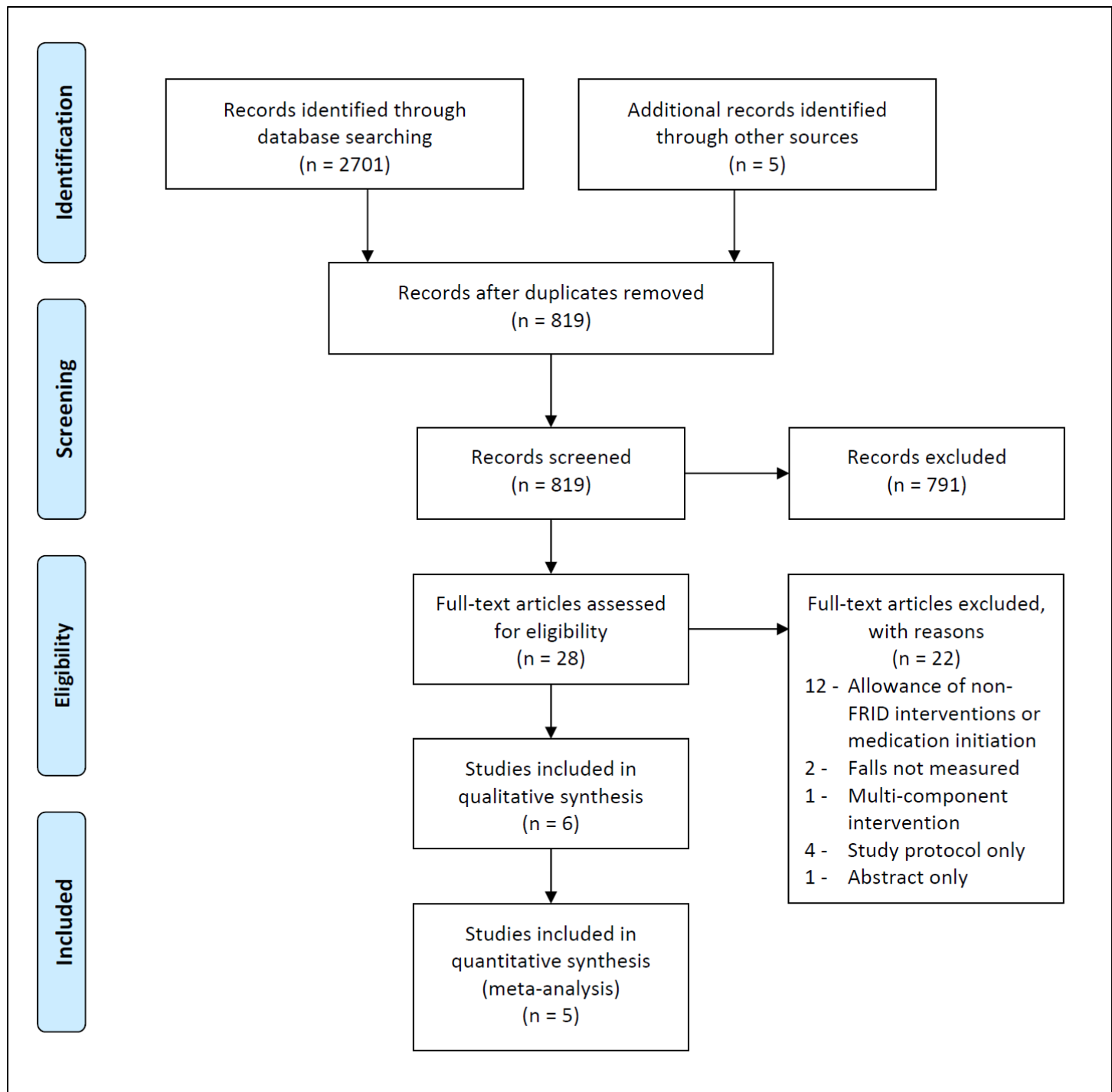
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3 **FIGURES**
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5 **Figure 1:** PRISMA Flow Diagram of Study Selection Process
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7 **Figure 2:** Forest Plots of FRID Withdrawal versus Usual Care
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9 **Figure 3:** Risk of Bias Assessments
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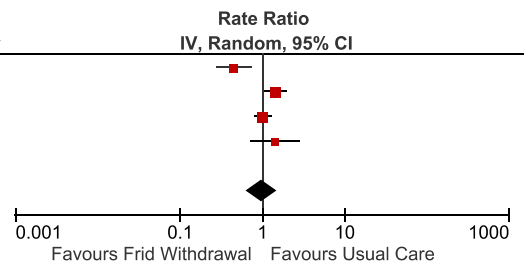


1.1 Falls Rate

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Study or Subgroup	FRID Withdrawal		Usual Care		Weight	Rate Ratio		Year
	log[Rate Ratio]	SE	Total	Total		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]	

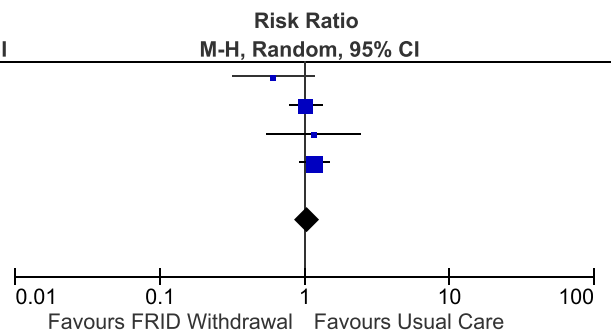
Heterogeneity: Tau² = 0.15; Chi² = 17.47, df = 3 (P = 0.0006); I² = 83%
Test for overall effect: Z = 0.11 (P = 0.92)



2.1 Falls Incidence – Risk Ratio

Study or Subgroup	FRID Withdrawal		Usual Care		Weight	Risk Ratio	
	Events	Total	Events	Total		M-H, Random, 95% CI	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]

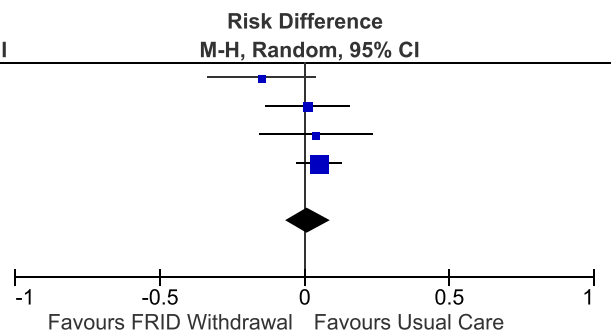
Total events: FRID Withdrawal = 190, Usual Care = 170
Heterogeneity: Tau² = 0.01; Chi² = 3.70, df = 3 (P = 0.30); I² = 19%
Test for overall effect: Z = 0.44 (P = 0.66)



2.2 Falls Incidence – Risk Difference

Study or Subgroup	FRID Withdrawal		Usual Care		Weight	Risk Difference	
	Events	Total	Events	Total		M-H, Random, 95% CI	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]

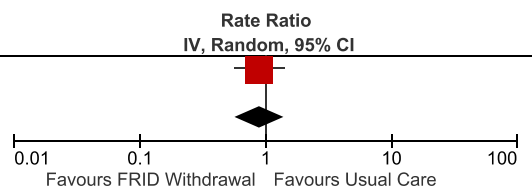
Total events: FRID Withdrawal = 190, Usual Care = 170
Heterogeneity: Tau² = 0.00; Chi² = 3.86, df = 3 (P = 0.28); I² = 22%
Test for overall effect: Z = 0.31 (P = 0.76)

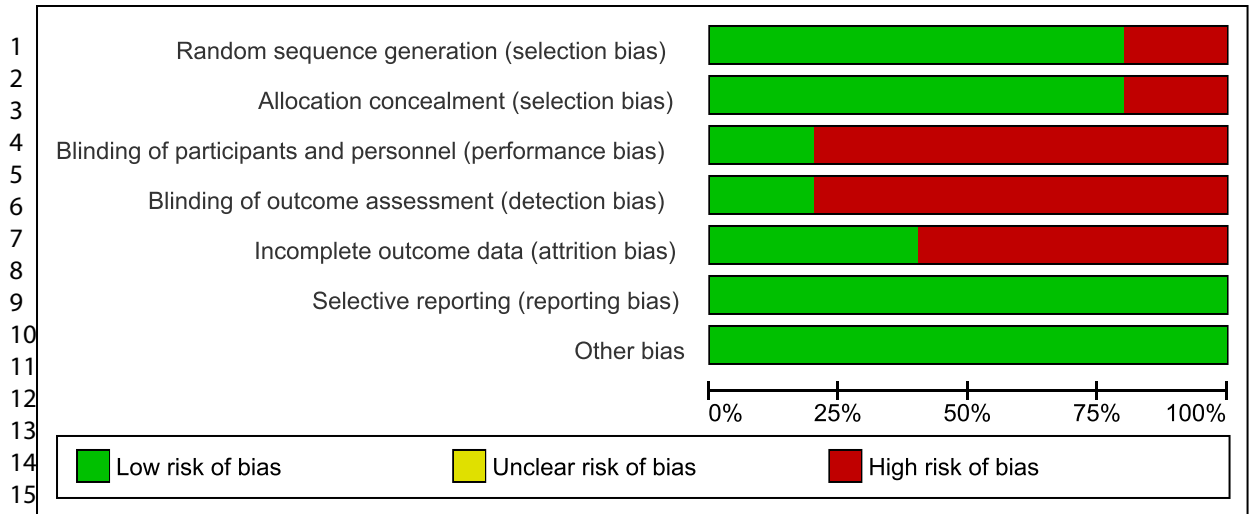


3.1 Fall-Related Injuries

Study or Subgroup	FRID Withdrawal		Usual Care		Weight	Rate Ratio		
	log[Rate Ratio]	SE	Total	Total		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)





	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
38 Blalock 2010	+	+	-	-	-	+	+
39 Boyé 2017	+	+	-	-	-	+	+
40 Campbell 1999	+	+	+	+	-	+	+
41 Mott 2016	-	-	-	-	+	+	+
42 Patterson 2010	+	+	-	-	+	+	+

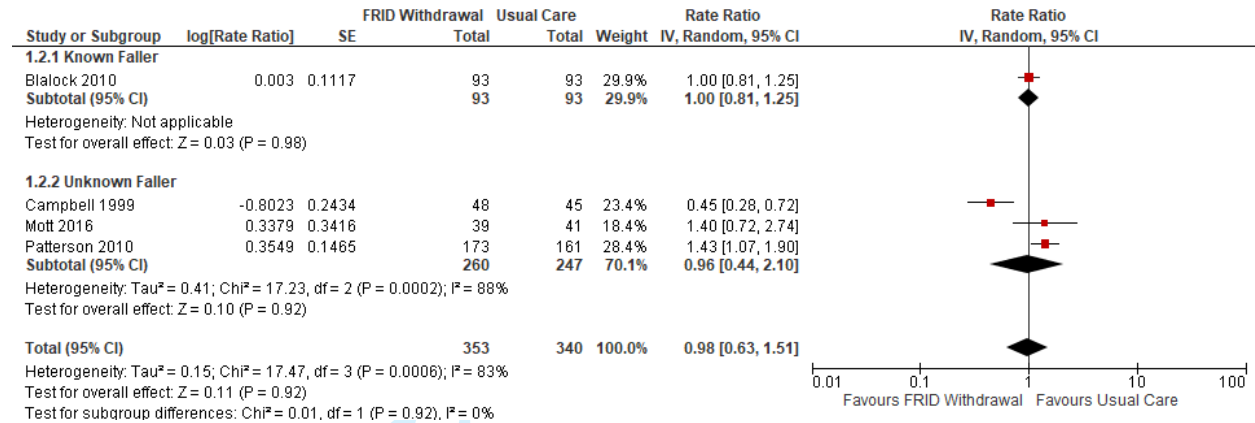
Supplementary Figure S1: OVID Medline Search Strategy

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:

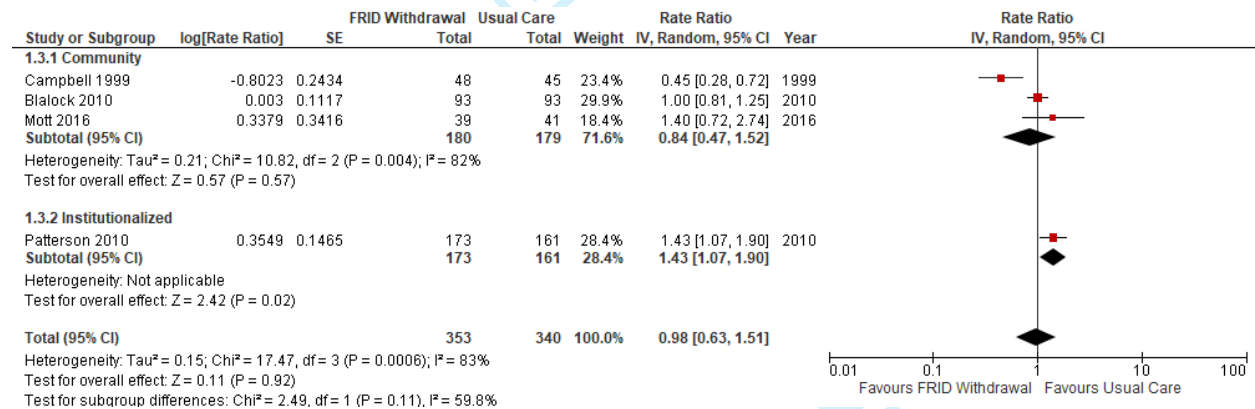
#	Searches
1	exp Accidental Falls/pc [Prevention & Control]
2	fall.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
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"/
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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.
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24	15 and 23

Supplementary Figure S2: Subgroup Analyses

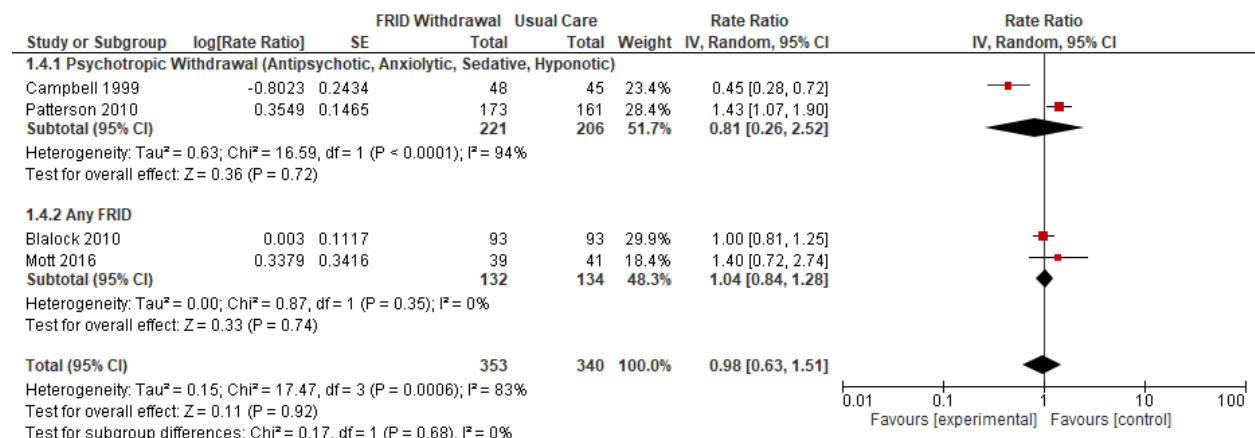
1.2 Falls Rate - Known vs. Unknown Faller



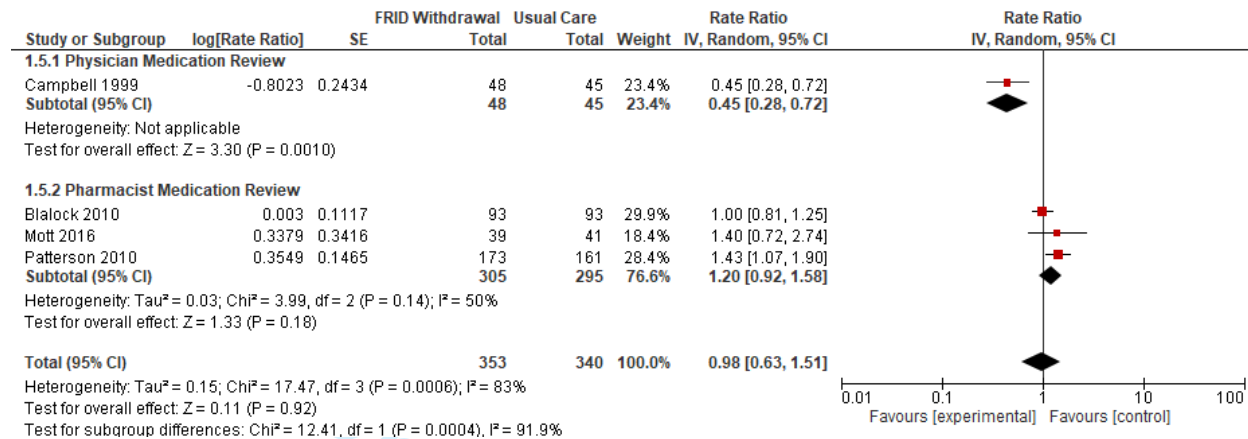
1.3 Falls Rate - Community vs. Institutionalized



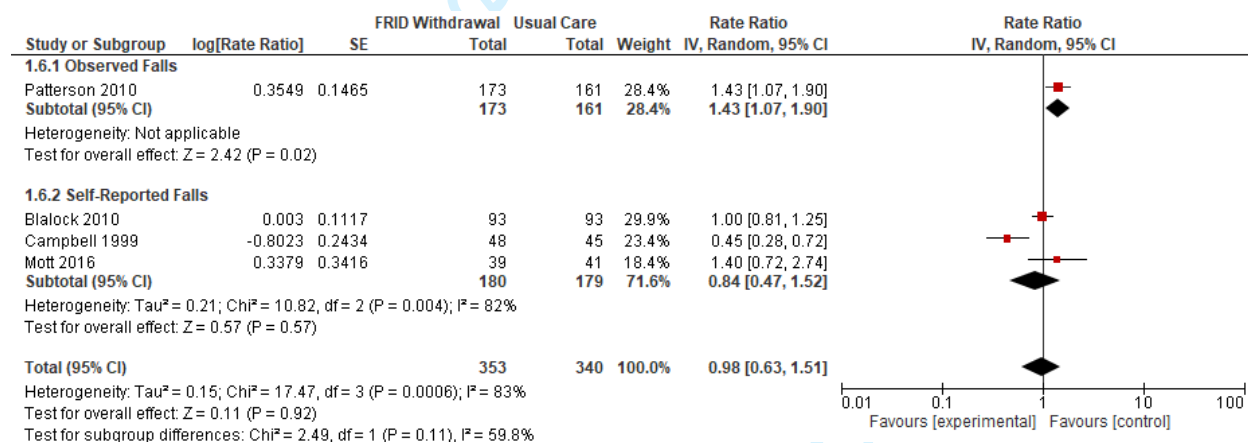
1.4 Falls Rate - Psychotropic Withdrawal vs. Any FRID Withdrawal



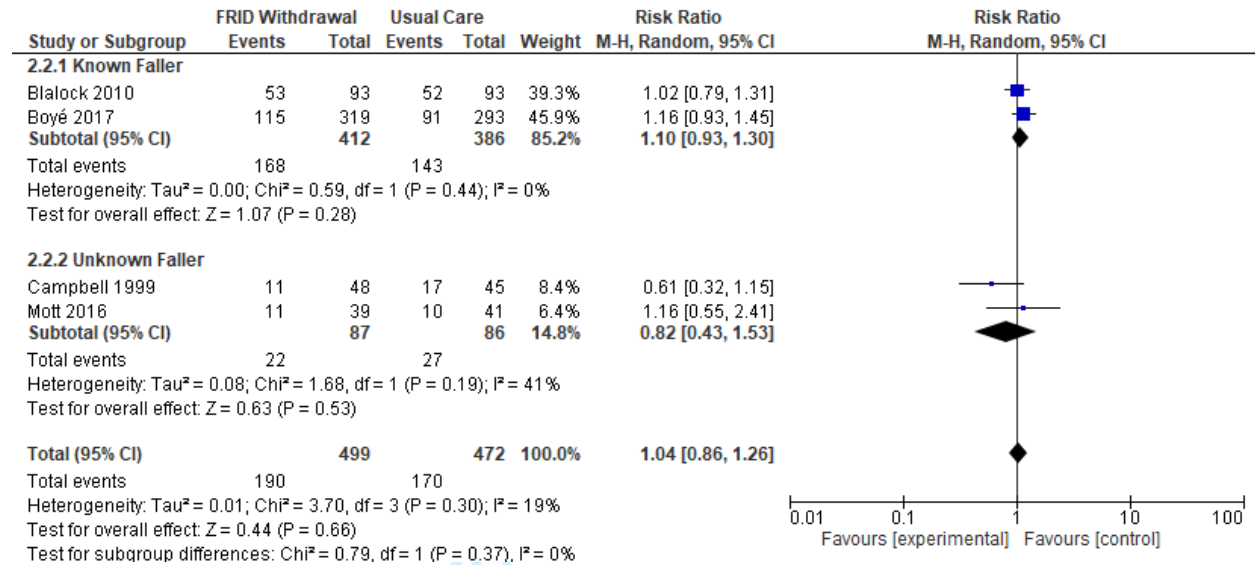
1.5 Falls Rate - Physician vs. Pharmacist Medication Review



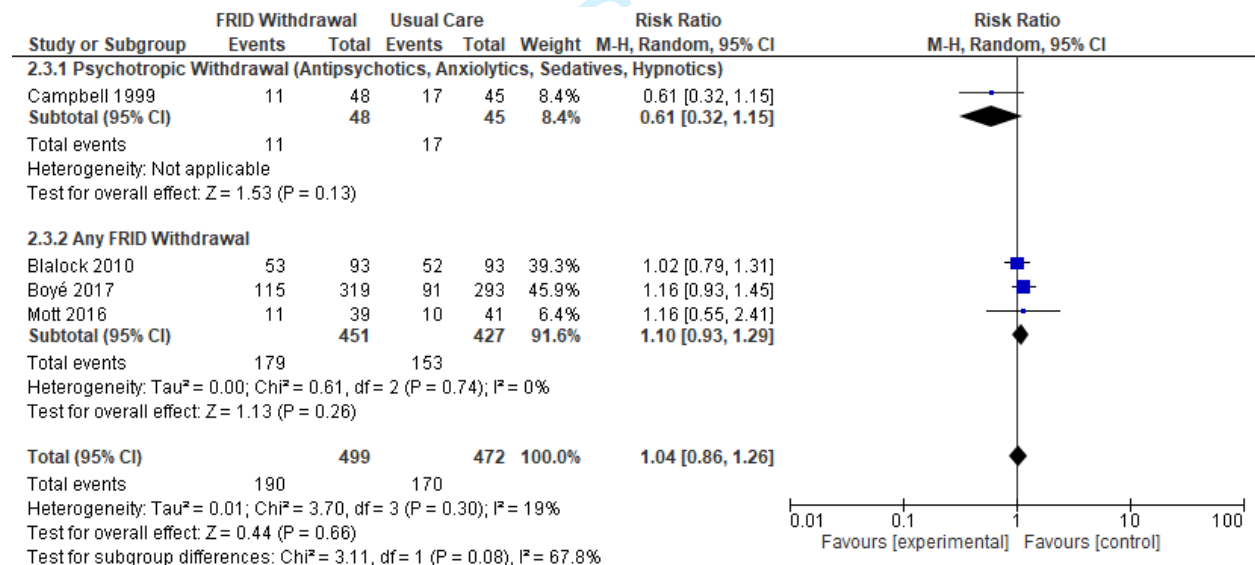
1.6 Falls Rate - Observed vs. Self-Reported Falls



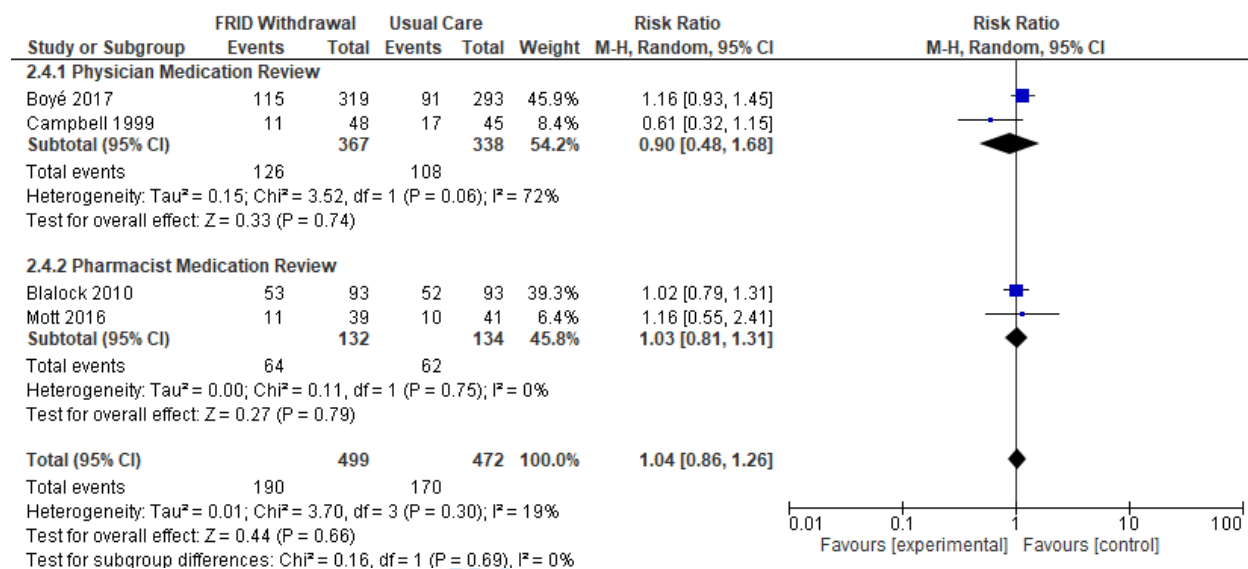
2.2 Falls Incidence - Known vs. Unknown Faller



2.3 Falls Incidence - Psychotropic Withdrawal vs. Any FRID Withdrawal



2.4 Falls Incidence - Physician vs. Pharmacist Medication Review



Peer review only

Supplementary Table S1: Subgroup Credibility Assessments**Physician vs. Pharmacist Medication Review Subgroup for Falls Rate**

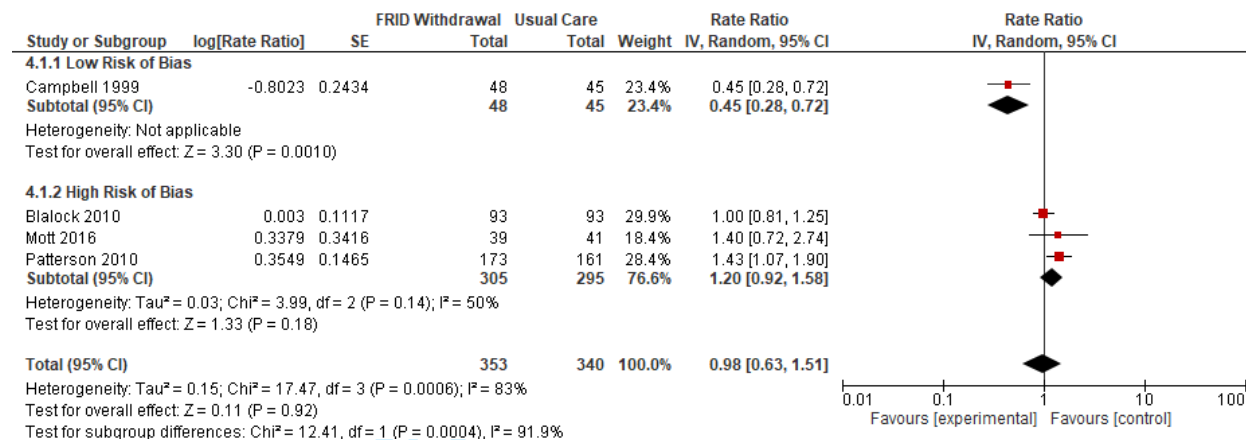
Design	Criteria Met?
Is the subgroup variable a characteristic measured at baseline or after randomization?	Yes – Variable determined at baseline
Is the effect suggested by comparisons within rather than between studies?	No – Comparison between studies
Was the hypothesis specified a priori?	Yes
Was the 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

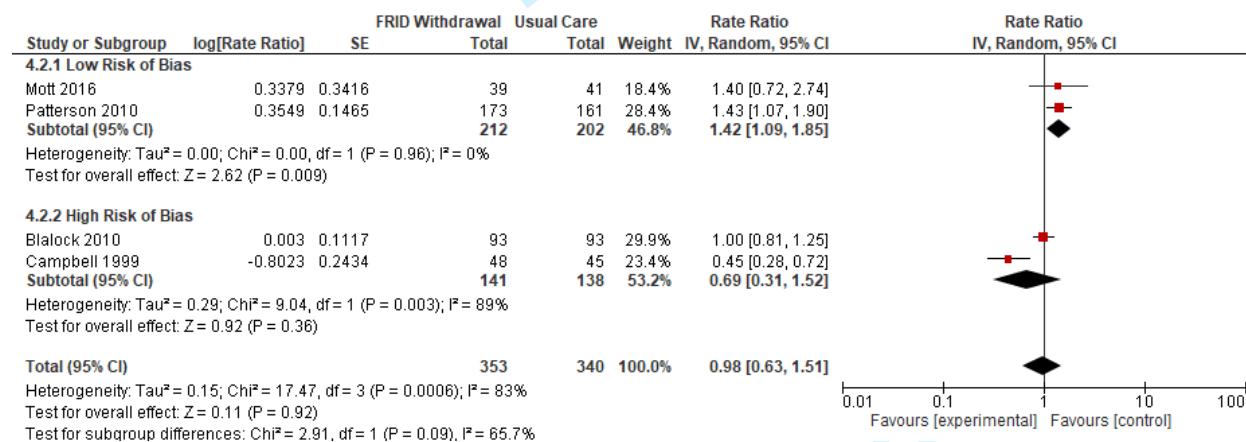
Design	Criteria Met?
Is the subgroup variable a characteristic measured at baseline or after randomization?	Yes – Variable determined at baseline
Is the effect suggested by comparisons within rather than between studies?	No – Comparison between studies
Was the hypothesis specified a priori?	Yes
Was the 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

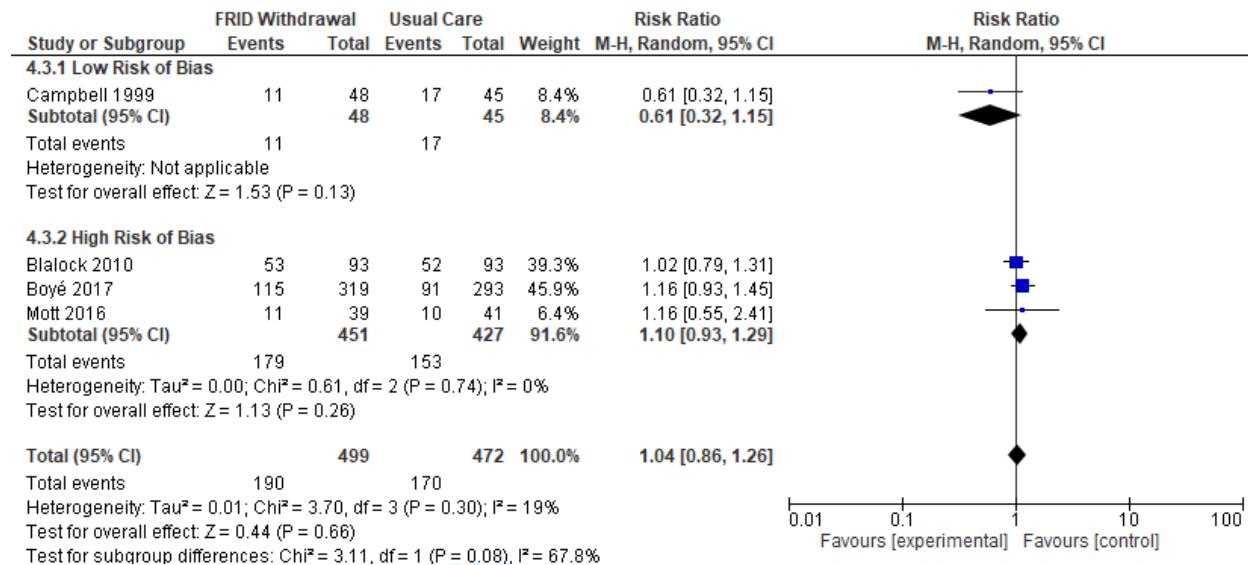
4.1 Falls Rate - Low vs. High Risk of Bias due to Blinding



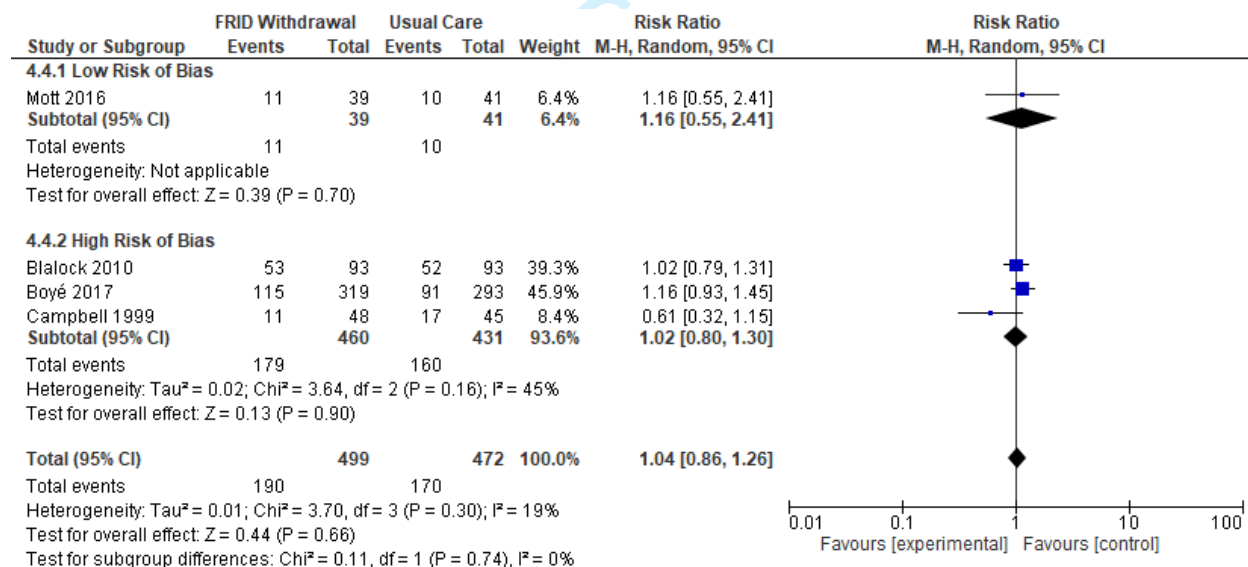
4.2 Falls Rate - Low vs. High Risk of Bias due to Attritional Bias



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

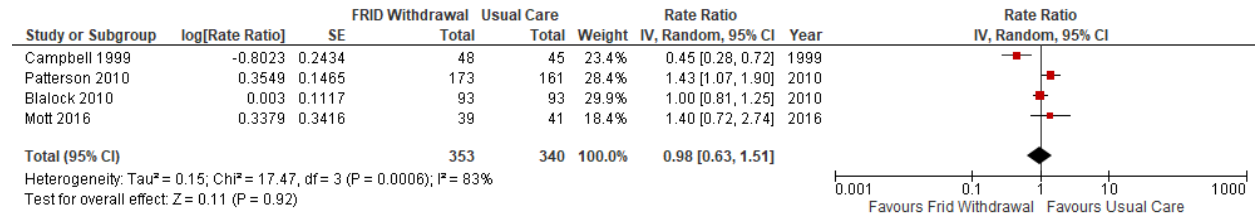


4.4 Falls Incidence - Low vs. High Risk of Bias due to Attrition Bias

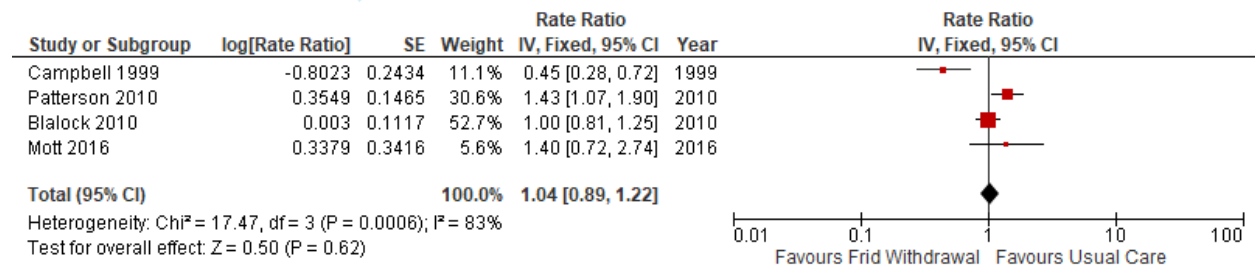


4.5 Falls Rate – Random vs. Effects Model

Random Effects Model

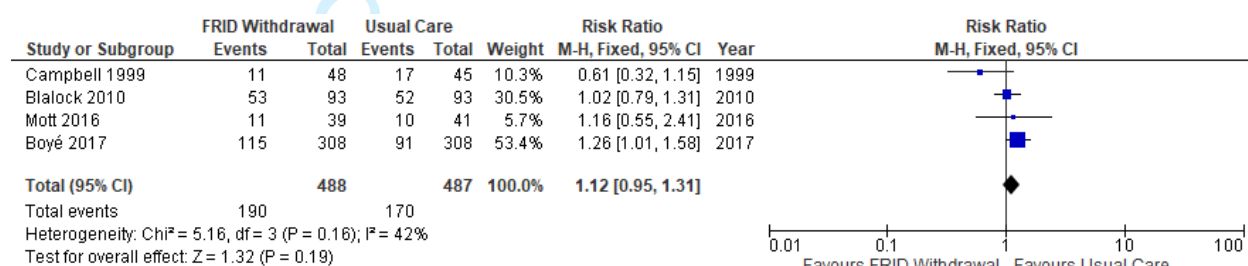
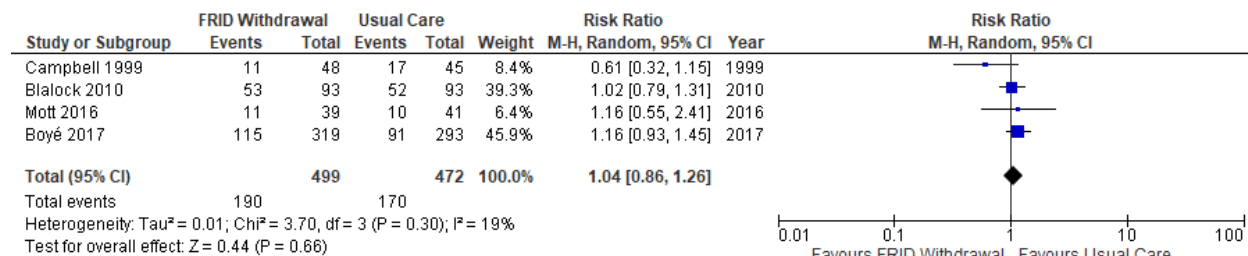


Fixed Effects Model

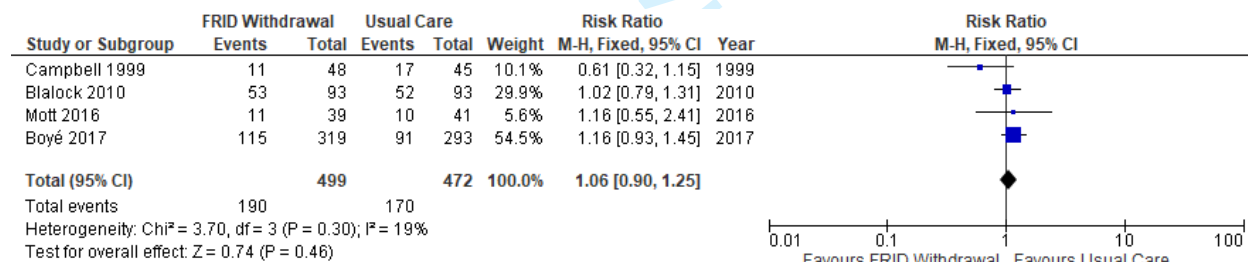


4.6 Falls Incidence – Random vs. Fixed Effects Model

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.	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

Page 1 of 2

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

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BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-035978.R1
Article Type:	Original research
Date Submitted by the Author:	12-Aug-2020
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Primary Subject Heading:	Geriatric medicine
Secondary Subject Heading:	Pharmacology and therapeutics, General practice / Family practice
Keywords:	INTERNAL MEDICINE, CLINICAL PHARMACOLOGY, GERIATRIC MEDICINE, PRIMARY CARE

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3 **TITLE:** Deprescribing Fall-Risk-Increasing Drugs (FRIDs) for the Prevention of Falls and
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5 Fall-related Complications: A Systematic Review and Meta-analysis
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10 **AUTHORS:** Justin Lee, BScPhm, ACPR, MD^{1,2,3}

11
12 Ahmed Negm, MD, MSc, PhD^{3,4}

13
14 Ryan Peters, BSc, MD⁵

15
16 Eric Wong, BSc, MD⁶

17
18 Anne Holbrook, MD, PharmD, MSc^{2,7}
19
20
21
22
23

24 ¹Division of Geriatric Medicine, Department of Medicine, McMaster University, Hamilton,
25 Ontario, Canada

26 ²Department of Health Research Methods, Evidence, and Impact, McMaster University,
27 Hamilton,
28 Ontario, Canada

29 ³Geriatric Education and Research in Aging Sciences (GERAS) Centre, Hamilton, Ontario,
30 Canada

31 ⁴School of Rehabilitation Sciences, Faculty of Health Sciences, McMaster University, Hamilton
32 Ontario, Canada;

33 ⁵Michael DeGroote School of Medicine, McMaster University, Hamilton, Ontario, Canada

34 ⁶Division of Geriatric Medicine, Department of Medicine, University of Toronto, Toronto,
35 Ontario, Canada

36 ⁷Division of Clinical Pharmacology and Toxicology, Department of Medicine, McMaster
37 University, Hamilton, Ontario, Canada
38
39
40

41 **CORRESPONDING AUTHOR:** Justin Lee
42 Geriatric Education and Research in Aging Sciences Centre
43 88 Maplewood Avenue, Room 158
44 Hamilton, Ontario, Canada L8M 1W9
45 Email: justin.lee@medportal.ca
46 Telephone: (905) 521-2100
47
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49 **MAIN TEXT WORD COUNT:** 3582 (excluding title page, abstract, references, tables)
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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

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3 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
4 of fall-related injuries (RaR 0.89, 95% CI 0.57 to 1.39) over a 6 to 12 month follow-up period. No
5
6 trials evaluated the impact of deprescribing FRIDs on fall-related fractures or hospitalizations.
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11
12 **Conclusion:** There is a paucity of robust high-quality evidence to support or refute that a FRID
13
14 deprescribing strategy is effective at preventing falls or falls-related injury in older adults.
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16 Although there may be other reasons to deprescribe FRIDs, our systematic review found that it
17
18 may result in little to no difference in the rate or risk of falls as an isolated falls reduction strategy.
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24 **Registration:** PROSPERO CRD42016040203
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28 **Key Words:** Falls, Falls prevention, Fall-risk increasing drug (FRID), Deprescribing, Medication
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30 withdrawal, Seniors, Older Adults, Systematic review
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35 **Word Count: 300**
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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.

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3 Although there is limited evidence of effectiveness, deprescribing medications known as
4 “fall-risk increasing drugs” (FRIDs) is common practice and typically included in both
5 multifactorial and single intervention strategies. The justification is based primarily on
6 observational studies that suggest certain medications are associated with increased falls risk.
7
8 These include anti-hypertensives, anti-arrhythmics, anti-cholinergics, anti-histamines, sedatives-
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10 hypnotics, anti-psychotics, anti-depressants, opioids and NSAIDs.[9–14] Although the
11
12 mechanisms are not fully understood, these drugs may influence falls risk by adversely affecting
13
14 the cardiovascular or central nervous system (e.g. orthostatic hypotension, bradycardia, sedation,
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16 sleep disturbance, confusion, dizziness).
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24 Key issues affecting the quality of this observational evidence and certainty of a causal
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26 relationship include: (1) variable adjustment for confounders, dosage or duration of therapy, (2)
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28 medication use confirmed only at baseline (but not throughout follow-up), and (3) potential
29
30 prescribing bias associated with specific medication classes. Most meta-analyses have also been
31
32 based on the pooling of unadjusted estimates and thus susceptible to bias including confounding
33
34 by indication. As a result, it is unclear whether the observed increase in falls is causally related to
35
36 such drug use versus the underlying conditions or patients for which the drugs are treating.
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40 With the aim of evaluating its effectiveness as a falls prevention strategy, we conducted
41
42 this systematic review to determine whether deprescribing FRIDs decreases the risk of falls
43
44 compared to usual care in older adults. To the best of our knowledge, no previous systematic
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46 review has addressed this specific question.
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51 **METHODS**

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

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17 MEDLINE, EMBASE, CINAHL and the Cochrane Central Register of Controlled Trials
18 (CENTRAL) electronic databases were searched from inception to August 1, 2020 using a
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21 combination of Medical Subject Headings, controlled and free-text terms synonymous for the
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24 intervention. The MEDLINE search strategy is shown in Supplementary Figure S1. This strategy
25
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27 was modified for use in other databases.

28
29 Reference lists of relevant studies, reviews and guidelines were reviewed to identify
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31
32 additional studies. Trial registries and geriatric medicine conference abstracts were also reviewed.
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35 **Study Eligibility Criteria**

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

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

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56 The comparator could be usual care (i.e. no change in usual activities and/or no FRID
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58
59 withdrawal) or a control intervention not thought to reduce falls. Studies focused on adults aged
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3 ≥65 years from all settings were included. Studies involving FRID withdrawal within multi-
4
5 component interventions were excluded if the effect of FRID withdrawal could not be isolated.
6
7

8 The primary outcomes of this review were the (1) rate of falls (defined as the total number
9
10 of falls per unit of person time that falls were monitored) and (2) incidence of falls (i.e. number of
11
12 fallers). Secondary outcomes included the incidence of (1) fall-related fractures, (2) fall-related
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14 injuries, (3) fall-related hospitalization, (4) adverse effects related to the withdrawal intervention
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16 (e.g. disease relapse, symptomatic withdrawal).
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22 **Data Extraction and Quality Assessment**

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24 Two reviewers independently abstracted data on study characteristics, participants,
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26 interventions, comparisons, and outcomes using standardized electronic data extraction forms.
27
28 Disagreements were resolved through consensus.
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31 Two reviewed independently conducted risk of bias (RoB) assessments using the Cochrane
32
33 Risk of Bias tool.[18] A previously published modification to the RoB assessment was employed
34
35 to estimate unclearly reported study methods and allow for sensitivity analysis.[19] This
36
37 modification involved a structured approach where a score of “definitely low risk”, “probably low
38
39 risk”, “probably high risk”, or “definitely high risk” was assigned to each RoB criterion.
40
41 “Definitely” and “probably” scores were collapsed for both low and high RoB scores.
42
43 Disagreements were resolved through consensus.
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49 **Data Synthesis and Analysis**

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51 The rate of falls was reported as a rate ratio (RaR) with a 95% confidence interval (CI).
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53 Dichotomous outcomes (i.e. incidences of falls, fall-related fracture, fall-related injury, fall-related
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3 hospitalization and adverse effects related to the withdrawal intervention) have been reported as
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5 risk ratios (RR) with 95% CIs.
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8 We used RevMan 5.3 and the intention-to-treat principle for all statistical analyses. We
9
10 conducted meta-analyses using the generic inverse variance method to allow pooling of effect
11
12 estimates. A random effects model was used given expected between-trial variations in
13
14 methodological, participant and medication characteristics between studies. We had originally
15
16 planned to pool data at various pre-specified time intervals, but all included studies had follow-up
17
18 between 6 to 12 months.
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21 We assessed heterogeneity through visual inspection of forest plots and statistical tests. A
22
23 two-tailed test with p-value <0.10 was considered significant for all Chi-square analyses as per
24
25 recommendations from the Cochrane Handbook and the I^2 was interpreted using the Cochrane
26
27 Collaboration thresholds.[15]
28

29
30 Heterogeneity was explored in subgroup analyses based on five a priori hypotheses
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32 (Supplementary Table S1).[17] These included differences in baseline propensity for falls as
33
34 influenced by (1) a history of recurrent falls (e.g. known faller or not) or (2) place of residence or
35
36 care (e.g. community, long-term care); differences in the intervention as influenced by (3) specific
37
38 medication class(es) chosen for withdrawal and (4) preceding medication review by a clinician for
39
40 FRID withdrawal appropriateness; as well as differences in methodology based on (5) definitions
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42 used for “falls” (e.g., observed vs. self-reported). We assessed the credibility of any apparent
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44 subgroup effects using eleven previously published criteria recommended by the Cochrane
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46 Handbook.[20]
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51 A priori sensitivity analyses were conducted to explore the impact of low vs. high RoB
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53 based on blinding and attrition. Studies did not report per-protocol results that would allow for our
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3 planned intention-to-treat vs. per-protocol sensitivity analysis. The impact of using a fixed vs.
4 random effects model was explored in a post hoc sensitivity analysis.
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8 The confidence in effect estimates for each reported outcome was assessed using the
9 Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.[21]
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13 14 **Patient and Public Involvement**

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16 Patients and the public were not involved in this review.
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20 21 **RESULTS**

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23 Of 891 citations identified, 31 were relevant for full text review and 6 met eligibility criteria
24 ($\kappa=0.79$, 95% CI 0.51-1.00, substantial agreement). One study was available as an abstract, but it
25 did not report its falls data.[22] Data were requested from the authors, but we did not receive a
26 response. The PRISMA flow diagram summarizing our search results is shown in Figure 1.
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32 33 34 35 **Study Characteristics**

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37 The included trials in our review are described in Table 1.
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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	<ol style="list-style-type: none"> 1) Community setting 2) Age \geq 65 3) Speak, read English 4) \geq 4 prescription medications 5) \geq 1 high falls-risk medication 6) \geq 1 fall not attributable to syncope within 1 year preceding randomization 	186 (93 I/93 C)	74.8 (6.9)	<ol style="list-style-type: none"> 1) Pharmacist medication review 2) Physician coordinated medication changes 3) Fall brochure, home safety checklist 	<ol style="list-style-type: none"> 1) Fall brochure, home safety checklist 	<ol style="list-style-type: none"> 1) Rate of falls 2) Incidence of falls
Campbell et al, 1999 [24]	RCT	<ol style="list-style-type: none"> 1) Community setting 2) Age \geq 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)	<u>Arm 1</u> <ol style="list-style-type: none"> 1) Withdrawal of psychotropic medication over 14 weeks 2) Placebo substitution 3) Home exercise programme <u>Arm 2</u> <ol style="list-style-type: none"> 1) Psychotropic medication withdrawal 2) Placebo substitution 3) No home exercise programme 	<u>Arm 3</u> <ol style="list-style-type: none"> 1) No change in psychotropic medication 2) Home exercise programme <u>Arm 4</u> <ol style="list-style-type: none"> 1) No change in psychotropic medication 2) No exercise programme 	<ol style="list-style-type: none"> 1) Rate of falls 2) Incidence of falls
Mott et al, 2016 [25]	Cluster RCT	<ol style="list-style-type: none"> 1) Community setting 2) Age \geq 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)	<ol style="list-style-type: none"> 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 	<ol style="list-style-type: none"> 1) Medications in falls pamphlet 	<ol style="list-style-type: none"> 1) Rate of falls 2) Incidence of falls
Patterson et al, 2010 [26]	Cluster RCT	<ol style="list-style-type: none"> 1) Nursing home setting with \geq 30 beds; not exclusive care of terminally ill 2) Age \geq 65 	334 (173 I/161 C)	82.7 (8.4)	<ol style="list-style-type: none"> 1) Monthly medication review via pharmacist for appropriateness 2) Nurse and prescriber collaboration to improve medications 	<ol style="list-style-type: none"> 1) Usual care 	<ol style="list-style-type: none"> 1) Rate of falls
Boyé et al, 2017 [27]	RCT	<ol style="list-style-type: none"> 1) Acute care emergency department setting; attended due to fall incident 2) Age \geq 65 3) \geq 1 FRID for \geq 2 weeks prior to the fall 4) MMSE \geq 21/30 5) Ambulates independently 6) Community dwelling 7) Informed consent by patient 	612 (319 I/293 C)	80.2 (7.3)	<ol style="list-style-type: none"> 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 	<ol style="list-style-type: none"> 1) Usual care 	<ol style="list-style-type: none"> 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

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3 Three studies were individually randomized, while two studies were cluster randomized by either
4 nursing home or health centre. Studies ranged in size from 80 to 612 participants. With exception
5 of one study[25], studies were multi-centre involving 144 sites and 4 countries. All were conducted
6 in the community setting except for one conducted in long-term care.[26] Follow-up periods
7 ranged from 6 to 12 months.
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11 Overall, there were 1305 participants across all trials. Most were female (>70%) and had a
12 falls history (78.9%). Several key confounders were not reported in the studies including: (1)
13 baseline number and types of FRIDs, (2) baseline number of medications, and (3) baseline number
14 and types of co-morbidities. All these factors are thought to potentially modify falls risk.[28,29]
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17 All interventions included a preceding assessment for FRID deprescribing appropriateness.
18 This was conducted by physicians in 2 trials and pharmacists in 3 trials. Three trials tried to
19 withdraw any FRID, while others focused on sedative-hypnotics, antipsychotics, or
20 antidepressants. Successful discontinuation and adherence to deprescribing protocols were low in
21 all studies. Rates of complete discontinuation of at least one FRID ranged from 10 to 40%.
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24 In terms of our study outcomes, 4 trials measured the rate of falls and 4 measured falls
25 incidence. One trial reported fall-related injuries.[23] Fall-related fractures, fall-related
26 hospitalization or deprescribing-related adverse effects were not measured by any of the trials.
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35 **Summary of Findings**

36 **Rate and Incidence of Falls**

37 Four studies reported the effect of deprescribing FRIDs on the rate of falls. Deprescribing
38 FRIDs did not reduce the rate of falling (RaR 0.98, 95% CI 0.63 to 1.51; Figure 2 – Analysis 1.1).
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3 Considerable statistical heterogeneity was present ($\chi^2=17.47$, $p=0.0006$, $I^2=83\%$) and subsequently
4 explored in subgroup analysis.
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8 Four studies reported the effect of deprescribing FRIDs on the risk of falls as measured by
9 falls incidence. Deprescribing FRIDs did not reduce the incidence of falls (RR 1.04, 95% CI 0.86
10 to 1.26, $I^2 = 19\%$, $\chi^2=3.70$, $p = 0.30$; Figure 2 – Analysis 2.1). In absolute terms, there was a non-
11 significant risk difference increase of 0.01 (95% CI -0.06 to 0.09, $I^2 = 22\%$, $p=0.76$; Figure 2 –
12 Analysis 2.2)
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19 20 21 ***Rate of Injurious Falls*** 22

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24 One trial reported the effect of deprescribing FRIDs on fall-related injuries.[23]
25 Deprescribing FRIDs did not reduce the rate of fall-related injuries (RaR 0.89, 95% CI 0.57 to
26 1.39; Figure 2 – Analysis 3.1). This trial did not report data that would allow for any of our pre-
27 planned subgroup analyses.
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33 34 35 **Risk of Bias Assessment** 36

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38 Figure 3 summarizes our RoB assessments. All studies were deemed at high risk of bias in
39 at least one domain. The overall mean weighted kappa across all assessments was 0.67 (moderate
40 agreement). For individual RoB assessments, kappa ranged from 0 to 0.85. Inter-rater agreement
41 is actually higher than indicated by the calculated scores due to the “kappa co-efficient
42 paradox”. [30,31] Low kappas (e.g. $\kappa=0$) occurred despite high levels of observed agreement (e.g.
43 $\geq 80\%$ agreement) for two RoB assessments. True agreement is falsely attributed to chance
44 agreement by the kappa calculation when there is substantial imbalance in marginal ratings.
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3 For falls rate and incidence, all studies except one[24] were judged at high risk of bias for
4 lack of blinding of participants, personnel and outcome assessors. It is unclear whether blinding
5 could have impacted behaviour or perceptions (e.g. activity risk-level, nocebo effect). Risk of
6 ascertainment bias was high in one study[26] (i.e. no standardized falls definition was used), but
7 all other studies used methods accepted to be low risk of bias (i.e. falls recorded daily on postcards
8 or calendars). Risk of attrition bias was deemed high in three studies based on high or unbalanced
9 lost to follow-up rates.[23,24,27]
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21 ***Publication Bias***

22 Since less than 10 eligible studies were found, a funnel plot was not constructed due to an
23 inability to make meaningful conclusions about publication bias.
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31 ***Subgroup Analyses and Exploration of Heterogeneity***

32 Our pre-specified subgroup analyses did not adequately explain the statistical
33 heterogeneity observed results for the rate and incidence of falls (Supplementary Figure S2).
34 Deprescribing FRIDs appeared more effective when a preceding medication review was conducted
35 by physicians compared to pharmacists ($p=0.0004$, $I^2=91.9\%$, Analysis 1.5), while psychotropic
36 withdrawal appeared more effective than strategies withdrawing any FRID ($p=0.08$, $I^2=67.8\%$,
37 Analysis 2.3). However, in both analyses, only 6 of 11 subgroup credibility criteria were met and
38 each subgroup was limited to one trial with less than 100 participants (Supplementary Table S2).
39 We, therefore, judged the credibility that these subgroup effects are real as poor and uncertain.
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3 The available data did not permit subgroup analyses by place of residence or falls
4 ascertainment method. The other subgroup analyses showed no evidence of difference beyond that
5 due to chance.
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10 11 12 **Sensitivity Analyses** 13

14 Our sensitivity analyses are shown in Supplementary Figure S3. The incorporation of trials
15 with high risk of performance bias appeared to mask the potential benefit of deprescribing FRIDs
16 on reducing the incidence and rate of falls, while the trials with high risk of attrition bias appeared
17 to mask a potential increase in falls rate with deprescribing FRIDs. These results should be
18 interpreted cautiously and definitive conclusions cannot be made. Data from trials with low risk
19 of performance bias were limited to one trial with less than 100 participants, and data from trials
20 with low risk of attrition bias were limited to two trials with less than 450 participants overall.
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30 A post-hoc sensitivity analysis examining the impact of using a fixed vs. random effects
31 model did not change conclusions regarding the effect of deprescribing FRIDs on the rate or
32 incidence of falls.
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40 **Quality of Evidence** 41

42 The GRADE evidence profile is shown in Table 2.
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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)	-	⊕○○○ VERY LOW	IMPORTANT
								33.7%				
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

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3 We judged the quality of evidence to be low or very low for all outcomes (falls rates, falls incidence
4 and fall-related injuries) after rating down for risk of bias, inconsistency and imprecision.
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8 We believe the optimal information size (OIS) to make definitive conclusions on the effect
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10 of deprescribing FRIDs has not yet been met as the body of evidence is based on fewer than 2000
11 participants and less than 400 events.[32,33] This is based on the OIS calculation figure
12 recommended by the GRADE guidelines using a well-established control falls event rate of 30%
13 described in the literature and conservative relative risk reduction (RRR) of 20% (assuming $\alpha =$
14 0.05 and $\beta = 0.2$).[33,34]
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24 **DISCUSSION**

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26 This systematic review sought to determine whether deprescribing FRIDs decreased the
27 risk of falls in older adults and found that there is a lack of robust high-quality evidence to support
28 or refute the deprescribing of FRIDs as an effective fall prevention strategy. Incorporating data
29 from 5 RCTs involving 1305 participants aged ≥ 65 years, our meta-analyses indicate that a FRID
30 deprescribing strategy did not significantly change the rate of falls (RaR 0.98, 95% CI 0.63 to
31 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.
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33 Although this intervention focuses on those medications thought to be associated with falls, the
34 conclusions are similar to previous systematic reviews evaluating the effectiveness of medication
35 reviews that had a broader focus on reducing polypharmacy and potentially inappropriate
36 prescribing (i.e. not focused solely on FRIDs).[35,36]
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49 There is also a significant absence of evidence for clinically- and patient-important
50 outcomes such as fall-related injuries, fractures and hospitalizations. The only trial to date that
51 evaluated the rate of fall-related injuries did not demonstrate a statistically significant effect (RaR
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3 0.89, 95% CI 0.57-1.39).[23] Our search found no trials measuring the impact on fall-related
4 fractures, fall-related hospitalizations or adverse effects related to a FRID deprescribing strategy.
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6 Although this may be rooted in the difficulty of conducting RCTs powered for such outcomes,
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8 their measurement and reporting are still important to inform systematic review meta-analyses that
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10 could lead to more precise estimates.
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15 Based on low-quality evidence, it is unclear whether deprescribing FRIDs as a stand-alone
16 intervention leads to any appreciable clinically important benefit or harm. Our current best effect
17 estimates for falls rate and incidence are centred around no appreciable difference (i.e. $RaR \approx 1$,
18 $RR \approx 1$, $RD \approx 0$). Although seemingly logical to assume, reducing isolated risk factors may not
19 necessarily lead to a reduction in falls and fall-related complications. The absence of change in the
20 incidence of hip fractures after statewide regulatory action on benzodiazepine prescribing in the
21 United States that reduced benzodiazepine use by 60.3% is a real-world example of this
22 phenomenon and the complexity of exposure-outcome relationships.[37]
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33 Our findings likely reflect the multi-factorial nature of falls and the varying risk of different
34 FRIDs. It is unclear as to what degree a particular risk factor or combination of risk factors (e.g.
35 specific FRIDs) must be reduced to produce an appreciable change in falls. Medications may only
36 have conditional or contributory causality to falls. It may be that medication-related interventions
37 work best in combination with other interventions or only in specific contexts.
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45 Only one trial[24] included in our review demonstrated a statistically significant benefit
46 with deprescribing FRIDs. This was also the only trial to use study capsules to operationalize
47 blinded deprescribing of FRIDs in participants, research personnel and outcome assessors. Its
48 results might be more reflective of the potential physiological effect of deprescribing FRIDs.
49 However, the magnitude of benefit achievable in the “real world” setting may be closer to those
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3 seen in the unblinded trials due to the strong psychological and behavioural factors (e.g. nocebo
4 effect) that may hinder successful deprescribing.
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8 These results raise several questions about the presumed effectiveness of deprescribing
9 FRIDs as an isolated falls prevention strategy. Given the amount of resources being invested into
10 falls prevention initiatives around the world, clinicians and organizations should examine: (1) what
11 is the strength of evidence supporting their current activities, (2) whether these activities are cost-
12 effective, and (3) whether resources are being appropriately prioritized to those interventions
13 shown to provide the most value. This should also be applied to what is being required of
14 healthcare organizations in national accreditation standards (e.g. Joint Commission, Accreditation
15 Canada) to help direct and encourage optimal use of limited healthcare resources.
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26 Clinicians and policy-makers need to consider the lack of strong evidence for deprescribing
27 FRIDs as an isolated intervention for the specific purpose of reducing falls, particularly in patients
28 who may be very reluctant or who have strong indications for specific FRIDs. FRID reduction is
29 one out of many possible interventions that need to be considered. As with prescribing medications,
30 deprescribing is a skill and comes with the potential for harm as well as benefit.[38] Thoughtful
31 consideration of the goals, appropriateness and safety of deprescribing is important.[39] Our
32 results highlight the need for a comprehensive and individualized approach to falls. Multi-
33 component interventions are ideal, but interventions may need to be prioritized depending on time,
34 resources and context.
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47 Despite insufficient evidence to support or refute the deprescribing of FRIDs for falls
48 prevention, our results do not mean that clinicians should avoid deprescribing FRIDs. There may
49 be many other reasons to deprescribe these medications. These include avoidance of adverse drug
50 events, improvements in cognition, increased medication adherence and drug costs savings. It is
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3 also unclear whether medication review and management with a broader focus on reducing
4 polypharmacy and potentially inappropriate prescribing in older adults may be beneficial in
5 preventing falls.
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10 Our review highlights the need for future FRID deprescribing trials that evaluate patient-
11 important outcomes (e.g. injuries, fractures and hospitalizations). Greater attention to optimal
12 design and reporting is needed to minimize risk of bias and enhance our interpretation of the results.
13 Examples include improved reporting of confounding baseline characteristics and intervention
14 fidelity (e.g. number and types of FRIDs, degree and duration of dose reduction). Deprescribing
15 is challenging and extra measures are likely needed to improve successful intervention adherence
16 and follow-up.
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28 **STRENGTHS AND LIMITATIONS**

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30 Our review has limitations. There was variation in the operationalization of FRID
31 deprescribing and degree of success achieved (e.g. dose reduction only, completion
32 discontinuation, non-adherence). This presumably makes the detection of any potential benefit less
33 likely and our conclusions more conservative. However, the effect estimates are likely more
34 indicative of what might be expected outside of the research setting. These phenomena likely
35 represent the real-life challenges of deprescribing (especially with certain types of FRIDs such as
36 psychotropics or opioids). Moreover, our ability to assess for confounders modifying falls risk was
37 limited due to inconsistent reporting of relevant baseline characteristics and lack of patient-level
38 data. Lastly, our ability to make definitive conclusions is limited because the total sample size
39 across studies for each outcome did not yet meet our calculated estimate for the required optimal
40 information size.
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3 Our review has several strengths. First, our search was comprehensive and we included a
4 rigorous grey literature search for unpublished studies. Second, we employed optimal analytical
5 and interpretational approaches including duplicate assessment, subgroup credibility criteria and
6 optimal information size considerations. Third, unlike previous medication-focused reviews, we
7 applied the GRADE approach to assess the quality of evidence and our degree of confidence in
8 the results.
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19 CONCLUSIONS

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

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

25
26 The authors have no potential conflicts of interest to declare.
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31 **Patient Consent for Publication:**

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33 None required.
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38 **Data Sharing Statement:**

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40 No unpublished data are available.
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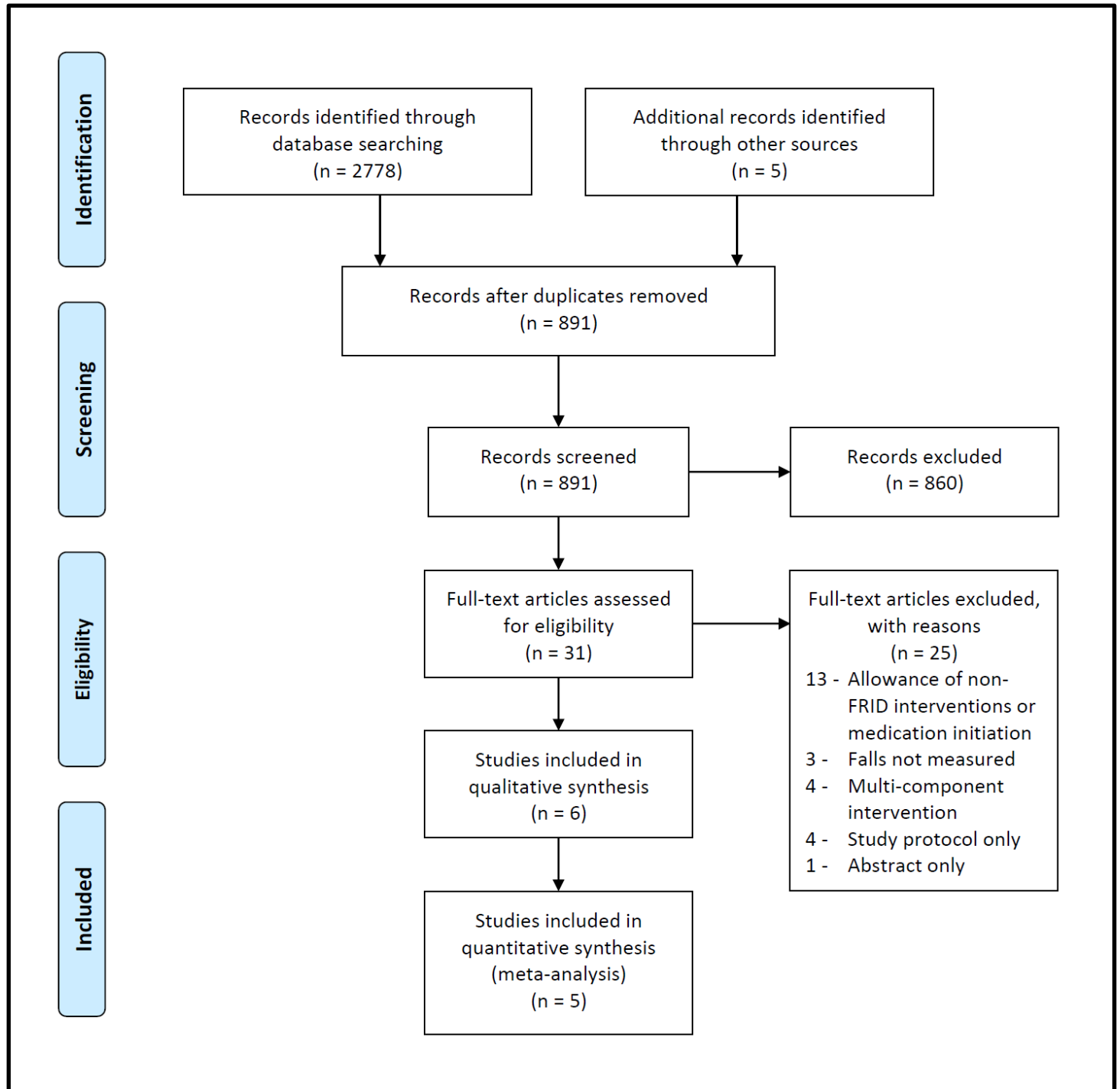
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3 **FIGURES**
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5 **Figure 1:** PRISMA Flow Diagram of Study Selection Process
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7 **Figure 2:** Forest Plots of FRID Withdrawal versus Usual Care
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9 **Figure 3:** Risk of Bias Assessments
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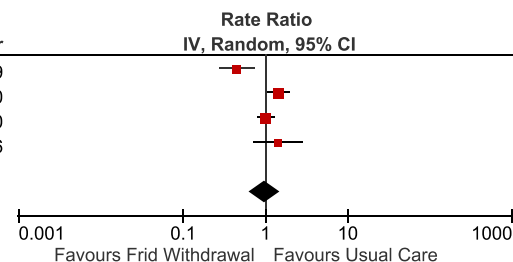


1.1 Falls Rate

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Study or Subgroup	FRID Withdrawal		Usual Care		Weight	Rate Ratio		Year
	log[Rate Ratio]	SE	Total	Total		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)

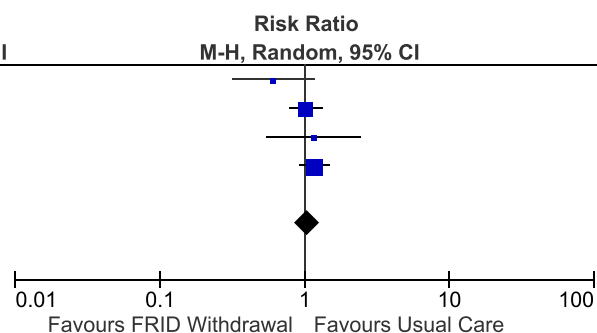


2.1 Falls Incidence – Risk Ratio

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Study or Subgroup	FRID Withdrawal		Usual Care		Weight	Risk Ratio	
	Events	Total	Events	Total		M-H, Random, 95% CI	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: FRID Withdrawal 190, Usual Care 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)

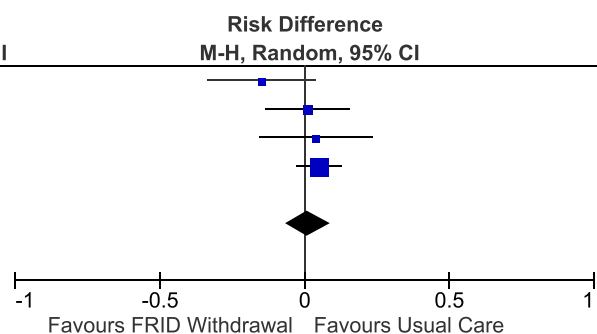


2.2 Falls Incidence – Risk Difference

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Study or Subgroup	FRID Withdrawal		Usual Care		Weight	Risk Difference	
	Events	Total	Events	Total		M-H, Random, 95% CI	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: FRID Withdrawal 190, Usual Care 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)

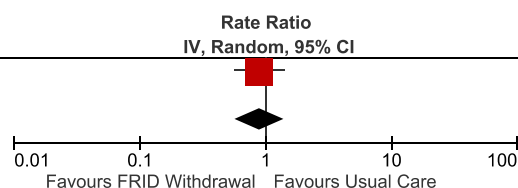


3.1 Fall-Related Injuries

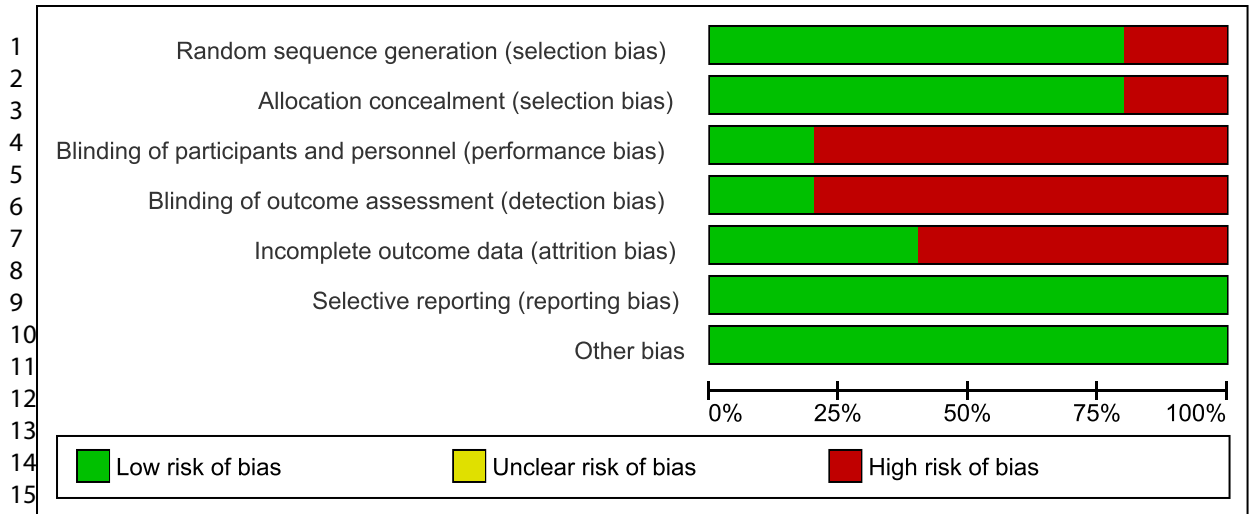
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Study or Subgroup	FRID Withdrawal		Usual Care		Weight	Rate Ratio		
	log[Rate Ratio]	SE	Total	Total		IV, Random, 95% CI	Year	
Blalock 2010	-0.1165	0.2273	93	93	100.0%	0.89	[0.57, 1.39]	2010
Total (95% CI)			93	93	100.0%	0.89	[0.57, 1.39]	

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



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	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Blalock 2010	+	+	-	-	-	+	+
Boyé 2017	+	+	-	-	-	+	+
Campbell 1999	+	+	+	+	-	+	+
Mott 2016	-	-	-	-	+	+	+
Patterson 2010	+	+	-	-	+	+	+

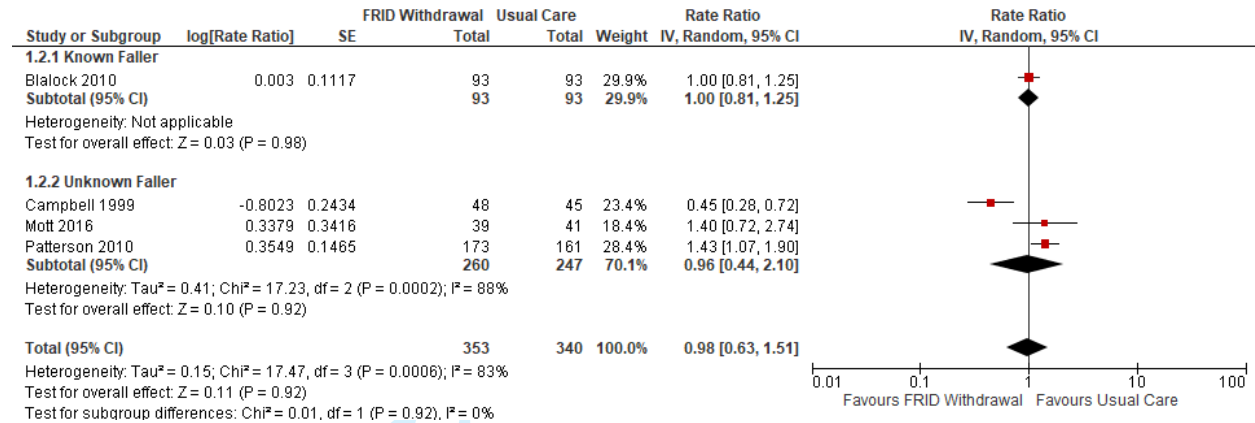
Supplementary Figure S1: OVID Medline Search Strategy

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:

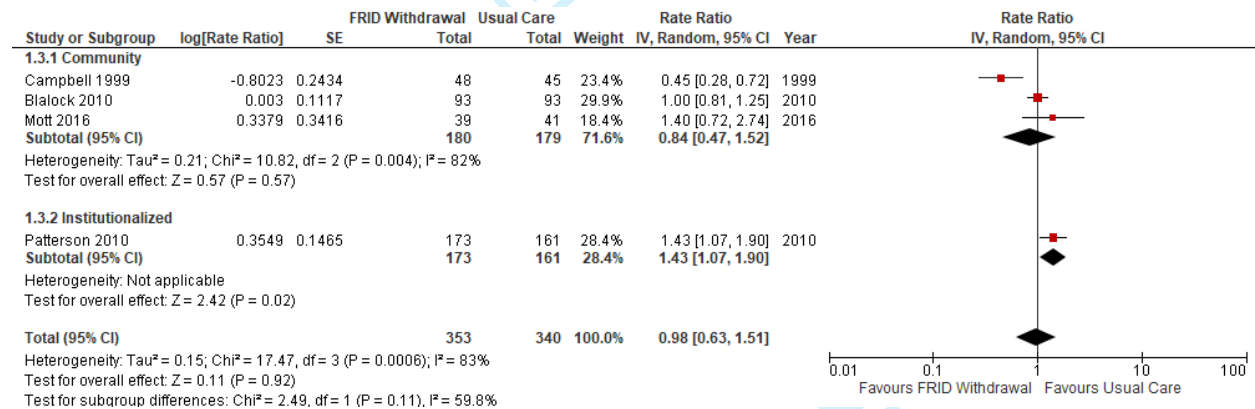
#	Searches
1	exp Accidental Falls/pc [Prevention & Control]
2	fall.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
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
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16	exp Clinical Trial/
17	(randomized or randomised).ab,ti.
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19	randomly.ab,ti.
20	groups.ab,ti.
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22	controlled clinical trial.pt.
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24	15 and 23

Supplementary Figure S2: Subgroup Analyses

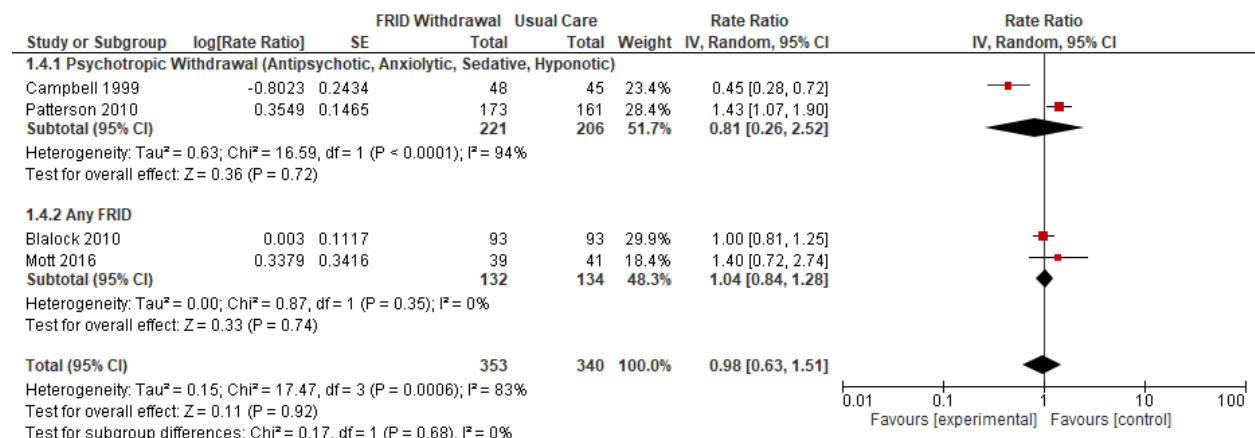
1.2 Falls Rate - Known vs. Unknown Faller



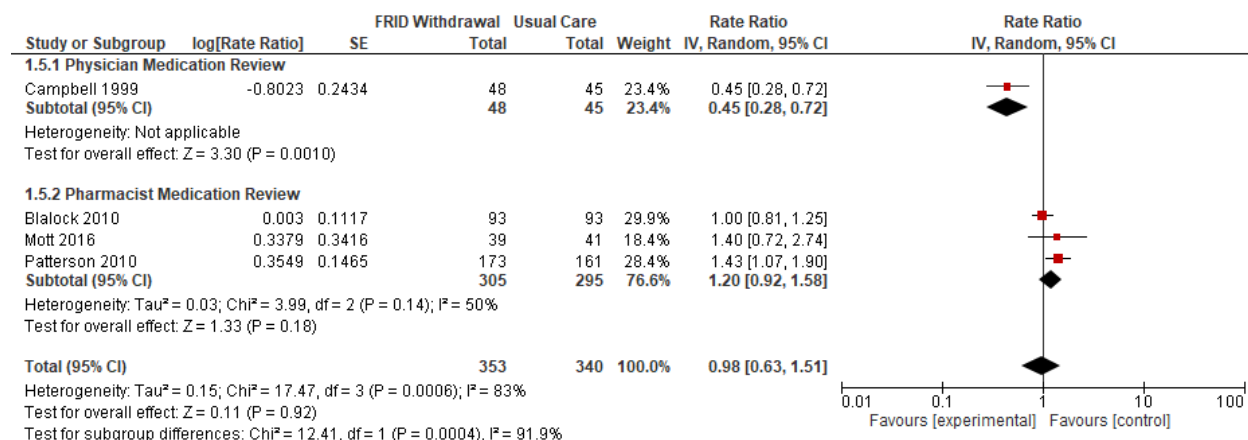
1.3 Falls Rate - Community vs. Institutionalized



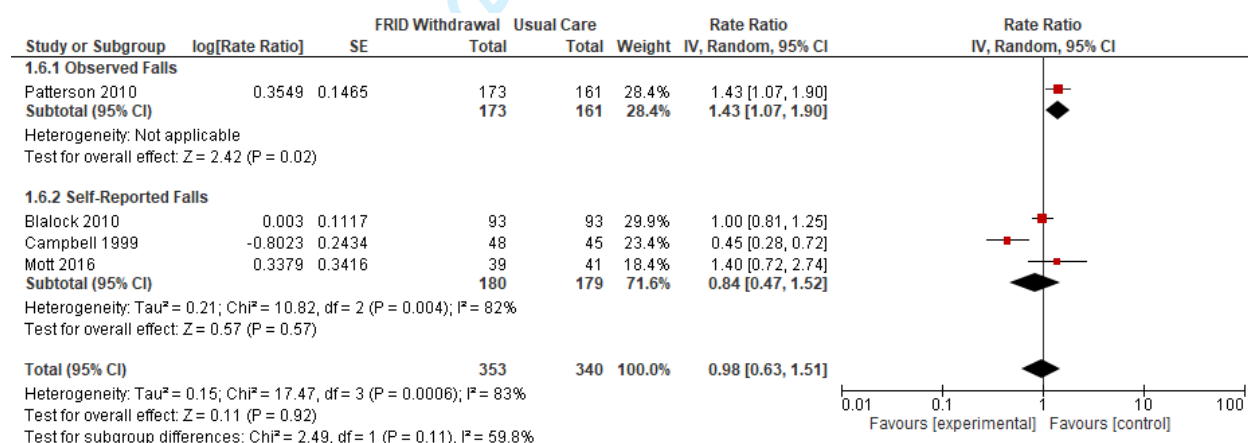
1.4 Falls Rate - Psychotropic Withdrawal vs. Any FRID Withdrawal



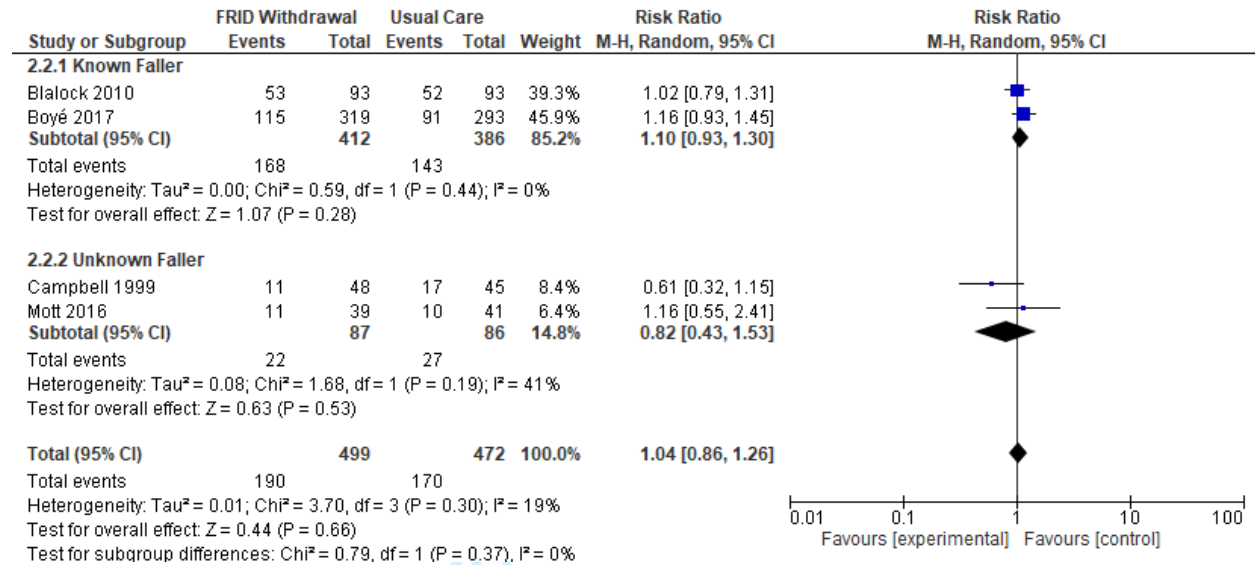
1.5 Falls Rate - Physician vs. Pharmacist Medication Review



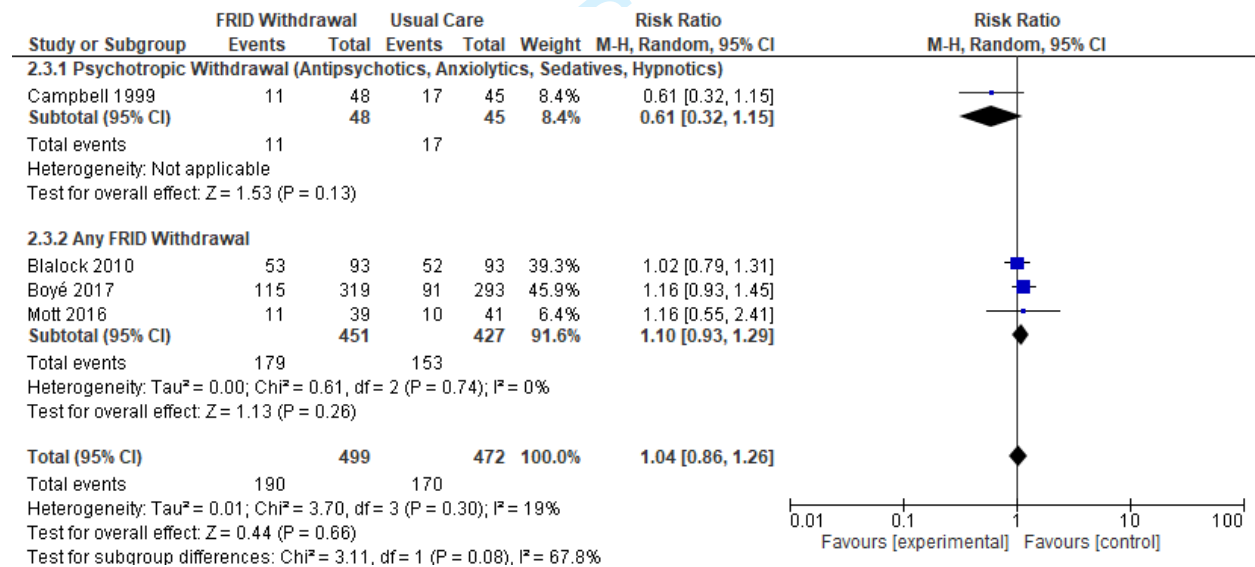
1.6 Falls Rate - Observed vs. Self-Reported Falls



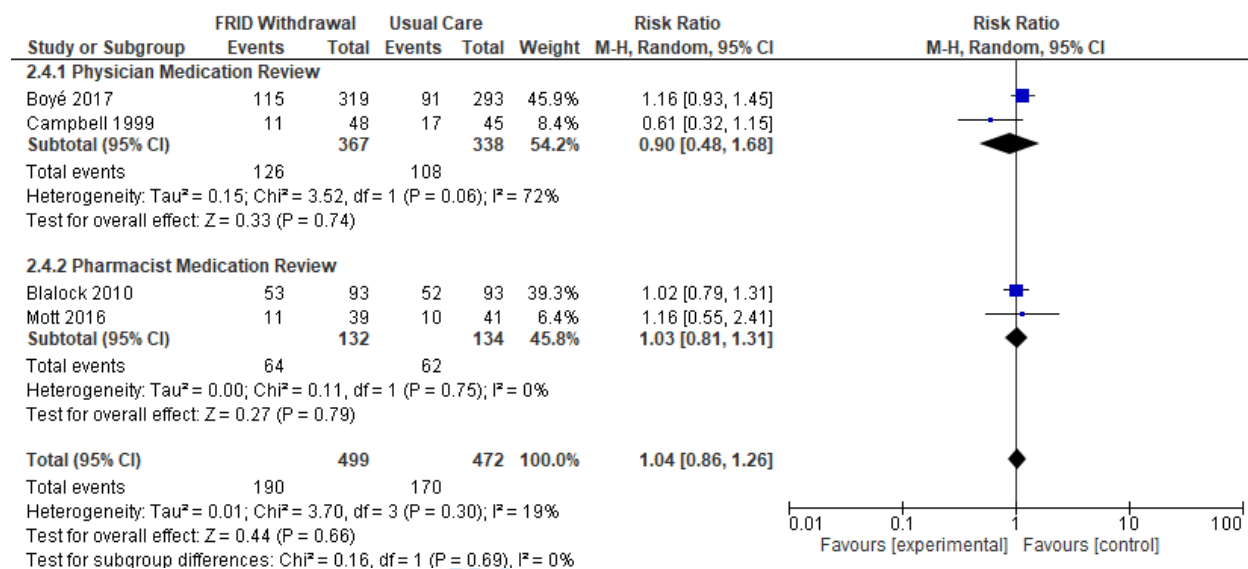
2.2 Falls Incidence - Known vs. Unknown Faller



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**

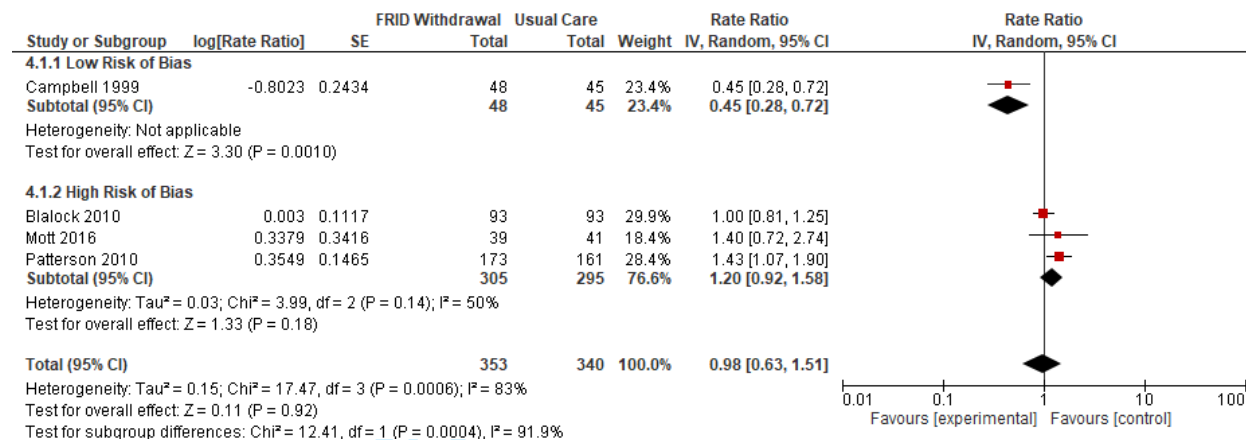
Design	Criteria Met?
Is the subgroup variable a characteristic measured at baseline or after randomization?	Yes – Variable determined at baseline
Is the effect suggested by comparisons within rather than between studies?	No – Comparison between studies
Was the hypothesis specified a priori?	Yes
Was the 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**

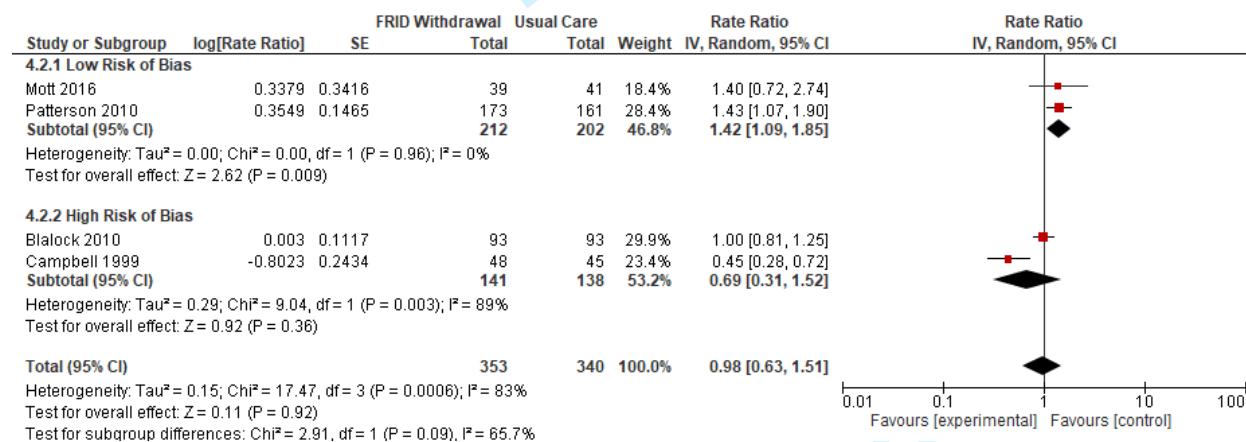
Design	Criteria Met?
Is the subgroup variable a characteristic measured at baseline or after randomization?	Yes – Variable determined at baseline
Is the effect suggested by comparisons within rather than between studies?	No – Comparison between studies
Was the hypothesis specified a priori?	Yes
Was the 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

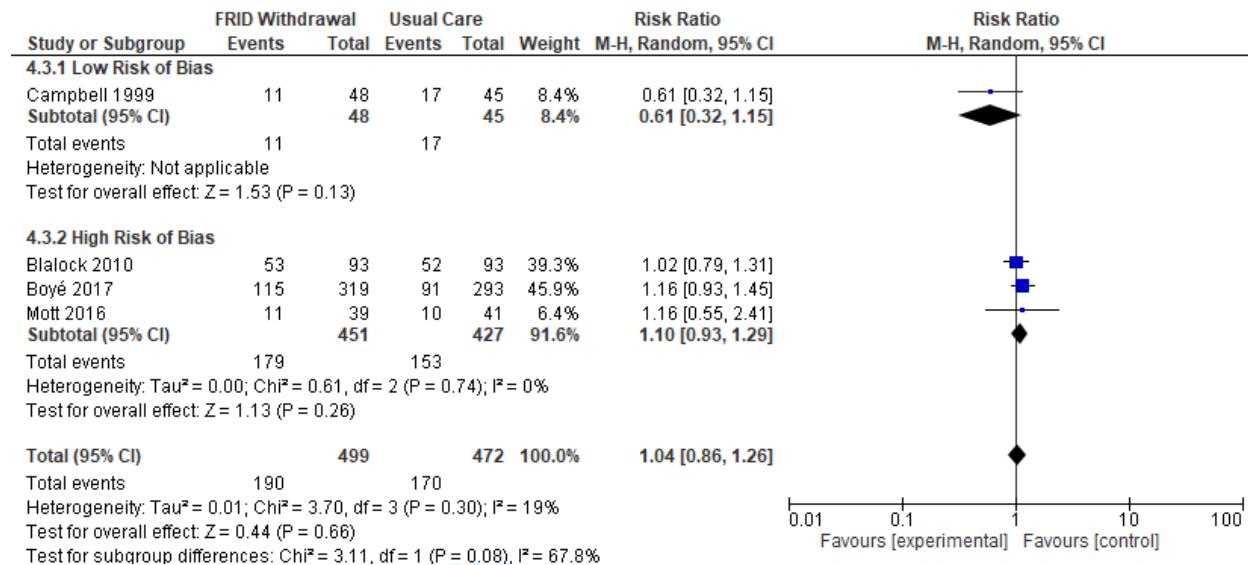
4.1 Falls Rate - Low vs. High Risk of Bias due to Blinding



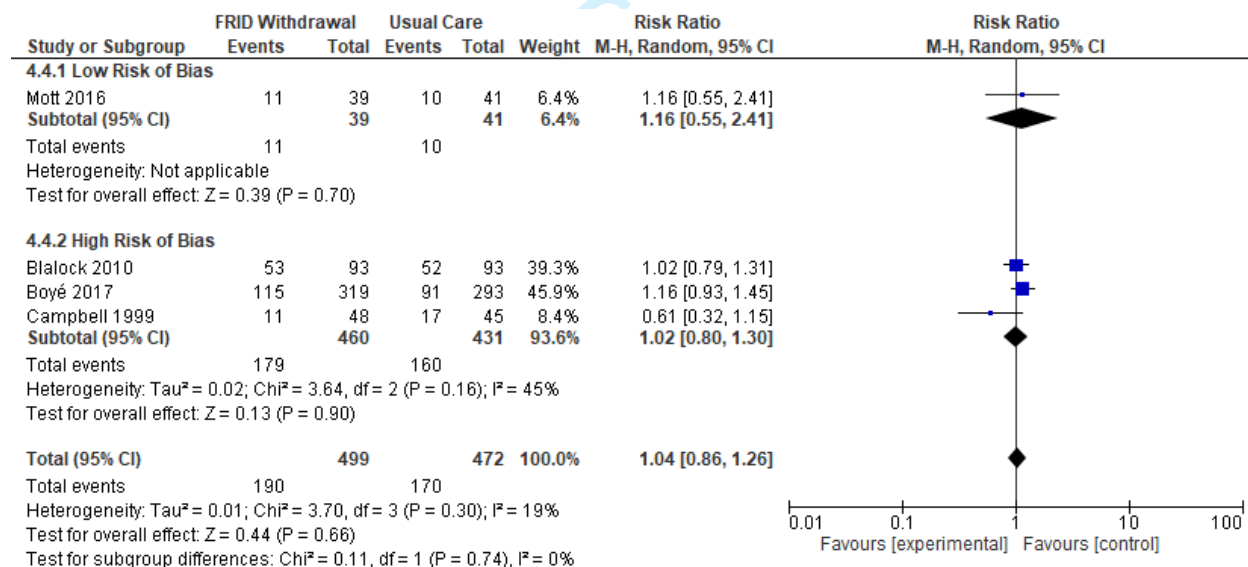
4.2 Falls Rate - Low vs. High Risk of Bias due to Attritional Bias



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

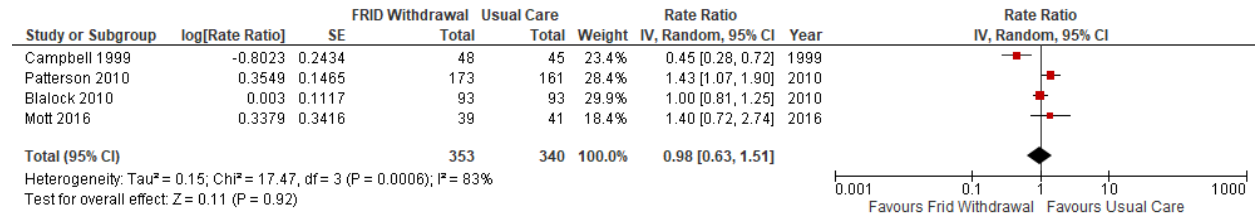


4.4 Falls Incidence - Low vs. High Risk of Bias due to Attrition Bias

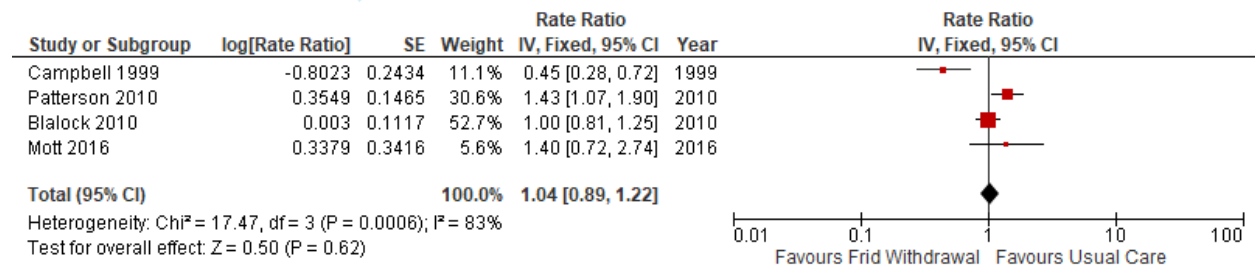


4.5 Falls Rate – Random vs. Effects Model

Random Effects Model

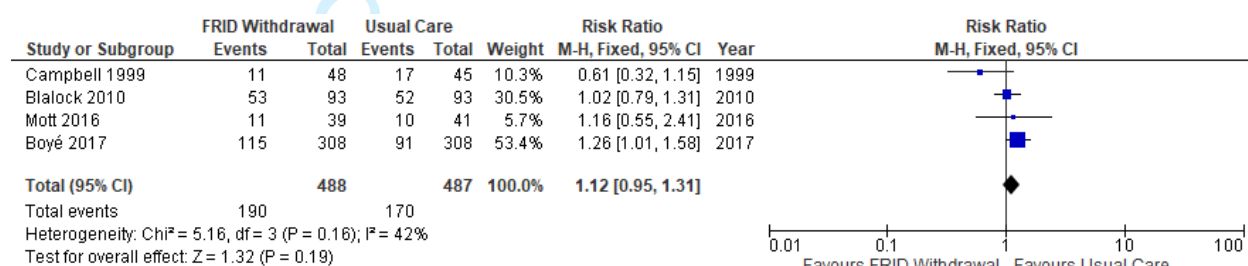
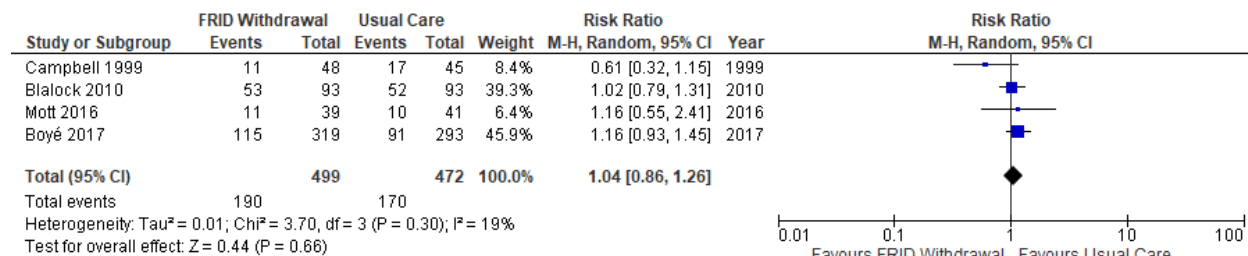


Fixed Effects Model

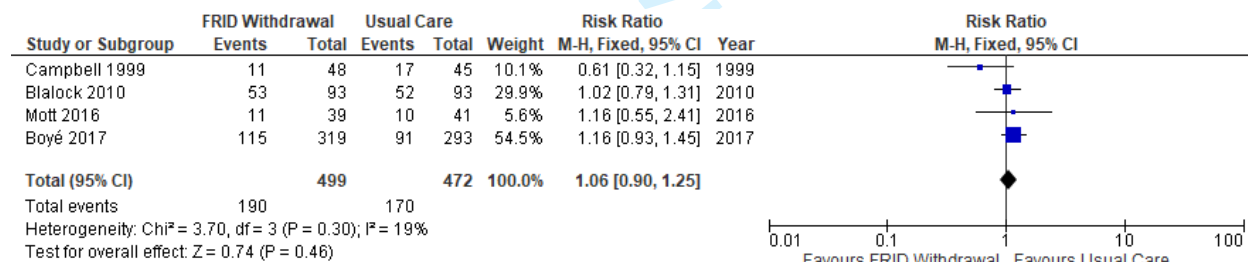


4.6 Falls Incidence – Random vs. Fixed Effects Model

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

Page 1 of 2

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

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PRISMA 2009 Checklist

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

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3 **TITLE:** Deprescribing Fall-Risk-Increasing Drugs (FRIDs) for the Prevention of Falls and
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5 Fall-related Complications: A Systematic Review and Meta-analysis
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10 **AUTHORS:** Justin Lee, BScPhm, ACPR, MD^{1,2,3}

11
12 Ahmed Negm, MD, MSc, PhD^{3,4}

13
14 Ryan Peters, BSc, MD⁵

15
16 Eric Wong, BSc, MD⁶

17
18 Anne Holbrook, MD, PharmD, MSc^{2,7}
19
20
21
22
23

24 ¹Division of Geriatric Medicine, Department of Medicine, McMaster University, Hamilton,
25 Ontario, Canada

26 ²Department of Health Research Methods, Evidence, and Impact, McMaster University,
27 Hamilton,
28 Ontario, Canada

29 ³Geriatric Education and Research in Aging Sciences (GERAS) Centre, Hamilton, Ontario,
30 Canada

31 ⁴School of Rehabilitation Sciences, Faculty of Health Sciences, McMaster University, Hamilton
32 Ontario, Canada;

33 ⁵Michael DeGroote School of Medicine, McMaster University, Hamilton, Ontario, Canada

34 ⁶Division of Geriatric Medicine, Department of Medicine, University of Toronto, Toronto,
35 Ontario, Canada

36 ⁷Division of Clinical Pharmacology and Toxicology, Department of Medicine, McMaster
37 University, Hamilton, Ontario, Canada
38
39
40

41 **CORRESPONDING AUTHOR:** Justin Lee
42 Geriatric Education and Research in Aging Sciences Centre
43 88 Maplewood Avenue, Room 158
44 Hamilton, Ontario, Canada L8M 1W9
45 Email: justin.lee@medportal.ca
46 Telephone: (905) 521-2100
47
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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

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3 of fall-related injuries (RaR 0.89, 95% CI 0.57 to 1.39) over a 6 to 12 month follow-up period. No
4 trials evaluated the impact of deprescribing FRIDs on fall-related fractures or hospitalizations.
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10 **Conclusion:** There is a paucity of robust high-quality evidence to support or refute that a FRID
11 deprescribing strategy alone is effective at preventing falls or falls-related injury in older adults.
12 Although there may be other reasons to deprescribe FRIDs, our systematic review found that it
13 may result in little to no difference in the rate or risk of falls as an sole falls reduction strategy.
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21 **Registration:** PROSPERO CRD42016040203
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26 **Key Words:** Falls, Falls prevention, Fall-risk increasing drug (FRID), Deprescribing, Medication
27 withdrawal, Seniors, Older Adults, Systematic review
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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]

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3 As an individual intervention, only exercise has robust evidence demonstrating reductions
4 in the incidence of fallers and rate of injurious falls.[6,8] It is unclear if other parts of the multi-
5 component strategy are effective, how large is their individual treatment effect, and which
6 components should be prioritized when resources are limited.
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12 Although there is limited evidence of effectiveness, deprescribing medications known as
13 “fall-risk increasing drugs” (FRIDs) is common practice and typically included in both
14 multifactorial and single intervention strategies. The justification is based on observational studies
15 that suggest certain medications are associated with increased falls risk as well as some
16 randomized controlled trials (RCTs) that have shown that medication management interventions
17 (including those with a broader focus of reducing polypharmacy and/or potentially inappropriate
18 prescribing) may reduce the risk of falls.[9] FRIDs include anti-hypertensives, anti-arrhythmics,
19 anti-cholinergics, anti-histamines, sedatives-hypnotics, anti-psychotics, anti-depressants, opioids
20 and NSAIDs.[10–15]. Although the mechanisms are not fully understood, these drugs may
21 influence falls risk by adversely affecting the cardiovascular or central nervous system (e.g.
22 orthostatic hypotension, bradycardia, sedation, sleep disturbance, confusion, dizziness).
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38 Key issues affecting the quality of this observational evidence and certainty of a causal
39 relationship include: (1) variable adjustment for confounders, dosage or duration of therapy, (2)
40 medication use confirmed only at baseline (but not throughout follow-up), and (3) potential
41 prescribing bias associated with specific medication classes. Most meta-analyses have also been
42 based on the pooling of unadjusted estimates and thus susceptible to bias including confounding
43 by indication. As a result, it is unclear whether the observed increase in falls is causally related to
44 such drug use versus the underlying conditions or patients for which the drugs are treating.
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3 With the aim of evaluating its effectiveness as a single falls prevention strategy, we
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5 conducted this systematic review to determine whether deprescribing FRIDs decreases the risk of
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7 falls compared to usual care in older adults aged ≥ 65 years. To the best of our knowledge, no
8
9 previous systematic review has addressed this specific research question.
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14 **METHODS**

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

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30 MEDLINE, EMBASE, CINAHL and the Cochrane Central Register of Controlled Trials
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32 (CENTRAL) electronic databases were searched from inception to August 1, 2020 using a
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34 combination of Medical Subject Headings, controlled and free-text terms synonymous for the
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36 intervention. The MEDLINE search strategy is shown in Supplementary Figure S1. This strategy
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38 was modified for use in other databases.
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42 Reference lists of relevant studies, reviews and guidelines were reviewed to identify
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44 additional studies. Trial registries and geriatric medicine conference abstracts were also reviewed.
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49 **Study Eligibility Criteria**

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51 After pilot testing the eligibility criteria, pairs of reviewers independently conducted
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53 screening. A third reviewer resolved disagreements.
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3 Studies were included if they were RCTs evaluating FRID deprescribing or withdrawal
4 with the intent of reducing falls. FRID deprescribing was defined as the planned and supervised
5 discontinuation or dose reduction of single or multiple medications thought to independently
6 increase falls risk.[10–12]
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12 The comparator could be usual care (i.e. no change in usual activities and/or no FRID
13 withdrawal) or a control intervention not thought to reduce falls. Studies focused on adults aged
14 ≥ 65 years from all settings were included. Studies involving FRID withdrawal within multi-
15 component interventions were excluded if the effect of FRID withdrawal could not be isolated.
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21 The primary outcomes of this review were the (1) rate of falls (defined as the total number
22 of falls per unit of person time that falls were monitored) and (2) incidence of falls (i.e. number of
23 fallers). Secondary outcomes included the incidence of (1) fall-related fractures, (2) fall-related
24 injuries, (3) fall-related hospitalization, (4) adverse effects related to the withdrawal intervention
25 (e.g. disease relapse, symptomatic withdrawal).
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35 **Data Extraction and Quality Assessment**

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37 Two reviewers independently abstracted data on study characteristics, participants,
38 interventions, comparisons, and outcomes using standardized electronic data extraction forms.
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41 Disagreements were resolved through consensus.
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45 Two reviewed independently conducted risk of bias (RoB) assessments using the Cochrane
46 Risk of Bias tool.[19] A previously published modification to the RoB assessment was employed
47 to estimate unclearly reported study methods and allow for sensitivity analysis.[20] This
48 modification involved a structured approach where a score of “definitely low risk”, “probably low
49 risk”, “probably high risk”, or “definitely high risk” was assigned to each RoB criterion.
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3 “Definitely” and “probably” scores were collapsed for both low and high RoB scores.
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5 Disagreements were resolved through consensus.
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10 **Data Synthesis and Analysis**

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12 The rate of falls was reported as a rate ratio (RaR) with a 95% confidence interval (CI).
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14 Dichotomous outcomes (i.e. incidences of falls, fall-related fracture, fall-related injury, fall-related
15 hospitalization and adverse effects related to the withdrawal intervention) have been reported as
16 risk ratios (RR) with 95% CIs.
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21 We used RevMan 5.3 and the intention-to-treat principle for all statistical analyses. We
22 conducted meta-analyses using the generic inverse variance method to allow pooling of effect
23 estimates. A random effects model was used given expected between-trial variations in
24 methodological, participant and medication characteristics between studies. We had originally
25 planned to pool data at various pre-specified time intervals, but all included studies had follow-up
26 between 6 to 12 months.
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35 We assessed heterogeneity through visual inspection of forest plots and statistical tests. A
36 two-tailed test with p-value <0.10 was considered significant for all Chi-square analyses as per
37 recommendations from the Cochrane Handbook and the I^2 was interpreted using the Cochrane
38 Collaboration thresholds.[16]
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44 Heterogeneity was explored in subgroup analyses based on five a priori hypotheses
45 (Supplementary Table S1).[18] These included differences in baseline propensity for falls as
46 influenced by (1) a history of recurrent falls (e.g. known faller or not) or (2) place of residence or
47 care (e.g. community, long-term care); differences in the intervention as influenced by (3) specific
48 medication class(es) chosen for withdrawal and (4) preceding medication review by a clinician for
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3 FRID withdrawal appropriateness; as well as differences in methodology based on (5) definitions
4 used for “falls” (e.g., observed vs. self-reported). We assessed the credibility of any apparent
5 subgroup effects using eleven previously published criteria recommended by the Cochrane
6 Handbook.[21]
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12 A priori sensitivity analyses were conducted to explore the impact of low vs. high RoB
13 based on blinding and attrition. Studies did not report per-protocol results that would allow for our
14 planned intention-to-treat vs. per-protocol sensitivity analysis. The impact of using a fixed vs.
15 random effects model was explored in a post hoc sensitivity analysis.
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21 The confidence in effect estimates for each reported outcome was assessed using the
22 Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.[22]
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28 **Patient and Public Involvement**

29 Patients and the public were not involved in this review.
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35 **RESULTS**

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

50 The included trials in our review are described in Table 1.
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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 \geq 65 3) Speak, read English 4) \geq 4 prescription medications 5) \geq 1 high falls-risk medication 6) \geq 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 \geq 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 \geq 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, benzotropine, trihexiphenidyl	1) FRID pharmacist review 2) Medication-related action plan (MAP) developed by pharmacist for patient 3) Pharmacist follow-up 4) Patient given pamphlet describing the role of medications in falls and monthly falls calendars 5) Pharmacist follow-up	1) Medications in falls pamphlet	1) Rate of falls 2) Incidence of falls
Patterson 2010 [27]	Cluster RCT	1) Nursing home setting with \geq 30 beds; not exclusive care of terminally ill 2) Age \geq 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 \geq 65 3) \geq 1 FRID for \geq 2 weeks prior to the fall 4) MMSE \geq 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, antihistaminics, 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

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3 Three studies were individually randomized, while two studies were cluster randomized by either
4 nursing home or health centre. Studies ranged in size from 80 to 612 participants. With exception
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6 of one study[26], studies were multi-centre involving 144 sites and 4 countries. All were conducted
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8 in the community setting except for one conducted in long-term care.[27] Follow-up periods
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10 ranged from 6 to 12 months.
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14 Overall, there were 1305 participants across all trials. Most were female (>70%) and had a
15 falls history (78.9%). Several key confounders were not reported in the studies including: (1)
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17 baseline number and types of FRIDs, (2) baseline number of medications, and (3) baseline number
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19 and types of co-morbidities. All these factors are thought to potentially modify falls risk.[29,30]
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23 All interventions included a preceding assessment for FRID deprescribing appropriateness.
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25 This was conducted by physicians in 2 trials and pharmacists in 3 trials. Three trials tried to
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27 withdraw any FRID, while others focused on sedative-hypnotics, antipsychotics, or
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29 antidepressants. Successful discontinuation and adherence to deprescribing protocols were low in
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31 all studies. Rates of complete discontinuation of at least one FRID ranged from 10 to 40%.
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35 In terms of our study outcomes, 4 trials measured the rate of falls and 4 measured falls
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37 incidence. One trial reported fall-related injuries.[24] Fall-related fractures, fall-related
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39 hospitalization or deprescribing-related adverse effects were not measured by any of the trials.
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44 **Summary of Findings**

45 **Rate and Incidence of Falls**

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49 Four studies reported the effect of deprescribing FRIDs on the rate of falls. Deprescribing
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51 FRIDs did not reduce the rate of falling (RaR 0.98, 95% CI 0.63 to 1.51; Figure 2 – Analysis 1.1).
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3 Considerable statistical heterogeneity was present ($\chi^2=17.47$, $p=0.0006$, $I^2=83\%$) and subsequently
4 explored in subgroup analysis.
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8 Four studies reported the effect of deprescribing FRIDs on the risk of falls as measured by
9 falls incidence. Deprescribing FRIDs did not reduce the incidence of falls (RR 1.04, 95% CI 0.86
10 to 1.26, $I^2 = 19\%$, $\chi^2=3.70$, $p = 0.30$; Figure 2 – Analysis 2.1). In absolute terms, there was a non-
11 significant risk difference increase of 0.01 (95% CI -0.06 to 0.09, $I^2 = 22\%$, $p=0.76$; Figure 2 –
12 Analysis 2.2)
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19 20 21 ***Rate of Injurious Falls*** 22

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24 One trial reported the effect of deprescribing FRIDs on fall-related injuries.[24]
25 Deprescribing FRIDs did not reduce the rate of fall-related injuries (RaR 0.89, 95% CI 0.57 to
26 1.39; Figure 2 – Analysis 3.1). This trial did not report data that would allow for any of our pre-
27 planned subgroup analyses.
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33 34 35 **Risk of Bias Assessment** 36

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38 Figure 3 summarizes our RoB assessments. All studies were deemed at high risk of bias in
39 at least one domain. The overall mean weighted kappa across all assessments was 0.67 (moderate
40 agreement). For individual RoB assessments, kappa ranged from 0 to 0.85. Inter-rater agreement
41 is actually higher than indicated by the calculated scores due to the “kappa co-efficient
42 paradox”. [31,32] Low kappas (e.g. $\kappa=0$) occurred despite high levels of observed agreement (e.g.
43 $\geq 80\%$ agreement) for two RoB assessments. True agreement is falsely attributed to chance
44 agreement by the kappa calculation when there is substantial imbalance in marginal ratings.
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3 For falls rate and incidence, all studies except one[25] were judged at high risk of bias for
4 lack of blinding of participants, personnel and outcome assessors. It is unclear whether blinding
5 could have impacted behaviour or perceptions (e.g. activity risk-level, placebo effect). Risk of
6 ascertainment bias was high in one study[27] (i.e. no standardized falls definition was used), but
7 all other studies used methods accepted to be low risk of bias (i.e. falls recorded daily on postcards
8 or calendars). Risk of attrition bias was deemed high in three studies based on high or unbalanced
9 lost to follow-up rates.[24,25,28]
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22 ***Publication Bias***

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24 Since less than 10 eligible studies were found, a funnel plot was not constructed due to an
25 inability to make meaningful conclusions about publication bias.
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31 ***Subgroup Analyses and Exploration of Heterogeneity***

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33 Our pre-specified subgroup analyses did not adequately explain the statistical
34 heterogeneity observed results for the rate and incidence of falls (Supplementary Figure S2).
35 Deprescribing FRIDs appeared more effective when a preceding medication review was conducted
36 by physicians compared to pharmacists ($p=0.0004$, $I^2=91.9\%$, Analysis 1.5), while psychotropic
37 withdrawal appeared more effective than strategies withdrawing any FRID ($p=0.08$, $I^2=67.8\%$,
38 Analysis 2.3). However, in both analyses, only 6 of 11 subgroup credibility criteria were met and
39 each subgroup was limited to one trial with less than 100 participants (Supplementary Table S2).
40 We, therefore, judged the credibility that these subgroup effects are real as poor and uncertain.
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3 The available data did not permit subgroup analyses by place of residence or falls
4 ascertainment method. The other subgroup analyses showed no evidence of difference beyond that
5 due to chance.
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10 11 12 **Sensitivity Analyses** 13

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15 Our sensitivity analyses are shown in Supplementary Figure S3. The incorporation of trials
16 with high risk of performance bias appeared to mask the potential benefit of deprescribing FRIDs
17 on reducing the incidence and rate of falls, while the trials with high risk of attrition bias appeared
18 to mask a potential increase in falls rate with deprescribing FRIDs. These results should be
19 interpreted cautiously and definitive conclusions cannot be made. Data from trials with low risk
20 of performance bias were limited to one trial with less than 100 participants, and data from trials
21 with low risk of attrition bias were limited to two trials with less than 450 participants overall.
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31 A post-hoc sensitivity analysis examining the impact of using a fixed vs. random effects
32 model did not change conclusions regarding the effect of deprescribing FRIDs on the rate or
33 incidence of falls.
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40 **Quality of Evidence** 41

42 The GRADE evidence profile is shown in Table 2.
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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%				
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

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3 We judged the quality of evidence to be low or very low for all outcomes (falls rates, falls incidence
4 and fall-related injuries) after rating down for risk of bias, inconsistency and imprecision.
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8 We believe the optimal information size (OIS) to make definitive conclusions on the effect
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10 of deprescribing FRIDs has not yet been met as the body of evidence is based on fewer than 2000
11 participants and less than 400 events.[33,34] This is based on the OIS calculation figure
12 recommended by the GRADE guidelines using a well-established control falls event rate of 30%
13 described in the literature and conservative relative risk reduction (RRR) of 20% (assuming $\alpha =$
14 0.05 and $\beta = 0.2$).[34,35]
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24 **DISCUSSION**

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26 This systematic review sought to determine whether deprescribing FRIDs decreased the
27 risk of falls in older adults and found that there is a lack of robust high-quality evidence to support
28 or refute the deprescribing of FRIDs alone as an effective fall prevention strategy. Incorporating
29 data from 5 RCTs involving 1305 participants aged ≥ 65 years, our meta-analyses indicate that a
30 FRID deprescribing strategy did not significantly change the rate of falls (RaR 0.98, 95% CI 0.63
31 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
32 period. Although this intervention focuses on those medications thought to be associated with falls,
33 the uncertainty of its effect on falls and conclusions of current lack of evidence of effectiveness
34 are similar to previous systematic reviews evaluating the effectiveness of medication reviews that
35 had a broader focus on reducing polypharmacy and potentially inappropriate prescribing (i.e. not
36 focused solely on FRIDs).[9,36]
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51 There is also a significant absence of evidence for clinically- and patient-important
52 outcomes such as fall-related injuries, fractures and hospitalizations. The only trial to date that
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3 evaluated the rate of fall-related injuries did not demonstrate a statistically significant effect (RaR
4 0.89, 95% CI 0.57-1.39).[24] Our search found no trials measuring the impact on fall-related
5 fractures, fall-related hospitalizations or adverse effects related to a FRID deprescribing strategy.
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7 Although this may be rooted in the difficulty of conducting RCTs powered for such outcomes,
8 their measurement and reporting are still important to inform systematic review meta-analyses that
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10 could lead to more precise estimates.
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17 Based on low-quality evidence, it is unclear whether deprescribing FRIDs as a single
18 intervention leads to any appreciable clinically important benefit or harm. Our current best effect
19 estimates for falls rate and incidence are centred around no appreciable difference (i.e. RaR \approx 1,
20 RR \approx 1, RD \approx 0). Although seemingly logical to assume, reducing isolated risk factors may not
21 necessarily lead to a reduction in falls and fall-related complications. The absence of change in the
22 incidence of hip fractures after statewide regulatory action on benzodiazepine prescribing in the
23 United States that reduced benzodiazepine use by 60.3% is a real-world example of this
24 phenomenon and the complexity of exposure-outcome relationships.[37]
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35 Our findings likely reflect the multi-factorial nature of falls and the varying risk of different
36 FRIDs. It is unclear as to what degree a particular risk factor or combination of risk factors (e.g.
37 specific FRIDs) must be reduced to produce an appreciable change in falls. Medications may only
38 have conditional or contributory causality to falls. It may be that medication-related interventions
39 work best in combination with other interventions or only in specific contexts.
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47 Only one trial[25] included in our review demonstrated a statistically significant benefit
48 with deprescribing FRIDs. This was also the only trial to use study capsules to operationalize
49 blinded deprescribing of FRIDs in participants, research personnel and outcome assessors. Its
50 results might be more reflective of the true potential physiological effect of deprescribing FRIDs
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3 because it minimized the risk of performance bias. However, the magnitude of benefit achievable
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5 in the non-research setting at this time may be closer to those seen in the unblinded trials due to
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7 the strong psychological and behavioural factors (e.g. placebo effect) that may hinder successful
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9 deprescribing. Further advances in implementation science and behavioural change strategies are
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11 likely needed to facilitate medication optimization.
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15 These results raise several questions about the presumed effectiveness of deprescribing
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17 FRIDs as an isolated falls prevention strategy. Given the amount of resources being invested into
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19 falls prevention initiatives around the world, clinicians and organizations should examine: (1) what
20
21 is the strength of evidence supporting their current activities, (2) whether these activities are cost-
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23 effective, and (3) whether resources are being appropriately prioritized to those interventions
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25 shown to provide the most value. This should also be applied to what is being required of
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27 healthcare organizations in national accreditation standards (e.g. Joint Commission, Accreditation
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29 Canada) to help direct and encourage optimal use of limited healthcare resources.
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33 Clinicians and policy-makers need to consider the current lack of strong evidence for
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35 deprescribing FRIDs as an isolated intervention for the specific purpose of reducing falls,
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37 particularly in patients who may be very reluctant or who have strong indications for specific
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39 FRIDs. FRID reduction is one out of many possible interventions that need to be considered. As
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41 with prescribing medications, deprescribing is a skill and comes with the potential for harm as well
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43 as benefit.[38] Thoughtful consideration of the goals, appropriateness and safety of deprescribing
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45 is important.[39] Our results highlight the need for a comprehensive and individualized approach
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47 to falls. Multi-component interventions are ideal, but interventions may need to be prioritized
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49 depending on time, resources and context.
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3 Despite insufficient evidence to support or refute the deprescribing of FRIDs for falls
4 prevention, our results do not mean that clinicians should avoid deprescribing FRIDs. There may
5 be many other reasons to deprescribe these medications. These include avoidance of adverse drug
6 events, improvements in cognition, increased medication adherence and drug costs savings. It is
7 also unclear whether medication review and management with a broader focus on reducing
8 polypharmacy and potentially inappropriate prescribing in older adults may be beneficial in
9 preventing falls. Some RCTs with such interventions have shown a reduction of falls risk, while
10 others have not demonstrated a significant difference.[40–46]
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21 Our review highlights the need for future FRID deprescribing trials that evaluate patient-
22 important outcomes (e.g. injuries, fractures and hospitalizations). Greater attention to optimal
23 design and reporting is needed to minimize risk of bias and enhance our interpretation of the results.
24 Examples include improved reporting of confounding baseline characteristics and intervention
25 fidelity (e.g. number and types of FRIDs, degree and duration of dose reduction). Deprescribing
26 is challenging and extra measures are likely needed to improve successful intervention adherence
27 and follow-up.
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40 **STRENGTHS AND LIMITATIONS**

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42 Our review has limitations. There was variation in the operationalization of FRID
43 deprescribing and degree of success achieved (e.g. dose reduction only, completion
44 discontinuation, non-adherence). This presumably makes the detection of any potential benefit less
45 likely and our conclusions more conservative. However, the effect estimates are likely more
46 indicative of what might be expected outside of the research setting. These phenomena likely
47 represent the real-life challenges of deprescribing (especially with certain types of FRIDs such as
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3 psychotropics or opioids). Moreover, our ability to assess for confounders modifying falls risk was
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5 limited due to inconsistent reporting of relevant baseline characteristics and lack of patient-level
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7 data. Lastly, our ability to make definitive conclusions is limited because the total sample size
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9 across studies for each outcome did not yet meet our calculated estimate for the required optimal
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11 information size.
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15 Our review has several strengths. First, our search was comprehensive and we included a
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17 rigorous grey literature search for unpublished studies. Second, we employed optimal analytical
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19 and interpretational approaches including duplicate assessment, subgroup credibility criteria and
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21 optimal information size considerations. Third, unlike previous medication-focused reviews, we
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23 applied the GRADE approach to assess the quality of evidence and our degree of confidence in
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25 the results.
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30 31 **CONCLUSIONS**

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33 Our systematic review found that deprescribing FRIDs as an isolated strategy results in
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35 little to no difference in the rate and risk of falls or falls-related injuries, but the evidence is still
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37 sparse and very low quality. Additional well-designed studies are needed to reach the optimal
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39 information size to reduce uncertainty about this intervention and establish its relative importance
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41 in the range of possible interventions that can be employed by clinicians and health systems to
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43 reduce falls.
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13
14 with citation review. RP and AN assisted with data extraction, risk of bias assessment and certainty
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16 of evidence grading. All authors contributed to the analysis and interpretation of results. JL drafted
17
18 the initial manuscript and all authors contributed to its revision and final approval.
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40 **Patient Consent for Publication:**

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42 None required.
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47 **Data Sharing Statement:**

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49 No unpublished data are available.
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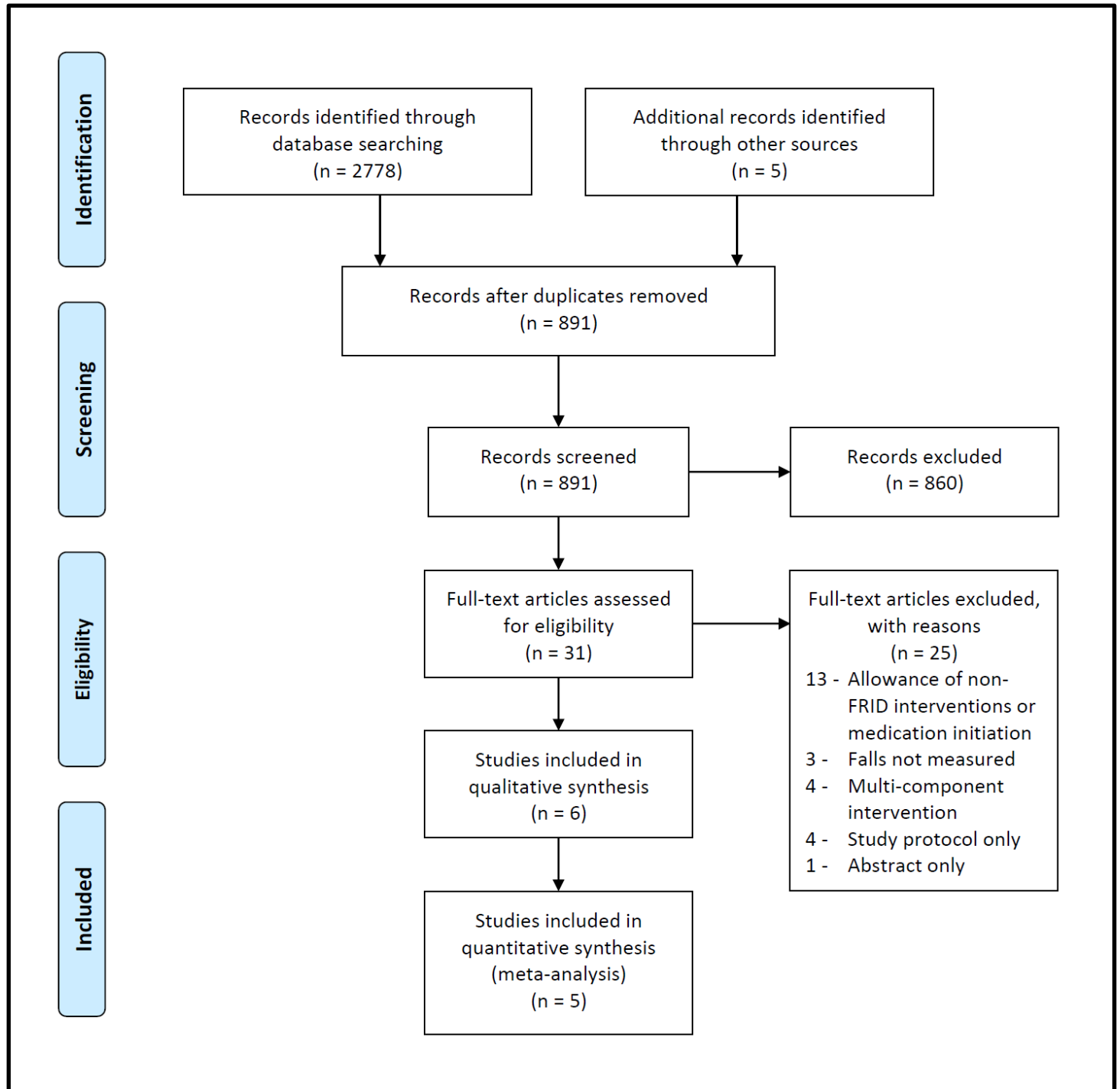
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3 **FIGURES**
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5 **Figure 1:** PRISMA Flow Diagram of Study Selection Process
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7 **Figure 2:** Forest Plots of FRID Withdrawal versus Usual Care
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9 **Figure 3:** Risk of Bias Assessments
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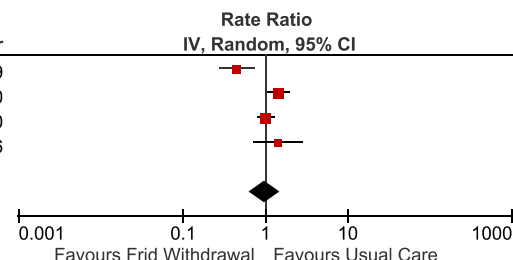


1.1 Falls Rate

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Study or Subgroup	FRID Withdrawal		Usual Care		Weight	Rate Ratio		Year
	log[Rate Ratio]	SE	Total	Total		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)

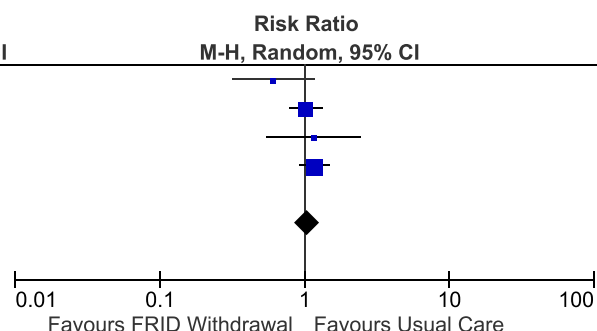


2.1 Falls Incidence – Risk Ratio

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Study or Subgroup	FRID Withdrawal		Usual Care		Weight	Risk Ratio	
	Events	Total	Events	Total		M-H, Random, 95% CI	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: FRID Withdrawal = 190, Usual Care = 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)

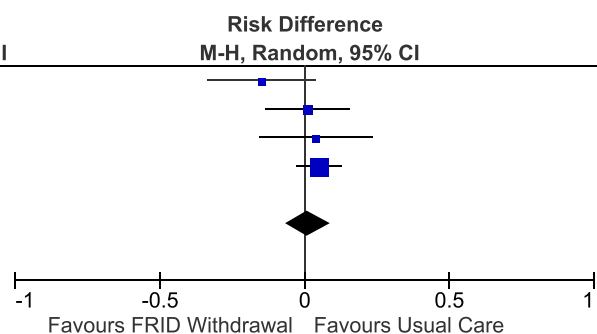


2.2 Falls Incidence – Risk Difference

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Study or Subgroup	FRID Withdrawal		Usual Care		Weight	Risk Difference	
	Events	Total	Events	Total		M-H, Random, 95% CI	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: FRID Withdrawal = 190, Usual Care = 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)

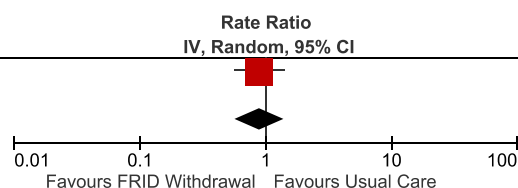


3.1 Fall-Related Injuries

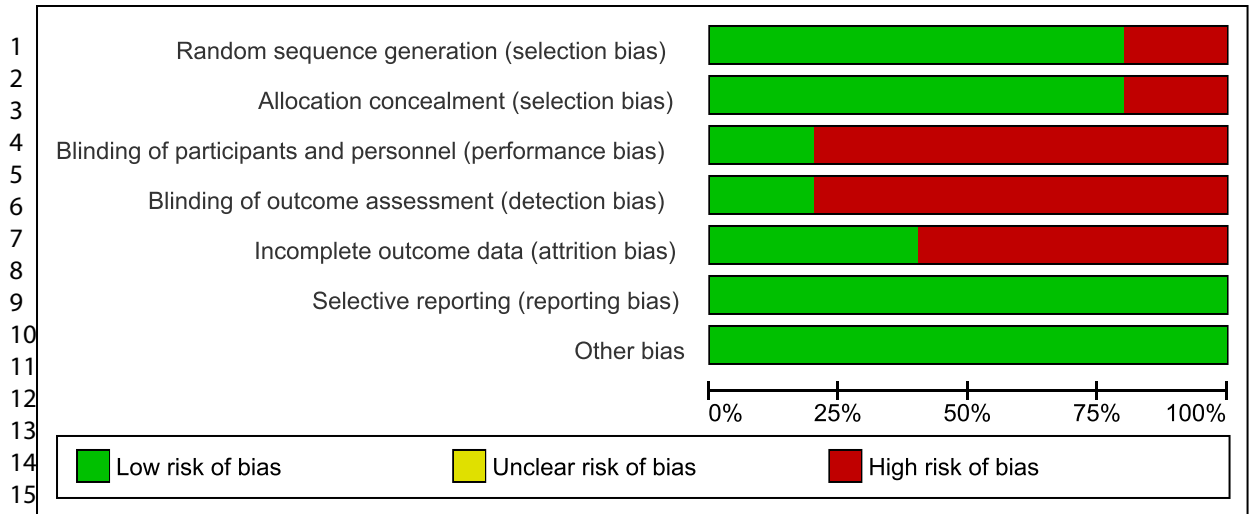
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Study or Subgroup	FRID Withdrawal		Usual Care		Weight	Rate Ratio		
	log[Rate Ratio]	SE	Total	Total		IV, Random, 95% CI	Year	
Blalock 2010	-0.1165	0.2273	93	93	100.0%	0.89	[0.57, 1.39]	2010
Total (95% CI)			93	93	100.0%	0.89	[0.57, 1.39]	

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



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	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
38 Blalock 2010	+	+	-	-	-	+	+
39 Boyé 2017	+	+	-	-	-	+	+
40 Campbell 1999	+	+	+	+	-	+	+
41 Mott 2016	-	-	-	-	+	+	+
42 Patterson 2010	+	+	-	-	+	+	+

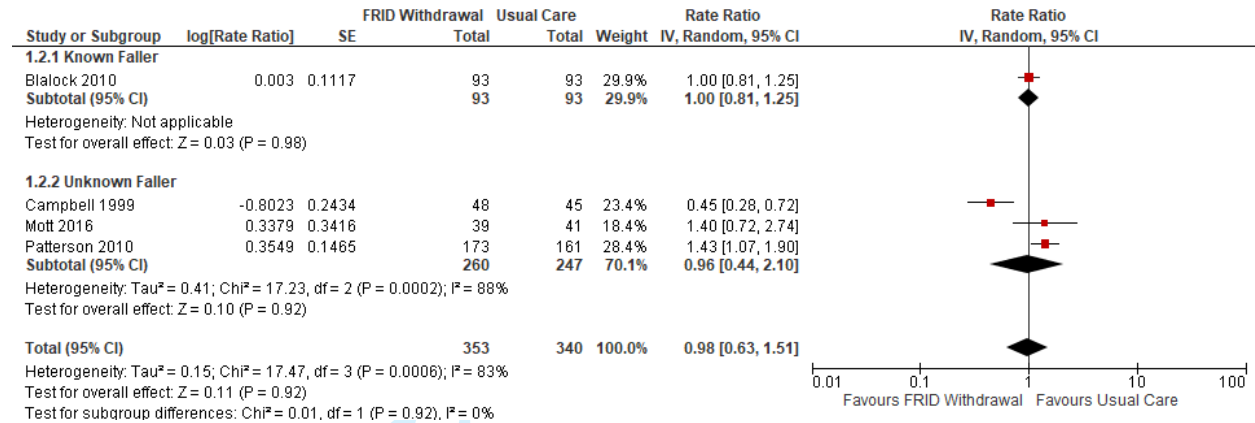
Supplementary Figure S1: OVID Medline Search Strategy

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:

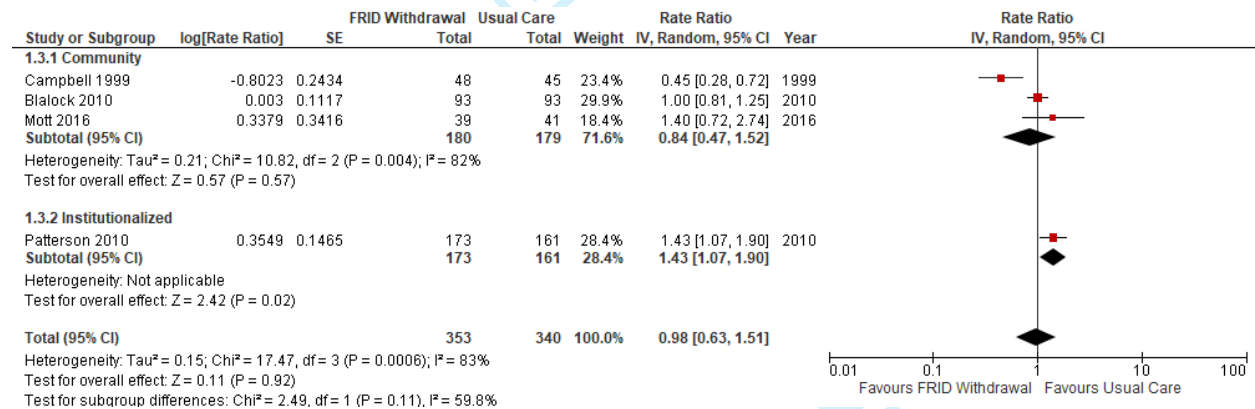
#	Searches
1	exp Accidental Falls/pc [Prevention & Control]
2	fall.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
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

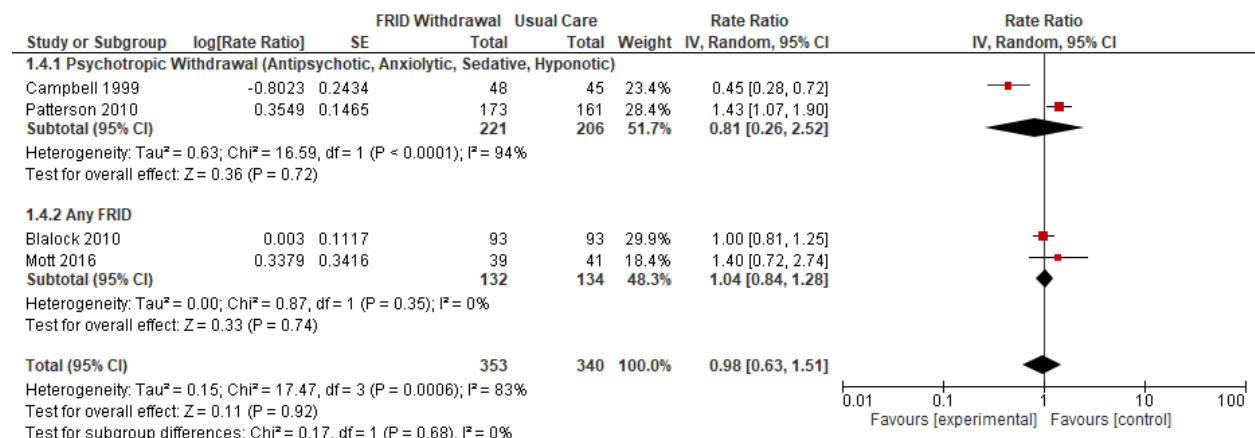
1.2 Falls Rate - Known vs. Unknown Faller



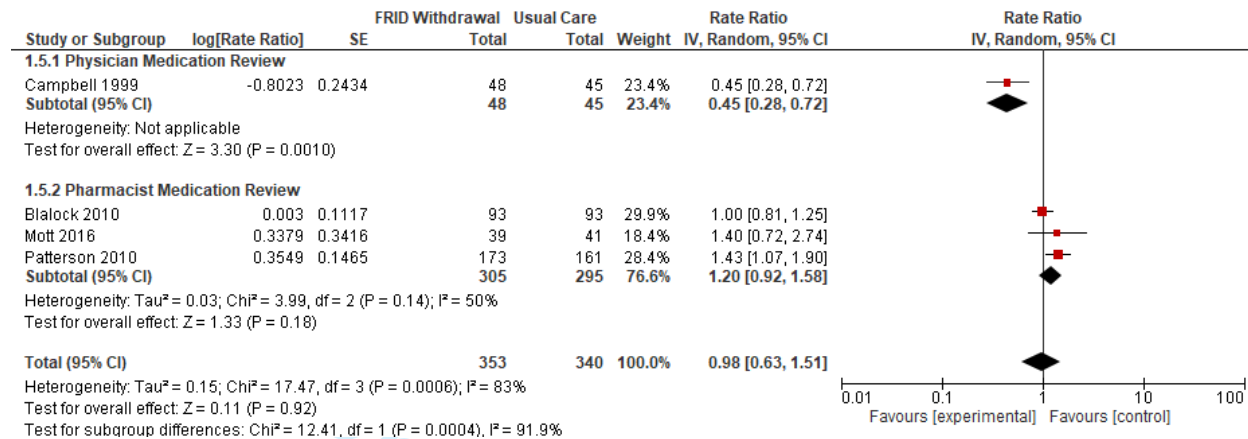
1.3 Falls Rate - Community vs. Institutionalized



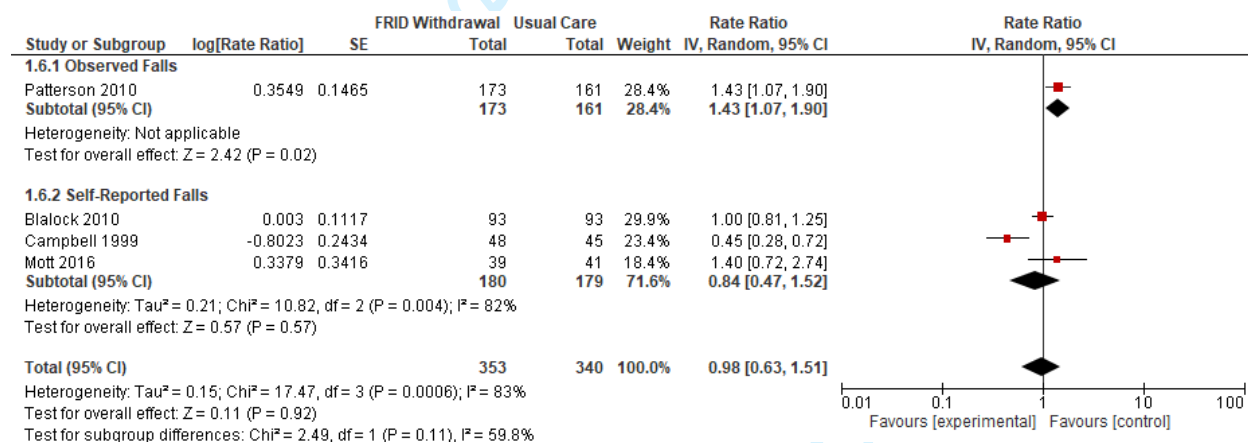
1.4 Falls Rate - Psychotropic Withdrawal vs. Any FRID Withdrawal



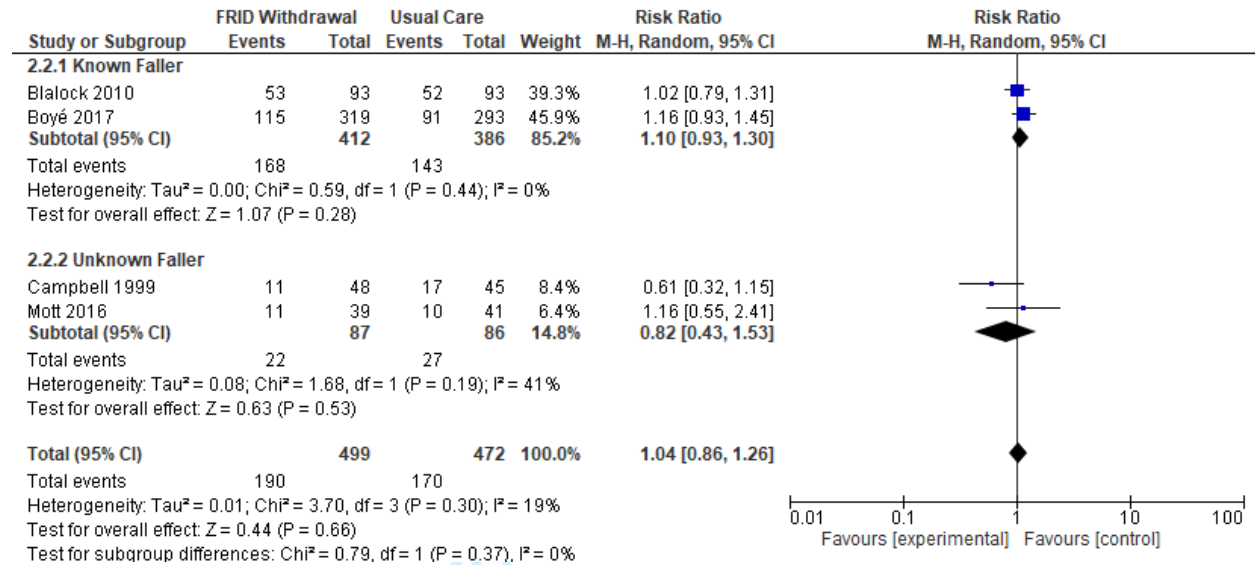
1.5 Falls Rate - Physician vs. Pharmacist Medication Review



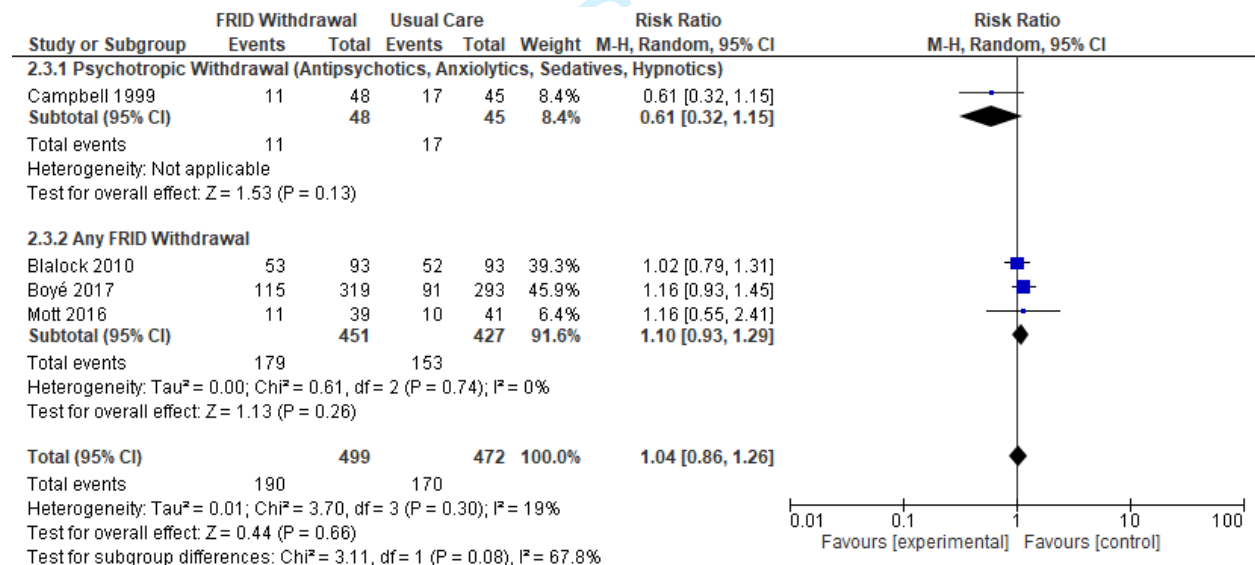
1.6 Falls Rate - Observed vs. Self-Reported Falls



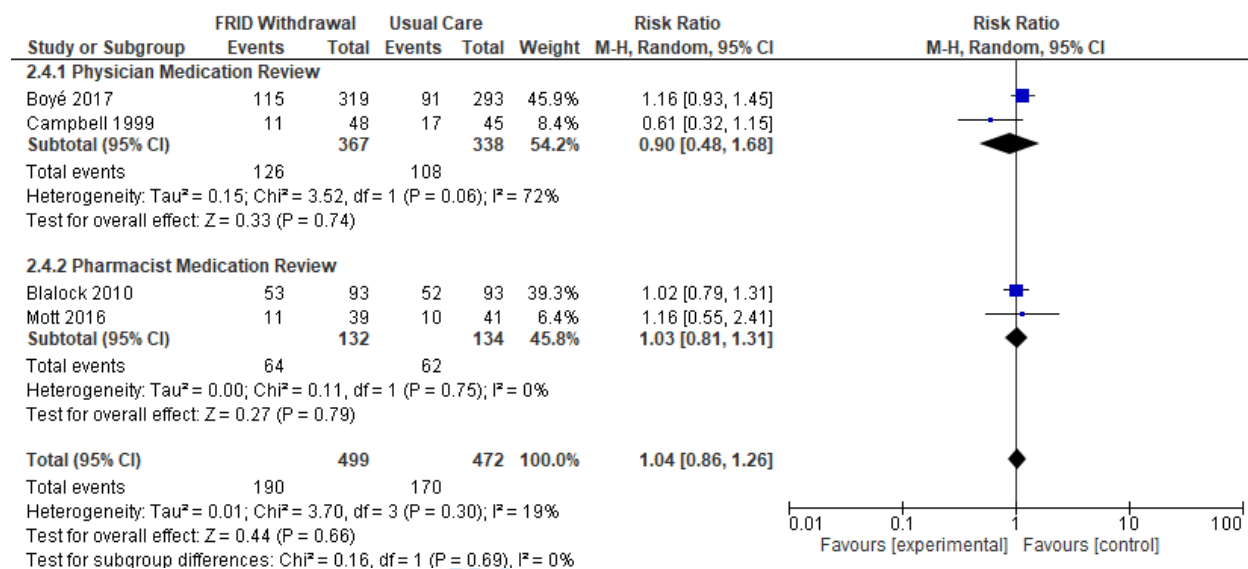
2.2 Falls Incidence - Known vs. Unknown Faller



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**

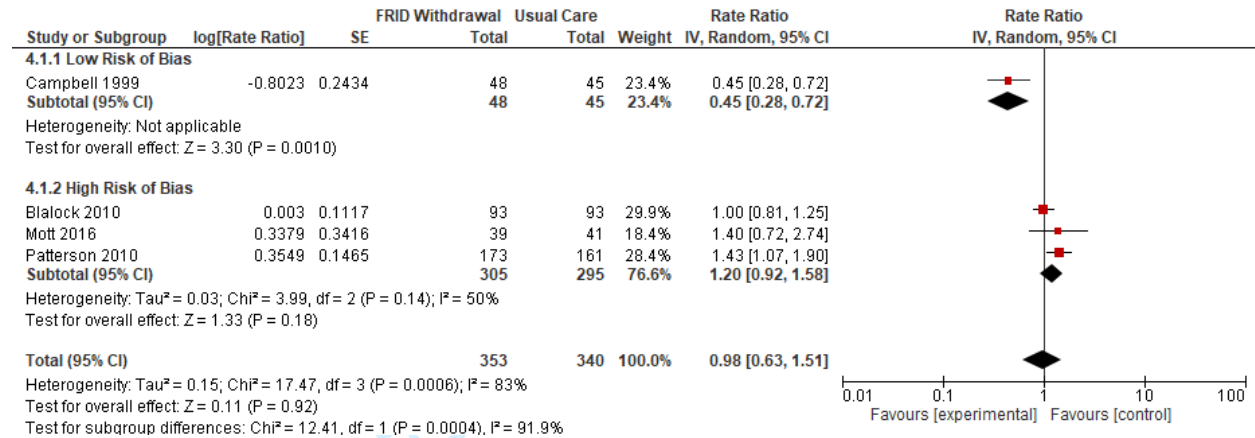
Design	Criteria Met?
Is the subgroup variable a characteristic measured at baseline or after randomization?	Yes – Variable determined at baseline
Is the effect suggested by comparisons within rather than between studies?	No – Comparison between studies
Was the hypothesis specified a priori?	Yes
Was the 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**

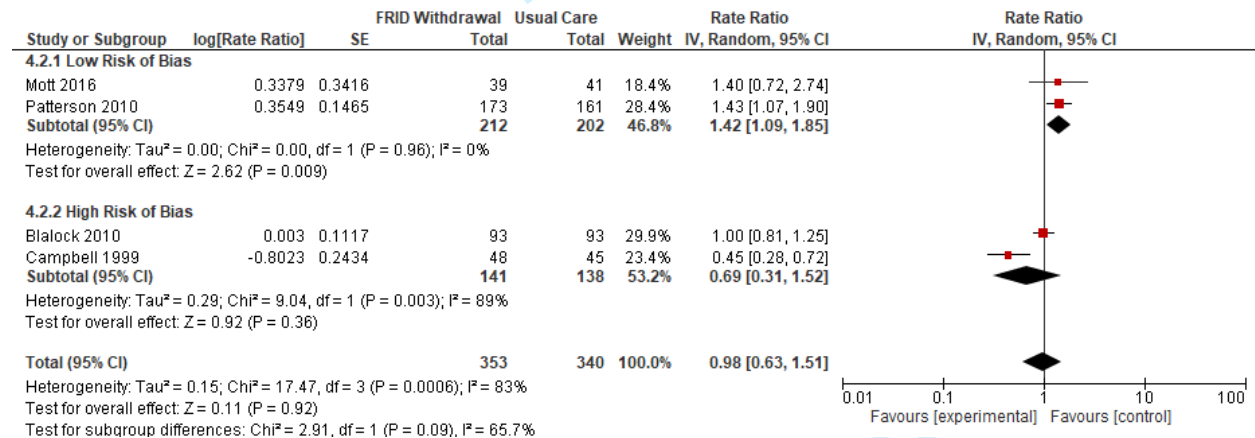
Design	Criteria Met?
Is the subgroup variable a characteristic measured at baseline or after randomization?	Yes – Variable determined at baseline
Is the effect suggested by comparisons within rather than between studies?	No – Comparison between studies
Was the hypothesis specified a priori?	Yes
Was the 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

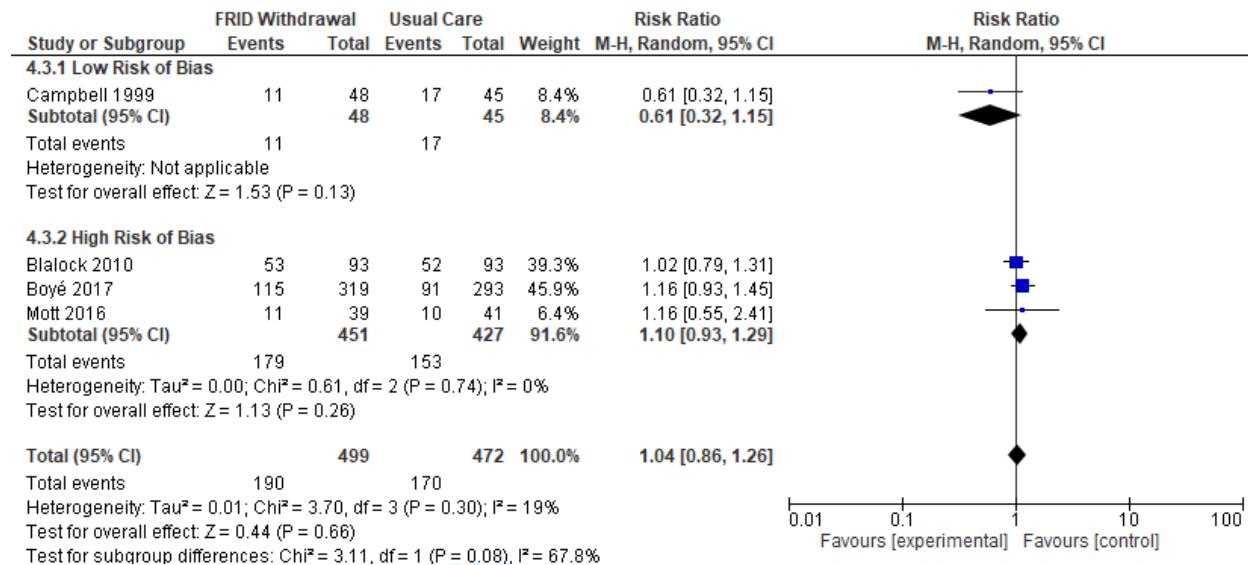
4.1 Falls Rate - Low vs. High Risk of Bias due to Blinding



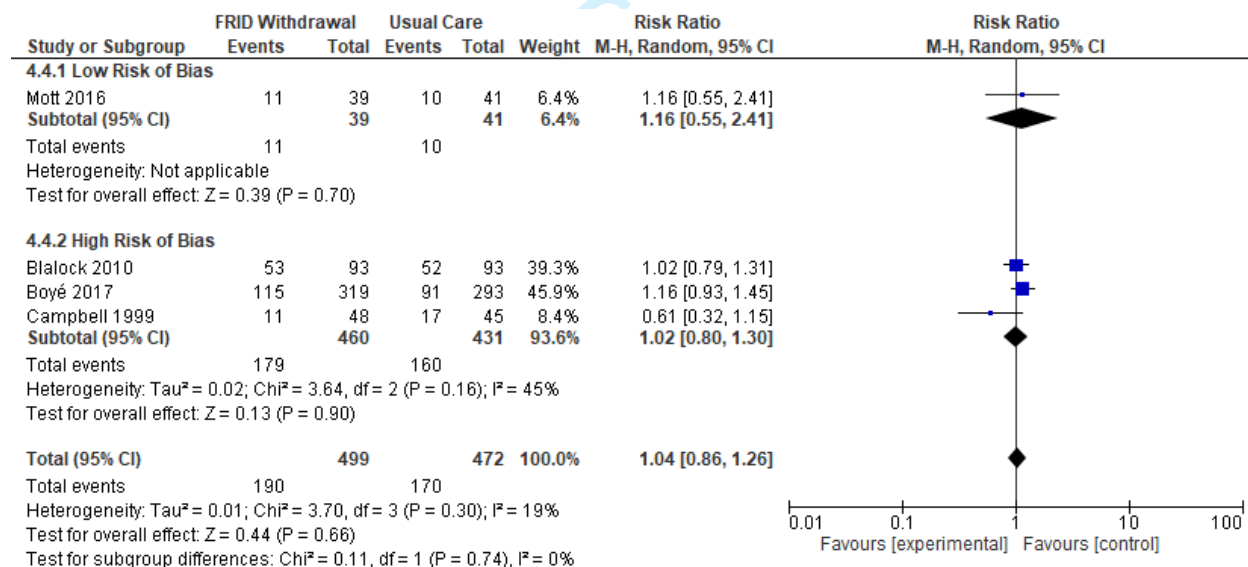
4.2 Falls Rate - Low vs. High Risk of Bias due to Attritional Bias



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

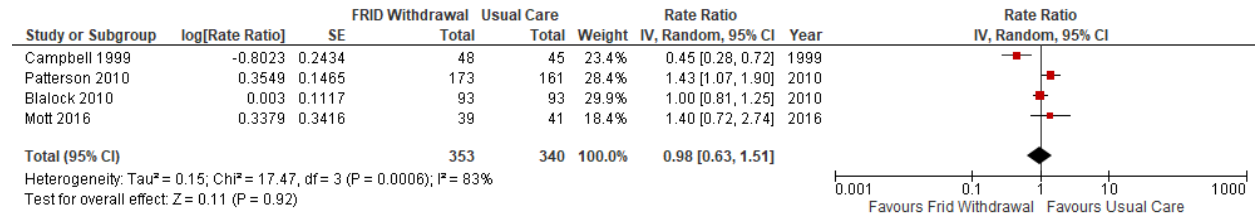


4.4 Falls Incidence - Low vs. High Risk of Bias due to Attrition Bias

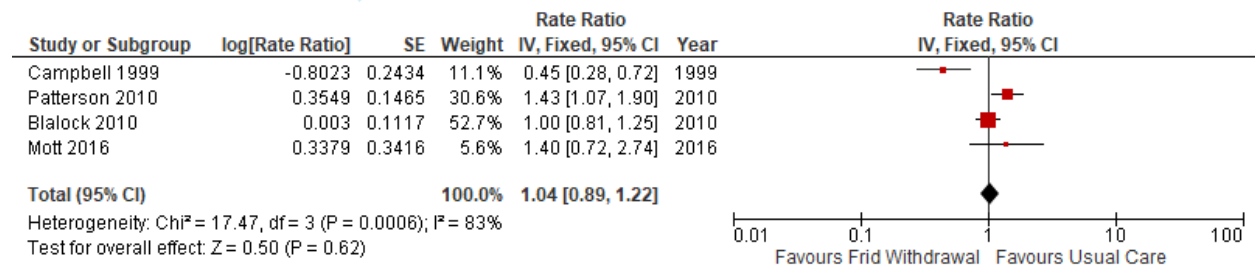


4.5 Falls Rate – Random vs. Effects Model

Random Effects Model

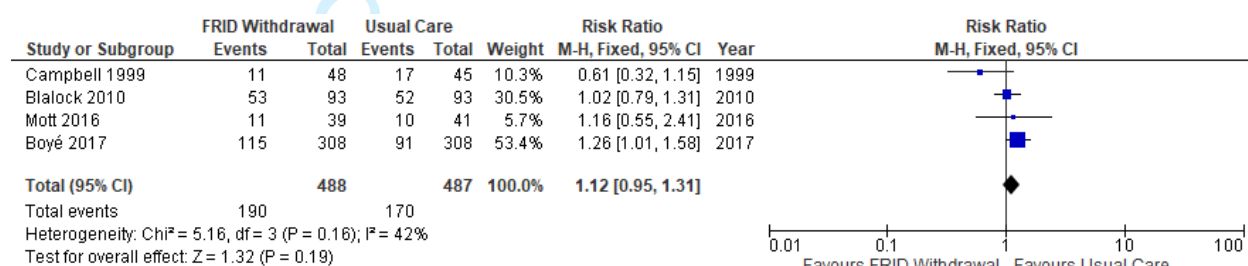
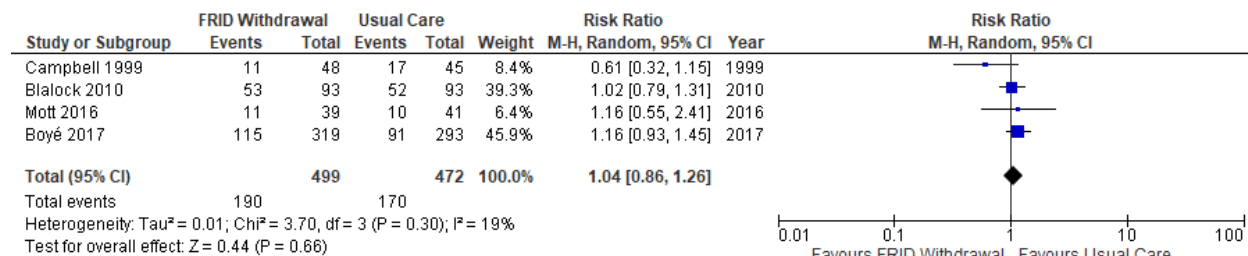


Fixed Effects Model

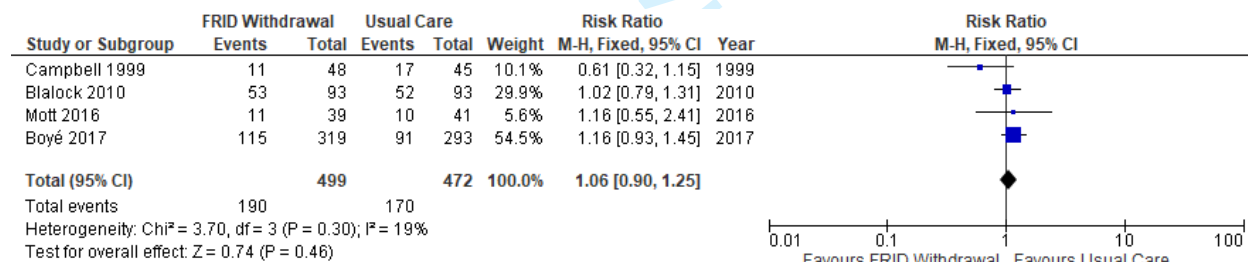


4.6 Falls Incidence – Random vs. Fixed Effects Model

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).	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

41

42 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.
43 doi:10.1371/journal.pmed1000097

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

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BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-035978.R3
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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

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3 **TITLE:** Deprescribing Fall-Risk-Increasing Drugs (FRIDs) for the Prevention of Falls and
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5 Fall-related Complications: A Systematic Review and Meta-analysis
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10 **AUTHORS:** Justin Lee, BScPhm, ACPR, MD^{1,2,3}

11
12 Ahmed Negm, MD, MSc, PhD^{3,4}

13
14 Ryan Peters, BSc, MD⁵

15
16 Eric Wong, BSc, MD⁶

17
18 Anne Holbrook, MD, PharmD, MSc^{2,7}
19
20
21
22
23

24 ¹Division of Geriatric Medicine, Department of Medicine, McMaster University, Hamilton,
25 Ontario, Canada

26 ²Department of Health Research Methods, Evidence, and Impact, McMaster University,
27 Hamilton,
28 Ontario, Canada

29 ³Geriatric Education and Research in Aging Sciences (GERAS) Centre, Hamilton, Ontario,
30 Canada

31 ⁴School of Rehabilitation Sciences, Faculty of Health Sciences, McMaster University, Hamilton
32 Ontario, Canada;

33 ⁵Department of Medicine, Queen's University, Kingston, Ontario, Canada

34 ⁶Division of Geriatric Medicine, Department of Medicine, University of Toronto, Toronto,
35 Ontario, Canada

36 ⁷Division of Clinical Pharmacology and Toxicology, Department of Medicine, McMaster
37 University, Hamilton, Ontario, Canada
38
39
40

41 **CORRESPONDING AUTHOR:** Justin Lee
42 Geriatric Education and Research in Aging Sciences Centre
43 88 Maplewood Avenue, Room 158
44 Hamilton, Ontario, Canada L8M 1W9
45 Email: justin.lee@medportal.ca
46 Telephone: (905) 521-2100
47
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49 **MAIN TEXT WORD COUNT:** 3724 (excluding title page, abstract, references, tables)
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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

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3 of fall-related injuries (RaR 0.89, 95% CI 0.57 to 1.39) over a 6 to 12 month follow-up period. No
4 trials evaluated the impact of deprescribing FRIDs on fall-related fractures or hospitalizations.
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10 **Conclusion:** There is a paucity of robust high-quality evidence to support or refute that a FRID
11 deprescribing strategy alone is effective at preventing falls or falls-related injury in older adults.
12 Although there may be other reasons to deprescribe FRIDs, our systematic review found that it
13 may result in little to no difference in the rate or risk of falls as an sole falls reduction strategy.
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21 **Registration:** PROSPERO CRD42016040203
22
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25

26 **Key Words:** Falls, Falls prevention, Fall-risk increasing drug (FRID), Deprescribing, Medication
27 withdrawal, Seniors, Older Adults, Systematic review
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33 **Word Count: 295**
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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]

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3 As an individual intervention, only exercise has robust evidence demonstrating reductions
4 in the incidence of fallers and rate of injurious falls.[6,8] It is unclear if other parts of the multi-
5 component strategy are effective, how large is their individual treatment effect, and which
6 components should be prioritized when resources are limited.
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12 Although there is limited evidence of effectiveness, deprescribing medications known as
13 “fall-risk increasing drugs” (FRIDs) is common practice and typically included in both
14 multifactorial and single intervention strategies. The justification is based on observational studies
15 that suggest certain medications are associated with increased falls risk as well as some
16 randomized controlled trials (RCTs) that have shown that medication management interventions
17 (including those with a broader focus of reducing polypharmacy and/or potentially inappropriate
18 prescribing) may reduce the risk of falls.[9] FRIDs include anti-hypertensives, anti-arrhythmics,
19 anti-cholinergics, anti-histamines, sedatives-hypnotics, anti-psychotics, anti-depressants, opioids
20 and NSAIDs.[10–15]. Although the mechanisms are not fully understood, these drugs may
21 influence falls risk by adversely affecting the cardiovascular or central nervous system (e.g.
22 orthostatic hypotension, bradycardia, sedation, sleep disturbance, confusion, dizziness).
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38 Key issues affecting the quality of this observational evidence and certainty of a causal
39 relationship include: (1) variable adjustment for confounders, dosage or duration of therapy, (2)
40 medication use confirmed only at baseline (but not throughout follow-up), and (3) potential
41 prescribing bias associated with specific medication classes. Most meta-analyses have also been
42 based on the pooling of unadjusted estimates and thus susceptible to bias including confounding
43 by indication. As a result, it is unclear whether the observed increase in falls is causally related to
44 such drug use versus the underlying conditions or patients for which the drugs are treating.
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3 With the aim of evaluating its effectiveness as a single falls prevention strategy, we
4 conducted this systematic review to answer the following: “In older adults aged 65 years or older,
5 does deprescribing and the withdrawal of fall-risk increasing drugs (FRIDs) decrease the risk of
6 falls compared to usual care and continuation of these drugs?” To the best of our knowledge, no
7 previous systematic review has addressed this specific research question.
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17 **METHODS**

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

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33 MEDLINE, EMBASE, CINAHL and the Cochrane Central Register of Controlled Trials
34 (CENTRAL) electronic databases were searched from inception to August 1, 2020 using a
35 combination of Medical Subject Headings, controlled and free-text terms synonymous for the
36 intervention. The MEDLINE search strategy is shown in Supplementary Figure S1. This strategy
37 was modified for use in other databases.
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44 Reference lists of relevant studies, reviews and guidelines were reviewed to identify
45 additional studies. Trial registries and geriatric medicine conference abstracts were also reviewed.
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51 **Study Eligibility Criteria**

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3 After pilot testing the eligibility criteria, pairs of reviewers independently conducted
4 screening. A third reviewer resolved disagreements.
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8 Studies were included if they were RCTs evaluating FRID deprescribing or withdrawal
9 with the intent of reducing falls. FRID deprescribing was defined as the planned and supervised
10 discontinuation or dose reduction of single or multiple medications thought to independently
11 increase falls risk.[10–12]
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17 The comparator could be usual care (i.e. no change in usual activities and/or no FRID
18 withdrawal) or a control intervention not thought to reduce falls. Studies focused on adults aged
19 ≥ 65 years from all settings were included. Studies involving FRID withdrawal within multi-
20 component interventions were excluded if the effect of FRID withdrawal could not be isolated.
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26 The primary outcomes of this review were the (1) rate of falls (defined as the total number
27 of falls per unit of person time that falls were monitored) and (2) incidence of falls (i.e. number of
28 fallers). Secondary outcomes included the incidence of (1) fall-related fractures, (2) fall-related
29 injuries, (3) fall-related hospitalization, (4) adverse effects related to the withdrawal intervention
30 (e.g. disease relapse, symptomatic withdrawal).
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40 **Data Extraction and Quality Assessment**

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42 Two reviewers independently abstracted data on study characteristics, participants,
43 interventions, comparisons, and outcomes using standardized electronic data extraction forms.
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46 Disagreements were resolved through consensus.
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49 Two reviewed independently conducted risk of bias (RoB) assessments using the Cochrane
50 Risk of Bias tool.[19] A previously published modification to the RoB assessment was employed
51 to estimate unclearly reported study methods and allow for sensitivity analysis.[20] This
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3 modification involved a structured approach where a score of “definitely low risk”, “probably low
4 risk”, “probably high risk”, or “definitely high risk” was assigned to each RoB criterion.
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6 “Definitely” and “probably” scores were collapsed for both low and high RoB scores.
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8 Disagreements were resolved through consensus.
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14 **Data Synthesis and Analysis**

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16 The rate of falls was reported as a rate ratio (RaR) with a 95% confidence interval (CI).
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18 Dichotomous outcomes (i.e. incidences of falls, fall-related fracture, fall-related injury, fall-related
19 hospitalization and adverse effects related to the withdrawal intervention) have been reported as
20 risk ratios (RR) with 95% CIs.
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26 We used RevMan 5.3 and the intention-to-treat principle for all statistical analyses. We
27 conducted meta-analyses using the generic inverse variance method to allow pooling of effect
28 estimates. A random effects model was used given expected between-trial variations in
29 methodological, participant and medication characteristics between studies. We had originally
30 planned to pool data at various pre-specified time intervals, but all included studies had follow-up
31 between 6 to 12 months.
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40 We assessed heterogeneity through visual inspection of forest plots and statistical tests. A
41 two-tailed test with p-value <0.10 was considered significant for all Chi-square analyses as per
42 recommendations from the Cochrane Handbook and the I^2 was interpreted using the Cochrane
43 Collaboration thresholds.[16]
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49 Heterogeneity was explored in subgroup analyses based on five a priori hypotheses
50 (Supplementary Table S1).[18] These included differences in baseline propensity for falls as
51 influenced by (1) a history of recurrent falls (e.g. known faller or not) or (2) place of residence or
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3 care (e.g. community, long-term care); differences in the intervention as influenced by (3) specific
4 medication class(es) chosen for withdrawal and (4) preceding medication review by a clinician for
5 FRID withdrawal appropriateness; as well as differences in methodology based on (5) definitions
6 used for “falls” (e.g., observed vs. self-reported). We assessed the credibility of any apparent
7 subgroup effects using eleven previously published criteria recommended by the Cochrane
8 Handbook.[21]
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12 A priori sensitivity analyses were conducted to explore the impact of low vs. high RoB
13 based on blinding and attrition. Studies did not report per-protocol results that would allow for our
14 planned intention-to-treat vs. per-protocol sensitivity analysis. The impact of using a fixed vs.
15 random effects model was explored in a post hoc sensitivity analysis.
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19 The confidence in effect estimates for each reported outcome was assessed using the
20 Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.[22]
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34 Patients and the public were not involved in this review.
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40 41 42 43 44 45 46 47 48 49 50 51 52 53 **RESULTS**

44 Of 891 citations identified, 31 were relevant for full text review and 6 met eligibility criteria
45 ($\kappa=0.79$, 95% CI 0.51-1.00, substantial agreement). One study was available as an abstract, but it
46 did not report its falls data.[23] Data were requested from the authors, but we did not receive a
47 response. The PRISMA flow diagram summarizing our search results is shown in Figure 1.
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53 54 55 56 57 58 59 60 **Study Characteristics**

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3 The included trials in our review are described in Table 1.
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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 \geq 65 3) Speak, read English 4) \geq 4 prescription medications 5) \geq 1 high falls-risk medication 6) \geq 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 \geq 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 \geq 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, benzotropine, trihexiphenidyl	1) FRID pharmacist review 2) Medication-related action plan (MAP) developed by pharmacist for patient 3) Pharmacist follow-up 4) Patient given pamphlet describing the role of medications in falls and monthly falls calendars 5) Patient given pamphlet 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 \geq 30 beds; not exclusive care of terminally ill 2) Age \geq 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 \geq 65 3) \geq 1 FRID for \geq 2 weeks prior to the fall 4) MMSE \geq 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, antihistaminics, 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

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

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

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3 Three studies were individually randomized, while two studies were cluster randomized by either
4 nursing home or health centre. Studies ranged in size from 80 to 612 participants. With exception
5 of one study[26], studies were multi-centre involving 144 sites and 4 countries. All were conducted
6 in the community setting except for one conducted in long-term care.[27] Follow-up periods
7 ranged from 6 to 12 months.
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11 Overall, there were 1305 participants across all trials. Most were female (>70%) and had a
12 falls history (78.9%). Several key confounders were not reported in the studies including: (1)
13 baseline number and types of FRIDs, (2) baseline number of medications, and (3) baseline number
14 and types of co-morbidities. All these factors are thought to potentially modify falls risk.[29,30]
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17 All interventions included a preceding assessment for FRID deprescribing appropriateness.
18 This was conducted by physicians in 2 trials and pharmacists in 3 trials. Three trials tried to
19 withdraw any FRID, while others focused on sedative-hypnotics, antipsychotics, or
20 antidepressants. Successful discontinuation and adherence to deprescribing protocols were low in
21 all studies. Rates of complete discontinuation of at least one FRID ranged from 10 to 40%.
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24 In terms of our study outcomes, 4 trials measured the rate of falls and 4 measured falls
25 incidence. One trial reported fall-related injuries.[24] Fall-related fractures, fall-related
26 hospitalization or deprescribing-related adverse effects were not measured by any of the trials.
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33 34 35 36 37 38 39 40 41 42 43 44 **Summary of Findings**

45 46 47 **Rate and Incidence of Falls**

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49 Four studies reported the effect of deprescribing FRIDs on the rate of falls. Deprescribing
50 FRIDs did not reduce the rate of falling (RaR 0.98, 95% CI 0.63 to 1.51; Figure 2 – Analysis 1.1).
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3 Considerable statistical heterogeneity was present ($\chi^2=17.47$, $p=0.0006$, $I^2=83\%$) and subsequently
4 explored in subgroup analysis.
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8 Four studies reported the effect of deprescribing FRIDs on the risk of falls as measured by
9 falls incidence. Deprescribing FRIDs did not reduce the incidence of falls (RR 1.04, 95% CI 0.86
10 to 1.26, $I^2 = 19\%$, $\chi^2=3.70$, $p = 0.30$; Figure 2 – Analysis 2.1). In absolute terms, there was a non-
11 significant risk difference increase of 0.01 (95% CI -0.06 to 0.09, $I^2 = 22\%$, $p=0.76$; Figure 2 –
12 Analysis 2.2)
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19 20 21 ***Rate of Injurious Falls*** 22

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24 One trial reported the effect of deprescribing FRIDs on fall-related injuries.[24]
25 Deprescribing FRIDs did not reduce the rate of fall-related injuries (RaR 0.89, 95% CI 0.57 to
26 1.39; Figure 2 – Analysis 3.1). This trial did not report data that would allow for any of our pre-
27 planned subgroup analyses.
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33 34 35 **Risk of Bias Assessment** 36

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38 Figure 3 summarizes our RoB assessments. All studies were deemed at high risk of bias in
39 at least one domain. The overall mean weighted kappa across all assessments was 0.67 (moderate
40 agreement). For individual RoB assessments, kappa ranged from 0 to 0.85. Inter-rater agreement
41 is actually higher than indicated by the calculated scores due to the “kappa co-efficient
42 paradox”. [31,32] Low kappas (e.g. $\kappa=0$) occurred despite high levels of observed agreement (e.g.
43 $\geq 80\%$ agreement) for two RoB assessments. True agreement is falsely attributed to chance
44 agreement by the kappa calculation when there is substantial imbalance in marginal ratings.
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3 For falls rate and incidence, all studies except one[25] were judged at high risk of bias for
4 lack of blinding of participants, personnel and outcome assessors. It is unclear whether blinding
5 could have impacted behaviour or perceptions (e.g. activity risk-level, placebo effect). Risk of
6 ascertainment bias was high in one study[27] (i.e. no standardized falls definition was used), but
7 all other studies used methods accepted to be low risk of bias (i.e. falls recorded daily on postcards
8 or calendars). Risk of attrition bias was deemed high in three studies based on high or unbalanced
9 lost to follow-up rates.[24,25,28]
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21 ***Publication Bias***

22 Since less than 10 eligible studies were found, a funnel plot was not constructed due to an
23 inability to make meaningful conclusions about publication bias.
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30 ***Subgroup Analyses and Exploration of Heterogeneity***

31 Our pre-specified subgroup analyses did not adequately explain the statistical
32 heterogeneity observed results for the rate and incidence of falls (Supplementary Figure S2).
33 Deprescribing FRIDs appeared more effective when a preceding medication review was conducted
34 by physicians compared to pharmacists ($p=0.0004$, $I^2=91.9\%$, Analysis 1.5), while psychotropic
35 withdrawal appeared more effective than strategies withdrawing any FRID ($p=0.08$, $I^2=67.8\%$,
36 Analysis 2.3). However, in both analyses, only 6 of 11 subgroup credibility criteria were met and
37 each subgroup was limited to one trial with less than 100 participants (Supplementary Table S2).
38 We, therefore, judged the credibility that these subgroup effects are real as poor and uncertain.
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3 The available data did not permit subgroup analyses by place of residence or falls
4 ascertainment method. The other subgroup analyses showed no evidence of difference beyond that
5 due to chance.
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10 11 12 **Sensitivity Analyses** 13

14 Our sensitivity analyses are shown in Supplementary Figure S3. The incorporation of trials
15 with high risk of performance bias appeared to mask the potential benefit of deprescribing FRIDs
16 on reducing the incidence and rate of falls, while the trials with high risk of attrition bias appeared
17 to mask a potential increase in falls rate with deprescribing FRIDs. These results should be
18 interpreted cautiously and definitive conclusions cannot be made. Data from trials with low risk
19 of performance bias were limited to one trial with less than 100 participants, and data from trials
20 with low risk of attrition bias were limited to two trials with less than 450 participants overall.
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30 A post-hoc sensitivity analysis examining the impact of using a fixed vs. random effects
31 model did not change conclusions regarding the effect of deprescribing FRIDs on the rate or
32 incidence of falls.
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40 **Quality of Evidence** 41

42 The GRADE evidence profile is shown in Table 2.
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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)	-	⊕○○○ 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

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3 We judged the quality of evidence to be low or very low for all outcomes (falls rates, falls incidence
4 and fall-related injuries) after rating down for risk of bias, inconsistency and imprecision.
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8 We believe the optimal information size (OIS) to make definitive conclusions on the effect
9 of deprescribing FRIDs has not yet been met as the body of evidence is based on fewer than 2000
10 participants and less than 400 events.[33,34] This is based on the OIS calculation figure
11 recommended by the GRADE guidelines using a well-established control falls event rate of 30%
12 described in the literature and conservative relative risk reduction (RRR) of 20% (assuming $\alpha =$
13 0.05 and $\beta = 0.2$).[34,35]
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24 **DISCUSSION**

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26 This systematic review sought to determine whether deprescribing FRIDs decreased the
27 risk of falls in older adults and found that there is a lack of robust high-quality evidence to support
28 or refute the deprescribing of FRIDs alone as an effective fall prevention strategy. Incorporating
29 data from 5 RCTs involving 1305 participants aged ≥ 65 years, our meta-analyses indicate that a
30 FRID deprescribing strategy did not significantly change the rate of falls (RaR 0.98, 95% CI 0.63
31 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
32 period. Although this intervention focuses on those medications thought to be associated with falls,
33 the uncertainty of its effect on falls and conclusions of current lack of evidence of effectiveness
34 are similar to previous systematic reviews evaluating the effectiveness of medication reviews that
35 had a broader focus on reducing polypharmacy and potentially inappropriate prescribing (i.e. not
36 focused solely on FRIDs).[9,36]
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51 There is also a significant absence of evidence for clinically- and patient-important
52 outcomes such as fall-related injuries, fractures and hospitalizations. The only trial to date that
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3 evaluated the rate of fall-related injuries did not demonstrate a statistically significant effect (RaR
4 0.89, 95% CI 0.57-1.39).[24] Our search found no trials measuring the impact on fall-related
5 fractures, fall-related hospitalizations or adverse effects related to a FRID deprescribing strategy.
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7 Although this may be rooted in the difficulty of conducting RCTs powered for such outcomes,
8 their measurement and reporting are still important to inform systematic review meta-analyses that
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10 could lead to more precise estimates.
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17 Based on low-quality evidence, it is unclear whether deprescribing FRIDs as a single
18 intervention leads to any appreciable clinically important benefit or harm. Our current best effect
19 estimates for falls rate and incidence are centred around no appreciable difference (i.e. RaR \approx 1,
20 RR \approx 1, RD \approx 0). Although seemingly logical to assume, reducing isolated risk factors may not
21 necessarily lead to a reduction in falls and fall-related complications. The absence of change in the
22 incidence of hip fractures after statewide regulatory action on benzodiazepine prescribing in the
23 United States that reduced benzodiazepine use by 60.3% is a real-world example of this
24 phenomenon and the complexity of exposure-outcome relationships.[37]
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35 Our findings likely reflect the multi-factorial nature of falls and the varying risk of different
36 FRIDs. It is unclear as to what degree a particular risk factor or combination of risk factors (e.g.
37 specific FRIDs) must be reduced to produce an appreciable change in falls. Medications may only
38 have conditional or contributory causality to falls. It may be that medication-related interventions
39 work best in combination with other interventions or only in specific contexts.
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47 Only one trial[25] included in our review demonstrated a statistically significant benefit
48 with deprescribing FRIDs. This was also the only trial to use study capsules to operationalize
49 blinded deprescribing of FRIDs in participants, research personnel and outcome assessors. Its
50 results might be more reflective of the true potential physiological effect of deprescribing FRIDs
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3 because it minimized the risk of performance bias. However, the magnitude of benefit achievable
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5 in the non-research setting at this time may be closer to those seen in the unblinded trials due to
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7 the strong psychological and behavioural factors (e.g. placebo effect) that may hinder successful
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9 deprescribing. Further advances in implementation science and behavioural change strategies are
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11 likely needed to facilitate medication optimization.
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15 These results raise several questions about the presumed effectiveness of deprescribing
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17 FRIDs as an isolated falls prevention strategy. Given the amount of resources being invested into
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19 falls prevention initiatives around the world, clinicians and organizations should examine: (1) what
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21 is the strength of evidence supporting their current activities, (2) whether these activities are cost-
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23 effective, and (3) whether resources are being appropriately prioritized to those interventions
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25 shown to provide the most value. This should also be applied to what is being required of
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27 healthcare organizations in national accreditation standards (e.g. Joint Commission, Accreditation
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29 Canada) to help direct and encourage optimal use of limited healthcare resources.
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33 Clinicians and policy-makers need to consider the current lack of strong evidence for
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35 deprescribing FRIDs as an isolated intervention for the specific purpose of reducing falls,
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37 particularly in patients who may be very reluctant or who have strong indications for specific
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39 FRIDs. FRID reduction is one out of many possible interventions that need to be considered. As
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41 with prescribing medications, deprescribing is a skill and comes with the potential for harm as well
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43 as benefit.[38] Thoughtful consideration of the goals, appropriateness and safety of deprescribing
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45 is important.[39] Our results highlight the need for a comprehensive and individualized approach
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47 to falls. Multi-component interventions are ideal, but interventions may need to be prioritized
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49 depending on time, resources and context.
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3 Despite insufficient evidence to support or refute the deprescribing of FRIDs for falls
4 prevention, our results do not mean that clinicians should avoid deprescribing FRIDs. There may
5 be many other reasons to deprescribe these medications. These include avoidance of adverse drug
6 events, improvements in cognition, increased medication adherence and drug costs savings. It is
7 also unclear whether medication review and management with a broader focus on reducing
8 polypharmacy and potentially inappropriate prescribing in older adults may be beneficial in
9 preventing falls. Some RCTs with such interventions have shown a reduction of falls risk, while
10 others have not demonstrated a significant difference.[40–46]
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21 Our review highlights the need for future FRID deprescribing trials that evaluate patient-
22 important outcomes (e.g. injuries, fractures and hospitalizations). Greater attention to optimal
23 design and reporting is needed to minimize risk of bias and enhance our interpretation of the results.
24 Examples include improved reporting of confounding baseline characteristics and intervention
25 fidelity (e.g. number and types of FRIDs, degree and duration of dose reduction). Deprescribing
26 is challenging and extra measures are likely needed to improve successful intervention adherence
27 and follow-up.
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40 **STRENGTHS AND LIMITATIONS**

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42 Our review has limitations. There was variation in the operationalization of FRID
43 deprescribing and degree of success achieved (e.g. dose reduction only, completion
44 discontinuation, non-adherence). This presumably makes the detection of any potential benefit less
45 likely and our conclusions more conservative. However, the effect estimates are likely more
46 indicative of what might be expected outside of the research setting. These phenomena likely
47 represent the real-life challenges of deprescribing (especially with certain types of FRIDs such as
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3 psychotropics or opioids). Moreover, our ability to assess for confounders modifying falls risk was
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5 limited due to inconsistent reporting of relevant baseline characteristics and lack of patient-level
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7 data. Lastly, our ability to make definitive conclusions is limited because the total sample size
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9 across studies for each outcome did not yet meet our calculated estimate for the required optimal
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11 information size.
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15 Our review has several strengths. First, our search was comprehensive and we included a
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17 rigorous grey literature search for unpublished studies. Second, we employed optimal analytical
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19 and interpretational approaches including duplicate assessment, subgroup credibility criteria and
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21 optimal information size considerations. Third, unlike previous medication-focused reviews, we
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23 applied the GRADE approach to assess the quality of evidence and our degree of confidence in
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25 the results.
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30 31 **CONCLUSIONS**

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33 Our systematic review found that deprescribing FRIDs as an isolated strategy results in
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35 little to no difference in the rate and risk of falls or falls-related injuries, but the evidence is still
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37 sparse and very low quality. Additional well-designed studies are needed to reach the optimal
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39 information size to reduce uncertainty about this intervention and establish its relative importance
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41 in the range of possible interventions that can be employed by clinicians and health systems to
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43 reduce falls.
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9

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11
12 JL conceptualized the study. JL and AH designed and developed the protocol. RP and EW assisted
13 with citation review. RP and AN assisted with data extraction, risk of bias assessment and certainty
14 of evidence grading. All authors contributed to the analysis and interpretation of results. JL drafted
15 the initial manuscript and all authors contributed to its revision and final approval.
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23

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32

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34
35 The authors have no potential conflicts of interest to declare.
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40 **Patient Consent for Publication:**

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42 None required.
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47 **Data Sharing Statement:**

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49 No unpublished data are available.
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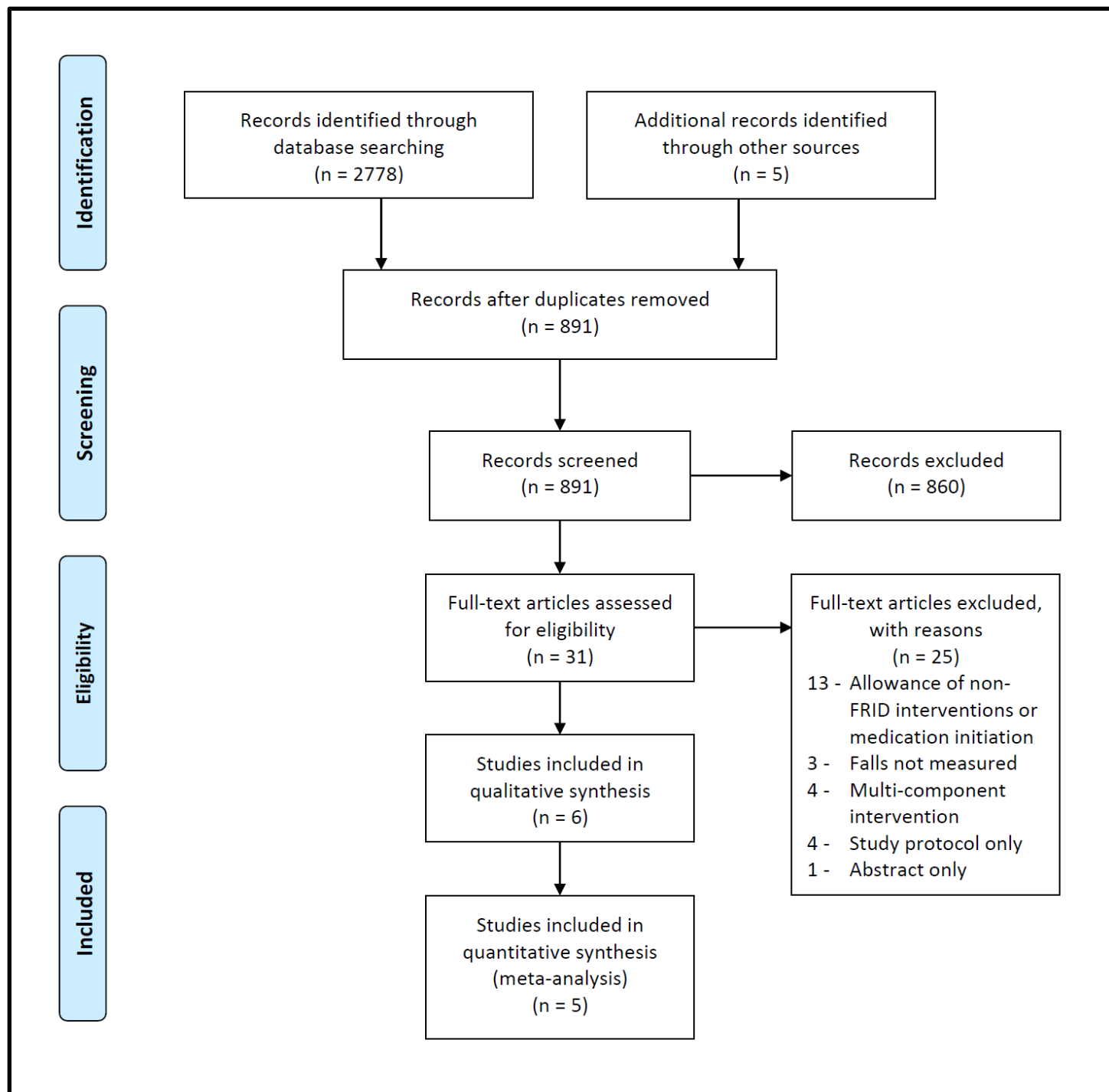
1
2
3 **FIGURES**
4

5 **Figure 1:** PRISMA Flow Diagram of Study Selection Process
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7 **Figure 2:** Forest Plots of FRID Withdrawal versus Usual Care
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9 **Figure 3:** Risk of Bias Assessments
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For peer review only



1.1 Falls Rate

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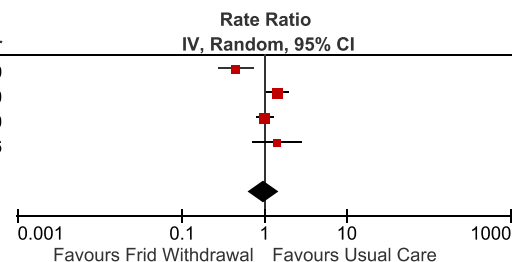
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Study or Subgroup	FRID Withdrawal		Usual Care		Weight	Rate Ratio		Year
	log[Rate Ratio]	SE	Total	Total		IV, Random, 95% CI	Year	
Campbell 1999	-0.8023	0.2434	48	45	23.4%	0.45	[0.28, 0.72]	1999
Patterson 2010	0.3549	0.1465	173	161	28.4%	1.43	[1.07, 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

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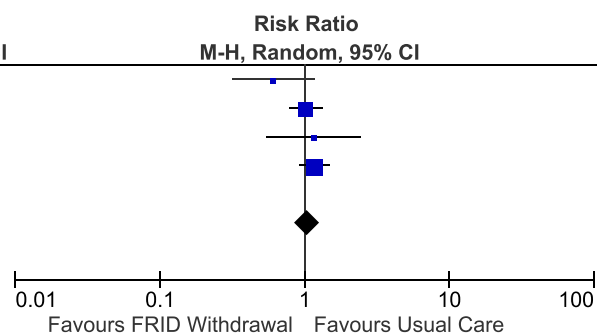
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Study or Subgroup	FRID Withdrawal		Usual Care		Weight	Risk Ratio	
	Events	Total	Events	Total		M-H, Random, 95% CI	M-H, Random, 95% CI
Campbell 1999	11	48	17	45	8.4%	0.61	[0.32, 1.15]
Blalock 2010	53	93	52	93	39.3%	1.02	[0.79, 1.31]
Mott 2016	11	39	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

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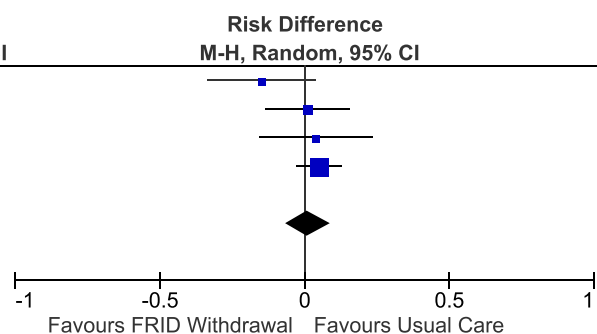
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Study or Subgroup	FRID Withdrawal		Usual Care		Weight	Risk Difference	
	Events	Total	Events	Total		M-H, Random, 95% CI	M-H, Random, 95% CI
Campbell 1999	11	48	17	45	14.2%	-0.15	[-0.33, 0.04]
Blalock 2010	53	93	52	93	21.8%	0.01	[-0.13, 0.15]
Mott 2016	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

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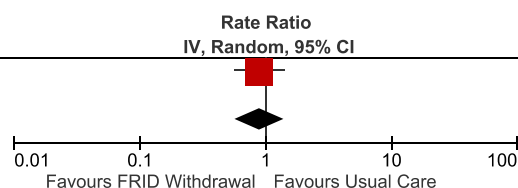
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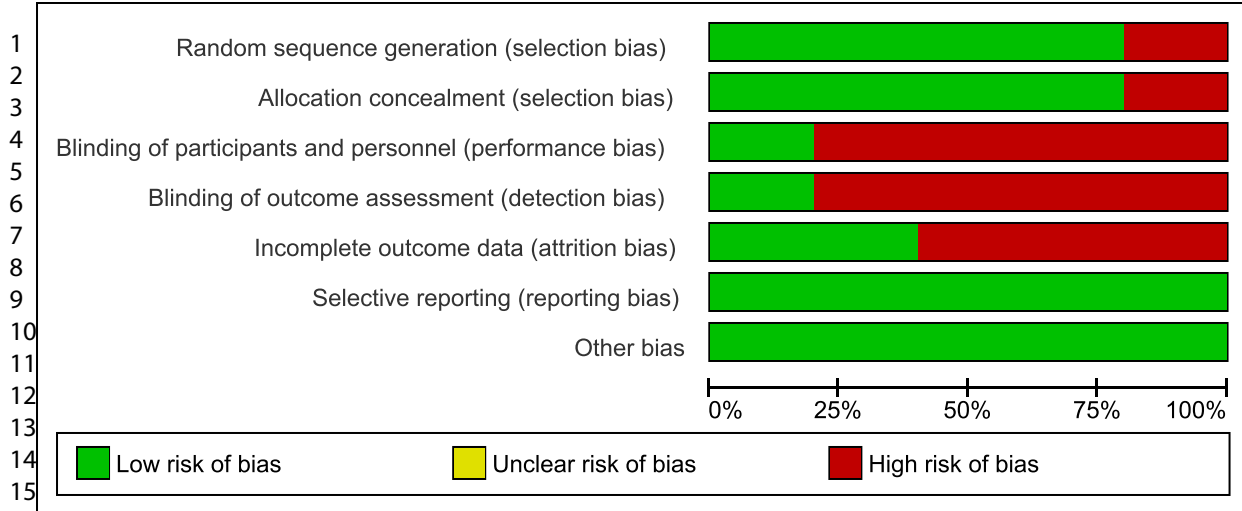
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Study or Subgroup	FRID Withdrawal		Usual Care		Weight	Rate Ratio		Year
	log[Rate Ratio]	SE	Total	Total		IV, Random, 95% CI	Year	
Blalock 2010	-0.1165	0.2273	93	93	100.0%	0.89	[0.57, 1.39]	2010
Total (95% CI)			93	93	100.0%	0.89	[0.57, 1.39]	

Heterogeneity: Not applicable

Test for overall effect: Z = 0.51 (P = 0.61)





	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Blalock 2010	+	+	-	-	-	+	+
Boyé 2017	+	+	-	-	-	+	+
Campbell 1999	+	+	+	+	-	+	+
Mott 2016	-	-	-	-	+	+	+
Patterson 2010	+	+	-	-	+	+	+

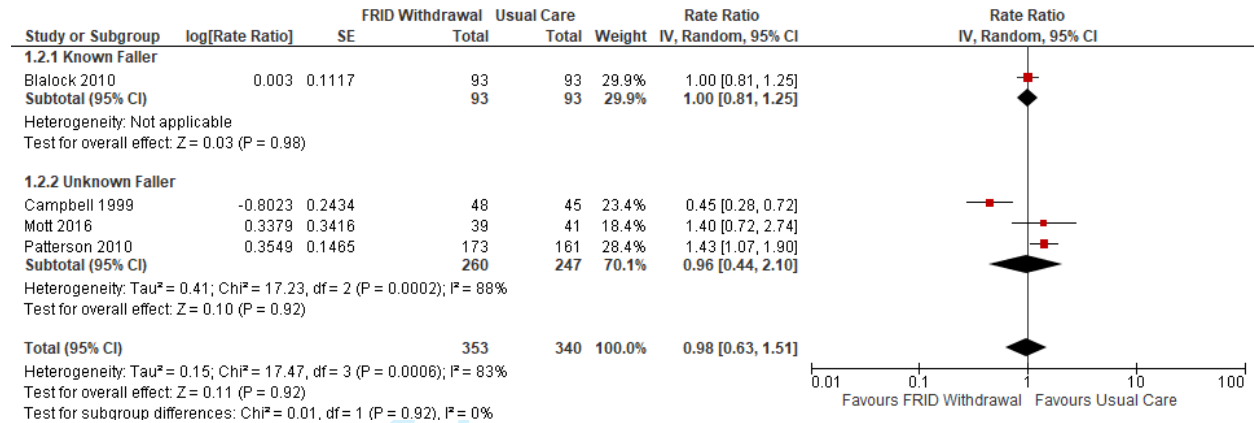
Supplementary Figure S1: OVID Medline Search Strategy

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:

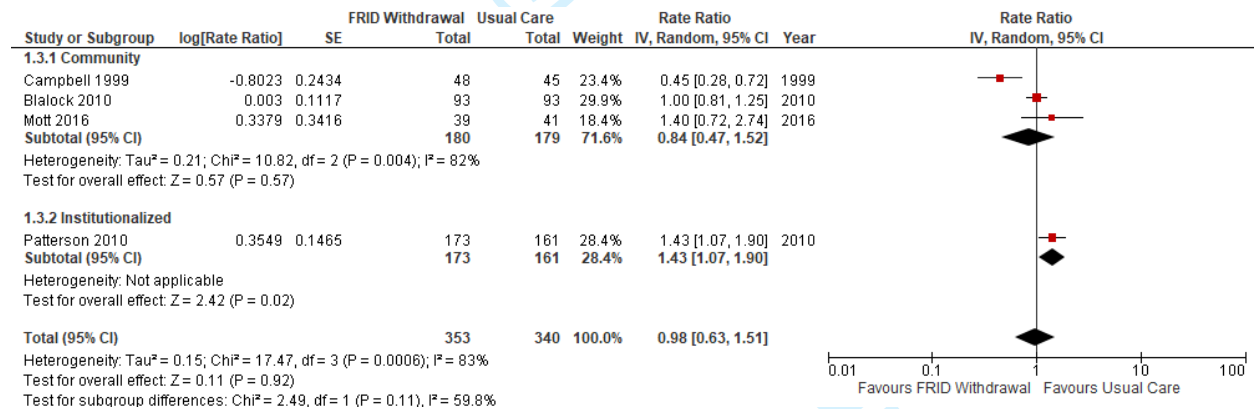
#	Searches
1	exp Accidental Falls/pc [Prevention & Control]
2	fall.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
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.
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19	randomly.ab,ti.
20	groups.ab,ti.
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24	15 and 23

Supplementary Figure S2: Subgroup Analyses

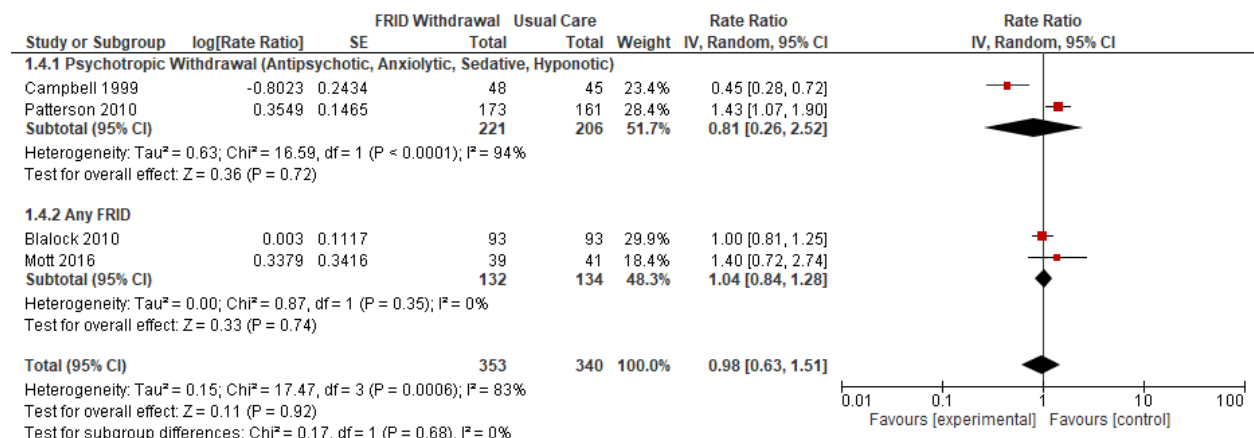
1.2 Falls Rate - Known vs. Unknown Faller



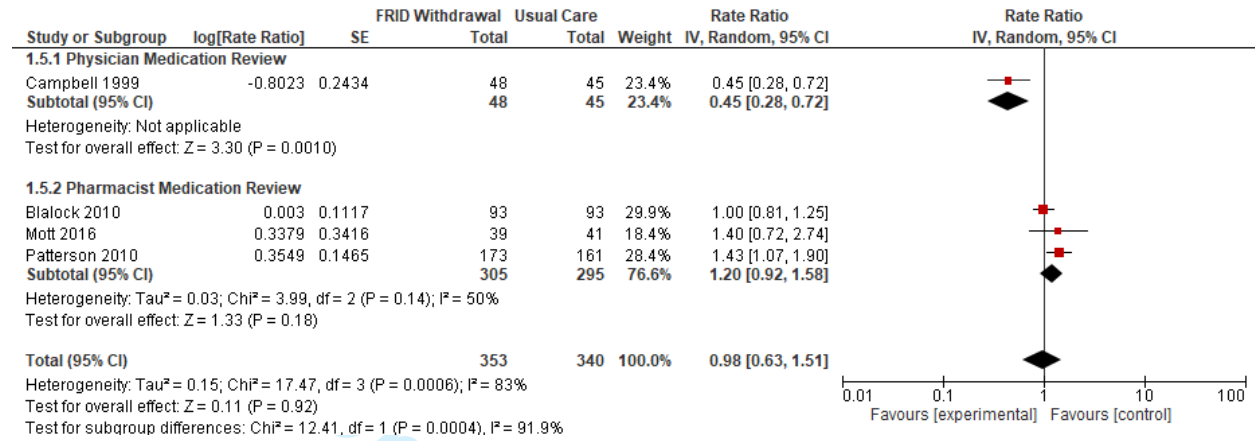
1.3 Falls Rate - Community vs. Institutionalized



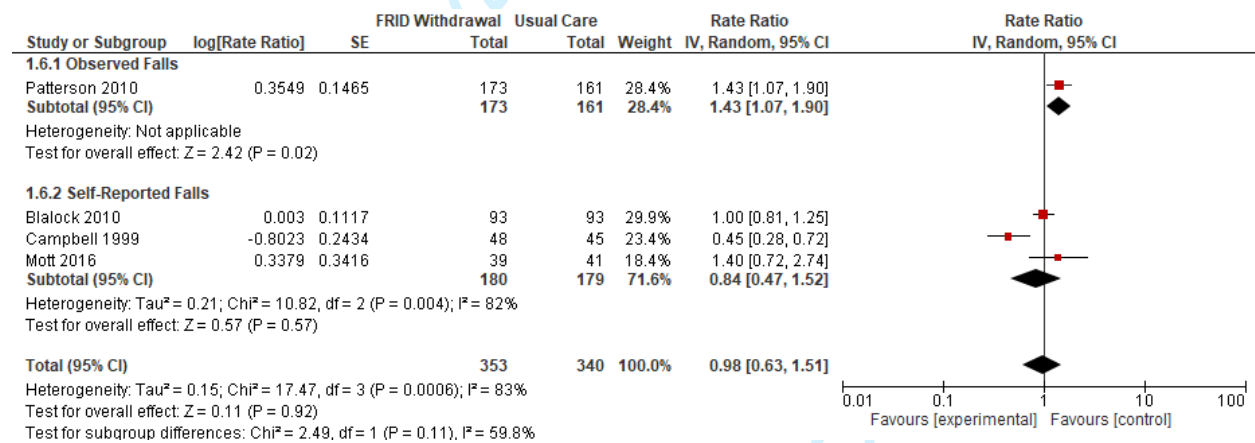
1.4 Falls Rate - Psychotropic Withdrawal vs. Any FRID Withdrawal



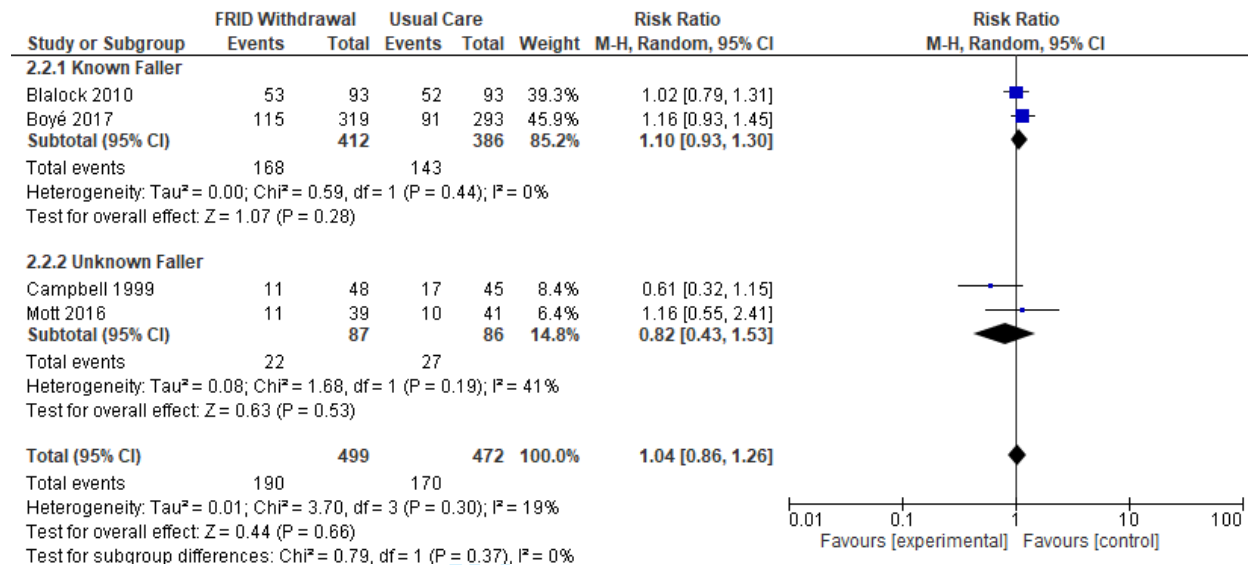
1.5 Falls Rate - Physician vs. Pharmacist Medication Review



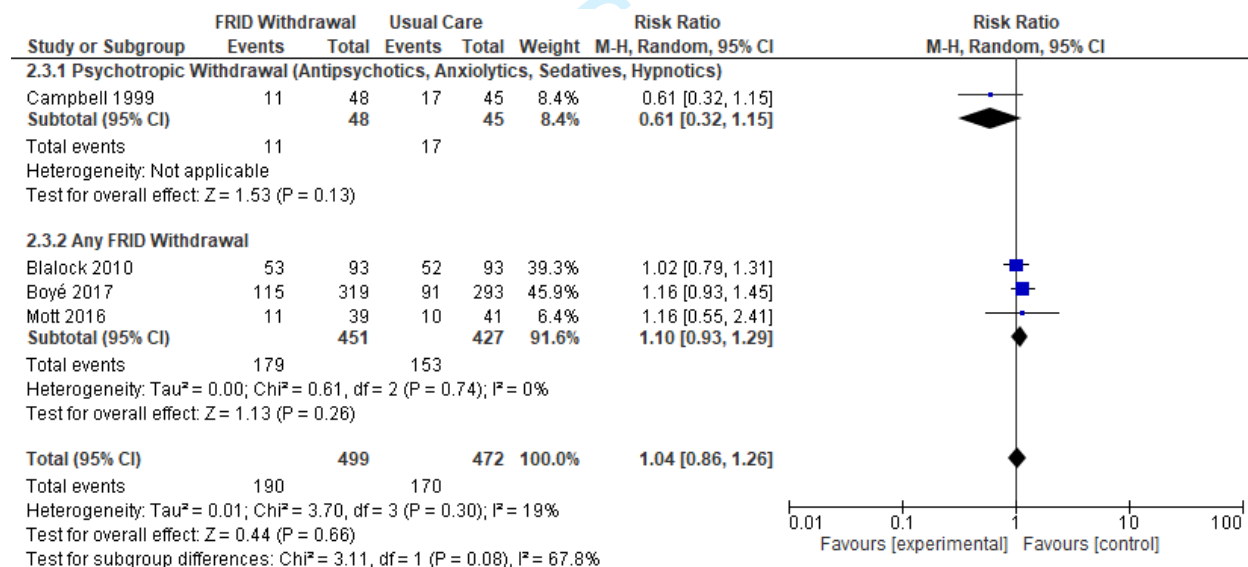
1.6 Falls Rate - Observed vs. Self-Reported Falls



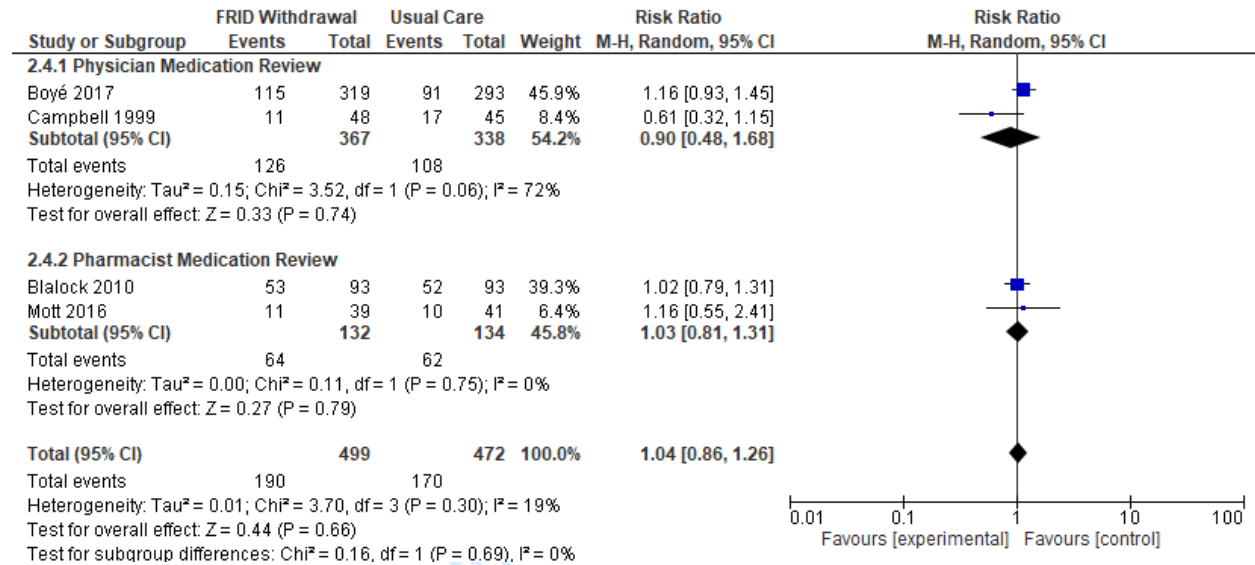
2.2 Falls Incidence - Known vs. Unknown Faller



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**

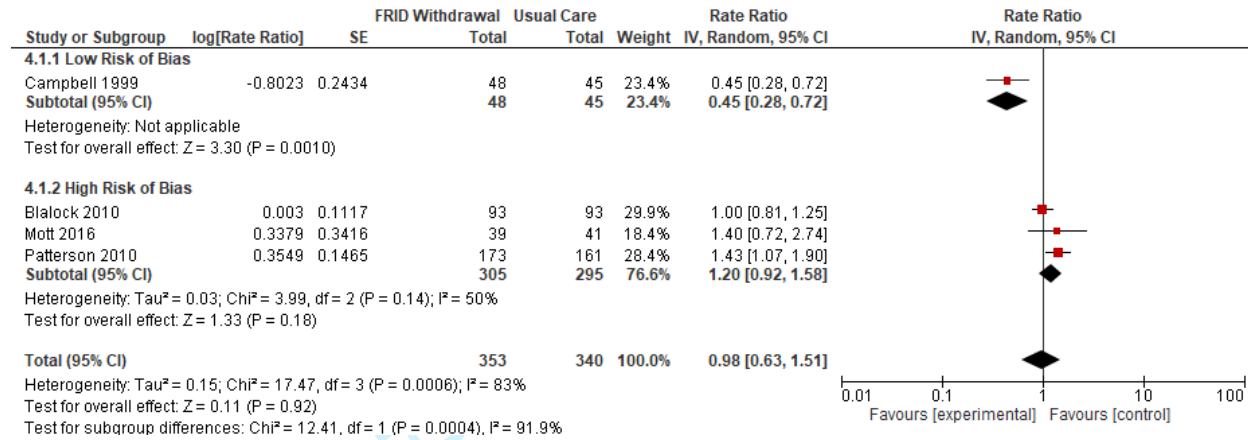
Design	Criteria Met?
Is the subgroup variable a characteristic measured at baseline or after randomization?	Yes – Variable determined at baseline
Is the effect suggested by comparisons within rather than between studies?	No – Comparison between studies
Was the hypothesis specified a priori?	Yes
Was the 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**

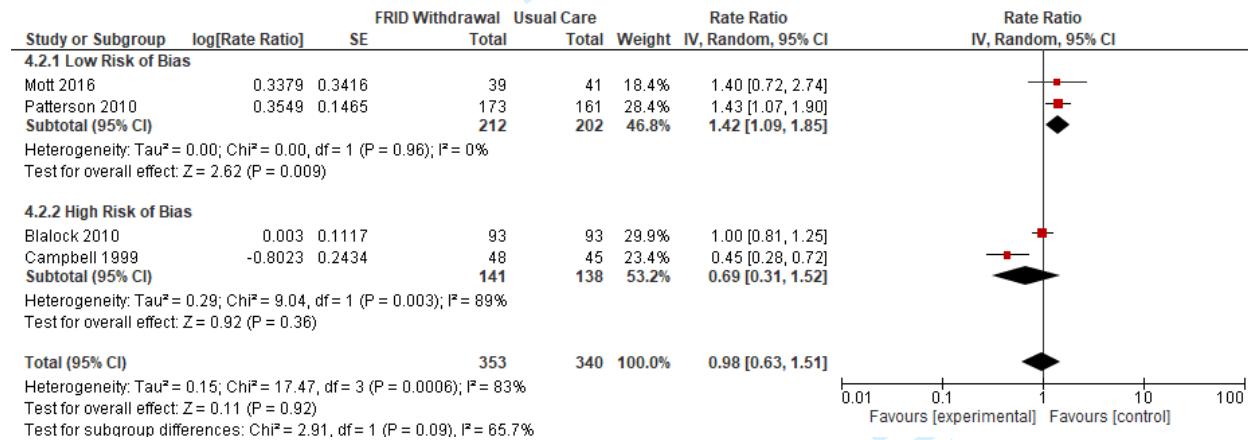
Design	Criteria Met?
Is the subgroup variable a characteristic measured at baseline or after randomization?	Yes – Variable determined at baseline
Is the effect suggested by comparisons within rather than between studies?	No – Comparison between studies
Was the hypothesis specified a priori?	Yes
Was the 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

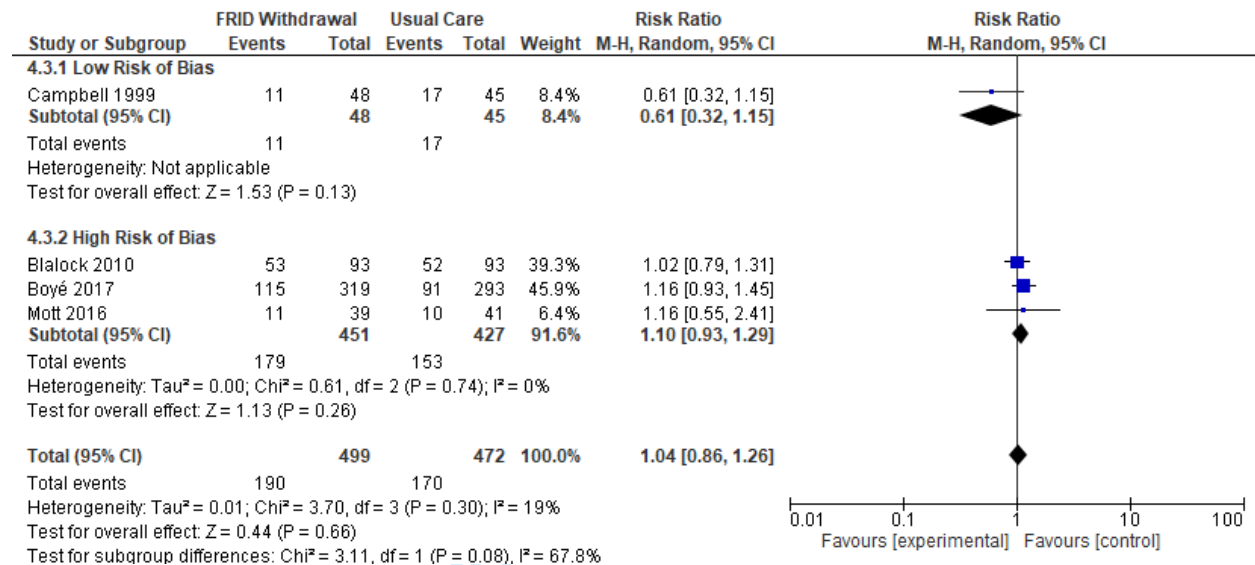
4.1 Falls Rate - Low vs. High Risk of Bias due to Blinding



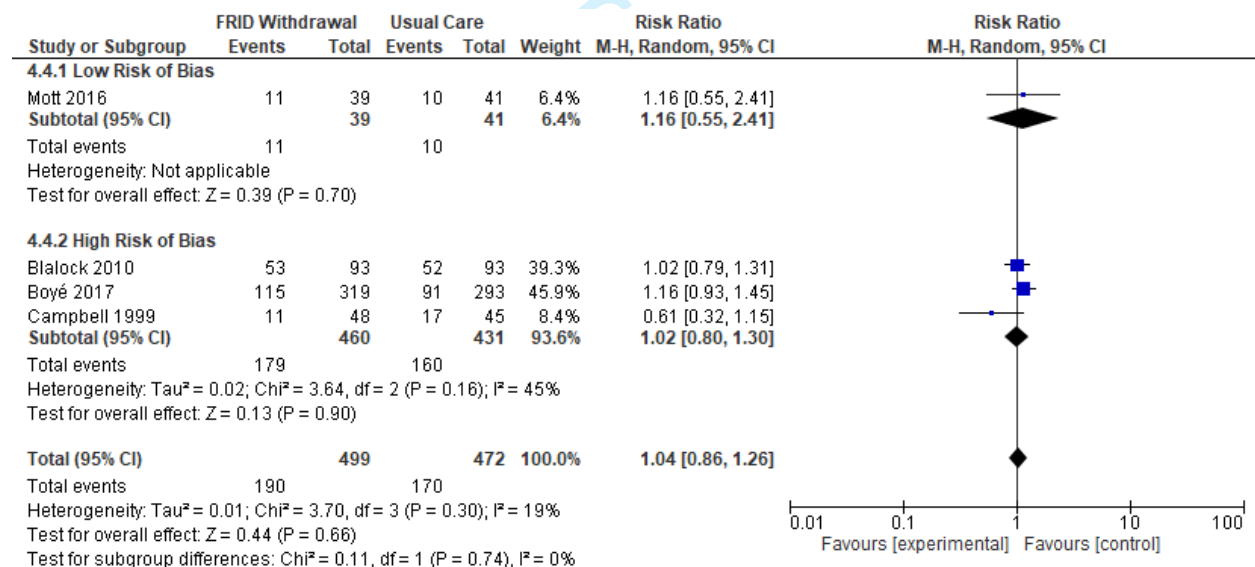
4.2 Falls Rate - Low vs. High Risk of Bias due to Attritional Bias



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

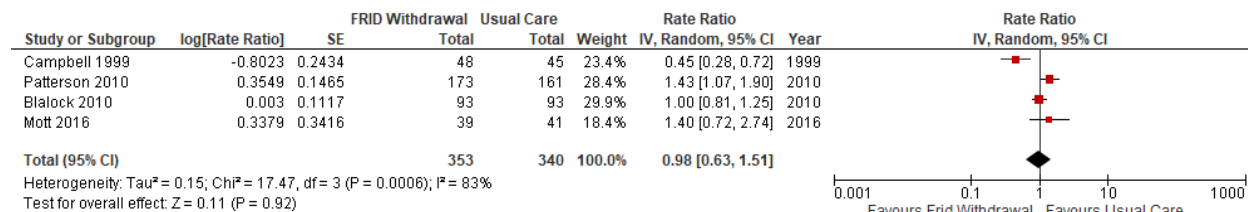


4.4 Falls Incidence - Low vs. High Risk of Bias due to Attrition Bias

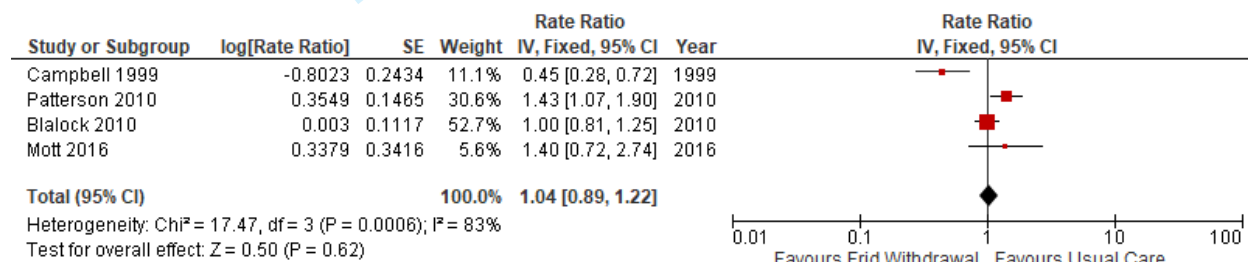


4.5 Falls Rate – Random vs. Effects Model

Random Effects Model

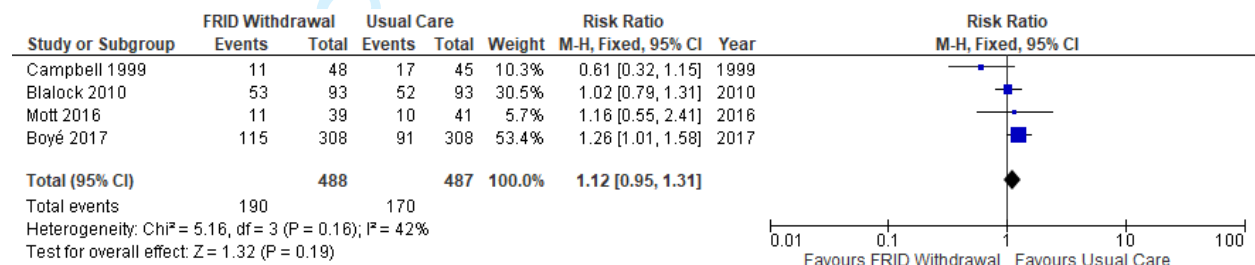
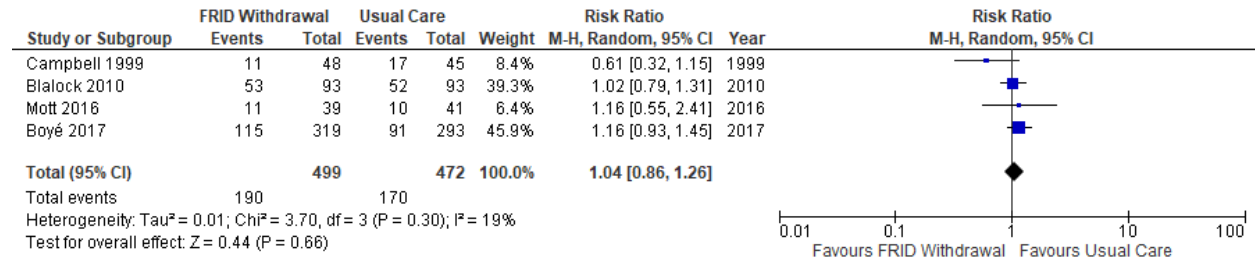


Fixed Effects Model

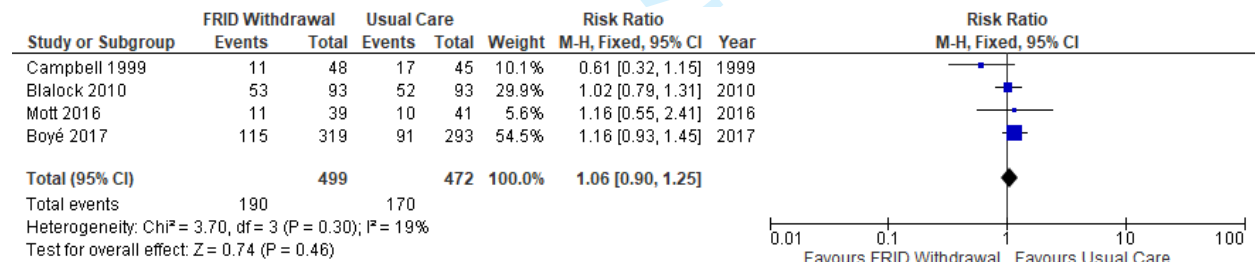


4.6 Falls Incidence – Random vs. Fixed Effects Model

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).	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

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