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Protocol for a systematic review and meta-analysis assessing the effectiveness of deprescribing in falls prevention in older people

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Keywords:	GERIATRIC MEDICINE, PUBLIC HEALTH, Adverse events < THERAPEUTICS

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Protocol for a systematic review and meta-analysis assessing the effectiveness of deprescribing in falls prevention in older people

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Abstract

Introduction

One of the known risk factors for fall incidents is the use of specific medications, fall-risk-increasing drugs (FRIDs). However, to date, there is uncertainty related to the effectiveness of deprescribing (reducing or stopping) FRIDs as a single intervention in falls prevention. Thus, a comprehensive update of the literature focusing on all geriatric settings and all deprescribing interventions is warranted to enhance the current knowledge.

Methods and analysis

This systematic review protocol was conducted following the PRISMA guidelines. A systematic search was performed in Cochrane Central Register of Controlled Trials, MEDLINE, Embase, and PsycINFO. We will also search in trial registers. We will include Randomized Controlled Trials, in which any deprescribing intervention is compared to usual care in falls prevention. Both title and abstract screening and full-text screening will be done by two reviewers. The Cochrane Collaboration revised tool of Risk of Bias will be applied to perform risk of bias assessment. We will categorize the results separately for every setting. If a group of sufficiently comparable studies will be identified, we will perform a meta-analysis applying random effects model. We will investigate heterogeneity using a combination of visual inspection of the forest plot along with consideration of the Chi^2 test and the I^2 statistic results. We have pre-specified several subgroup and sensitivity analyses.

Ethics and dissemination

Ethics approval is not applicable for this study since no original data will be collected. The results will be disseminated through peer-reviewed publication and conference presentations. Furthermore, this systematic review will inform the recommendations of working group of polypharmacy and fall-risk-increasing drugs of the anticipated World's Falls Guidelines.

Registration: CRD42020218231

Key words: Medication withdrawal, deprescribing, older adults, accidental falls, falls prevention

Article summary

Strengths and limitations of this study

- we aim to create the most comprehensive systematic review of the effectiveness of deprescribing as a single intervention in falls prevention to date by focusing on all geriatric settings and all deprescribing interventions
- we will use rigorous methodology in accordance with the Cochrane handbook and the results will be reported as stated by PRISMA statement
- the search algorithm was developed by an experienced librarian and customized to four large databases
- no language restriction will be applied in the selection of the studies
- the certainty of the evidence of this systematic review may be limited by the limited number of studies available and the possible low quality of the individual studies

Background

Fall incidents are a growing major public health concern leading to associated morbidity, mortality and substantial healthcare costs (1). Of the community-dwelling older adults aged 65 years and older, approximately a third will sustain a fall each year (1). In long term care, residents are even at higher risk of falls; more than half of the residents will fall each year (2). One of the well-established risk factors for fall incidents is the use of specific medications, so-called fall-risk-increasing drugs (FRIDs) (3-5). The prevalence of FRID use in older person with a fall-related injury is high, ranging from 65%-93% (6). However, to date, there is uncertainty related to the effectiveness of deprescribing (reducing or stopping) FRIDs as a single intervention in falls prevention.

Few systematic reviews and meta-analyses have aimed to summarize the evidence-related to FRIDs deprescribing as a single intervention (6-8). A comparison of the conclusions of these systematic reviews is difficult due to the variation in included trials in the reviews and the heterogeneous results of the individual studies. The trials performed in long-term care settings or hospitals were summarized by Cameron et al. in 2018 (8). They concluded that general medication review may make little or no difference to the rate of falls or risk of falling in long term care facilities. However, there was very high heterogeneity between the studies (I^2=93%), and three of the six pooled studies reported an effect. In addition, they identified only one deprescribing intervention study that was performed in a hospital. Furthermore, the Cochrane review by Gillespie et al. in 2012 assessing fall prevention approaches in community-dwelling older adults identified a total of five studies investigating medication withdrawal as a single intervention (9). Two of the five included studies found an effect of the intervention. Furthermore, Hart et al. concluded in 2020 that reducing FRIDs use as a stand-alone intervention may not be effective (6). However, only studies performed in older adults presenting with a fall-related injury or a history of falls were included in the review. Eventually, only four intervention studies were identified and the two studies, which had shown an effect and identified by Gillespie et al. were not included.

Thus, a comprehensive update of the literature focusing on all geriatric settings and all deprescribing interventions is warranted to enhance the current knowledge. Therefore, our aim is to perform a systematic review concerning the effectiveness of deprescribing (e.g., including general medication reviews or FRIDs deprescribing) as a single intervention in falls prevention performed in any geriatric setting among older persons. Furthermore, we aim to perform a meta-analysis if sufficiently comparable studies will be identified.

Methods

This systematic review will be conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Eligibility criteria

Type of studies

Only Randomized Controlled Trials (RCTs), including quasi-randomized trials (for example, allocation by alternation), cluster-randomized trials and trials in which treatment allocations are inadequately concealed, will be included. We will include studies without language restriction.

Types of Participants

Trials will be considered for inclusion if they included participants aged ≥60 years or if the majority of participants are aged >65 years or the mean age is >65 years. We will include trials from all settings e.g., community, hospital ward, long term care facilities.

Type of interventions

The intervention can be any deprescribing intervention. "Deprescribing" has been described as "the process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes" (10). The interventions can be, for example, pharmacist-led medication reviews, physician-led interventions, prescriber education programs, multidisciplinary interventions or clinical decision support systems. The intervention can target specific drug classes (e.g., psychotropics) or general medication regimen (i.e. comprehensive medication review). If deprescribing intervention is a part of a multi-modal intervention (e.g., including an exercise component in addition to deprescribing), the study will be excluded.

Type of Control

The comparison intervention will be usual care (i.e. no deprescribing or no change in usual activities of care).

Type of outcomes

We will include trials that report raw data or statistics related to falls outcomes. We will include any type of falls outcome: number of falls, number of fallers/non-fallers/frequent fallers, fall rate per person-year, and time to first fall. Our secondary outcome is injurious falls (for example fall-related fractures, fall-related hospital admissions or fall-related healthcare use).

Information sources

A systematic search was be performed in Cochrane Central Register of Controlled Trials, MEDLINE, Embase, and PsycINFO to search for literature published from onset until 2nd of November. A customized search strategy was conducted for each database. We will also search in trial registers. In the case that a relevant conference abstract is identified, we will contact the authors to obtain full text article. Reference lists of included studies, reviews (e.g., Cochrane reviews) and falls prevention guidelines will be reviewed to identify additional studies.

Search strategy

The search contained the following key search concepts: 1) “deprescribing” AND “falls/health care assessment” AND “geriatric” OR 2) “prescribing tools” (e.g. Screening tool of inappropriate prescriptions of older persons [STOPP]). The strategies 1-2 were combined with “RCT filter”. A search for Medline is provided as an example and provided in Appendix I.

Data records and management

First, title and abstract screening will be done independently by two reviewers using Rayyan, a web-based systematic review program. In case of disagreement, a third reviewer will be consulted. Following the title and abstract screening, a full-text screening will be done using Rayyan by two independent reviewers. A third reviewer will be consulted in case of disagreement. Reasons for exclusion of studies will be collected during the full-text screening phase.

Two authors will independently extract data from each article using a structured data collection form. In case of disagreement, a third reviewer will be consulted. The following information will be collected: study design, country, setting, inclusion criteria, total number of participants and age (mean and standard deviation), intervention type, control type, all fall-related outcomes, and how collected, adjustment of outcomes if applicable, follow-up duration, compliance to the intervention and if the trials have reported possible adverse effects related to the intervention or economic outcomes. If data to be extracted are missing, incomplete or unclear, inquiries will be sent to the authors.

Effect measures

We will report the treatment effects between the intervention and control group as a Rate Ratio (RaR), a Risk Ratio (RR) and/or a Hazard Ratio (HR) and accompanying 95% confidence intervals (95% CI).

For rate of falls, we will use RaR as a treatment effect measure and the rate is the total number of falls per unit of person time that falls were monitored. We will use the unadjusted RaR, unless the adjustment is performed due to clustering. Furthermore, if needed due to missing reporting, we will calculate RaR from appropriate the raw data if possible. For dichotomous outcomes e.g., fallers or frequent fallers, we will use RR as a treatment effect measure. We will use the unadjusted RR, unless the adjustment is performed due to clustering. Furthermore, if needed due to missing reporting or if Odds Ratio is reported, we will calculate RR from the raw data if possible. For survival time-to-event data, we will use HR as a treatment effect measure. We will use the unadjusted HR, unless the adjustment is performed due to clustering.

Furthermore, we will adjust for clustering, if not already done in the published report using intra-cluster coefficient estimates and average cluster size.

Risk of bias

Two reviewers will assess the risk of bias independently by applying the Cochrane Collaboration revised tool of Risk of Bias (RoB 2.0) to all the included studies. In case of disagreement, a third reviewer will be consulted. The tool covers five domains: bias arising from randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of outcome, bias in selection of the reported result. In addition, an additional domain is available for cluster randomized trials; bias arising from identification or recruitment of individual participants within clusters. Each domain has signalling questions aiming to elicit relevant information. Responses to these questions are fed into algorithms to score each domain either low risk of bias, some concerns or high risk of bias. The scores of each domain are further mapped into overall risk-of-bias-judgement including categories of low risk of bias, some concerns and high risk of bias.

Data synthesis

We will categorize the results separately for every setting (e.g., community, hospital, or long term care facilities) due to different participant and environment characteristics.

First, a narrative synthesis will be provided in the text and tables to summarize the study characteristics and results.

If a group of studies with a sufficiently comparable intervention and outcome and performed in a same setting will be identified, we will perform a meta-analysis applying the intention-to-treat principle.

The results will be pooled using a random-effects model considering the expected heterogeneity between the studies. We will try to minimize the heterogeneity by grouping the trials per setting and similar intervention. We will investigate remaining heterogeneity within a pooled group of trials using a combination of visual inspection of the forest plot along with consideration of the Chi^2 test (with statistical significance set at $P < 0.10$), and the I^2 statistic results according to the recommendations

from the Cochrane Handbook. We will explore heterogeneity by conducting a subgroup analysis based on 1) age, 2) whether the trial is targeted to known fallers (or recurrent fallers if applicable) or also non-fallers are included, 3) different possible healthcare professionals conducting the medication review e.g., by physician or pharmacist, 4) whether the medication review is done with the help of a prescribing tool e.g., STOPP/START or the Beers criteria and which tool is used and 5) population e.g. if the trial is conducted only in dementia patients in comparison to general nursing home population. We will perform a sensitivity analysis according to overall study quality; low risk of bias, some concerns and high risk of bias, by comparing random and fixed-effect model and by excluding possible outlying studies, if the visual inspection of the forest plot shows poorly overlapping confidence intervals.

We will explore the possibility of publication bias by constructing funnel plots and by conducting Eggers test for analyses that contain more than ten studies.

The software Review Manager (RevMan) will be used for all statistical tests (Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Confidence in cumulative evidence

The confidence in effect estimates for each reported outcome will be assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach by two reviewers and possible disagreement will be assessed by third reviewer.

Ethics and dissemination

Ethics approval is not applicable for this study since no original data will be collected. The results will be disseminated through peer-reviewed publication and conference presentations. Furthermore, this

systematic review will inform the recommendations of working group of polypharmacy and fall-risk-increasing drugs of the anticipated World's Falls Guidelines.

Discussion

Although FRIDs use is an important risk factor for falls, there is uncertainty regarding the effectiveness of deprescribing interventions as a single intervention in falls prevention in older people. Identifying effective falls prevention interventions is of importance, considering the burden-related to fall injuries to both individuals and society.

This systematic review will help update the knowledge on the effectiveness of deprescribing, since we aim to create the most comprehensive systematic review to date by focusing on all geriatric settings and all deprescribing interventions. In addition, we will use rigorous methodology in accordance with the Cochrane handbook and the results will be reported as stated by PRISMA statement. Therefore, we will provide relevant knowledge that will be implemented into anticipated World's Falls Guidelines and may influence future clinical practice. However, the certainty of the evidence of this systematic review may be limited by the limited number of studies available and the possible low quality of the individual studies.

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Authors' contributions

L.S. and N.V. designed the protocol. L.S. and N.V. wrote the first draft of the protocol. All the authors contributed and approved the final version of the protocol.

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Competing interests

The authors declare that they have no competing interests.

Word Count

Abstract: 265

Text: 1991

12

292

293

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Appendix 1. Search strategy for Medline

1. inappropriate prescribing/ or exp medication errors/ or deprescriptions/ or exp drug prescriptions/ or exp drug utilization/
2. (deprescri* or ((antidepres* anti depress* or antipsychotic* or anti psychotic* or medicine or medication or drug? or frid? or polypharmac*) adj2 withdrawal) or ((dose or dosage) adj3 reduc*) or ((discontinu* or problem* or alternative?) adj3 (antidepres* anti depress* or antipsychotic* or anti psychotic* or medicine or medication or drug? or frid? or polypharmac*)) or (chang* adj5 (antidepres* anti depress* or antipsychotic* or anti psychotic* or medicine or medication or drug? or frid? or polypharmac*)) or ((polypharmac* or medication) adj2 (risk? or review)) or ((polypharmac* or medication) adj2 management) or prescribing problem? or overprescri* or underprescri* or under prescri* or over prescri* or (frid? and adverse) or medication errors or inappropriate prescri* or (appropriat* adj2 (prescri* or medicine or medication)) or harmful medic* or medication reconciliation).ab,kf,ti
3. or/1-2 [deprescription]
4. accidental falls/
5. (fall? or fell or falling or fallen or faller or stumble? or stumbling or stumbles or slip or slips or slipping or slipped or trip or tripped or physical self maintenance or ambulation or ambulatory).ab,kf,. ti.
6. "Outcome Assessment, Health Care"/
7. (assess* and health care).mp.
8. or/4-7 [Falls | health care assessment]
9. Geriatric assessment/ or frail elderly/ or exp aged/ or middle aged/ or exp nursing homes/ or "homes for the aged"/ or exp aging/
10. (older person? or older patient? or seniors or senior citiz* or elder or elders or elderly or geriatric* or frailty or postmenopausal women or community-dwelling or nursing home? or resident* or old* people or old* person? or old* patient? or old* client? or old* adult? or older m?n or older wom?n).ab,kf,ti.
11. (geriatr* or age or aging or elderl*).in,jw.
12. or/9-11 [Geriatric]
13. and/3,8,12
14. (Beers criteria or Stuck criteria or Beers-Fick criteria or McLeod criteria or Zhan criteria or Rancourt criteria or Lindblad criteria or HEDIS or "Healthcare Effectiveness Data and Information Set" or Japanese Beers or French criteria or Thailand criteria or STOPP or "Screening Tool of Older Person's Prescriptions" or NORGEP or "Norwegian General Practice criteria" or Italian Criteria or Priscus or Korean criteria or Taiwan criteria or Austrian Criteria or Australian Prescribing Indicators Tool or APIT or New Mexico criteria or Czech National criteria or Clyne criteria or Castillo-Paramo criteria or FORTA or "Fit fOR The Aged list" or Galan-Retamal criteria or "EU 7 PIM list" or "European list of potentially inappropriate medications for older people" or Kim criteria or GheOP3S or "Ghent Older People's Prescriptions community Pharmacy Screening" or Chilean criteria or Mazhar criteria or Khodyakov criteria or "Systematic Tool to Reduce Inappropriate Prescribing" or (STRIP adj2 criteria) or Medication Appropriateness Index or MAI or (Assessment of Underutilization adj2 index) or WWADR Profile or West Wales ADR or "lawton and brody").mp [specific tools | outcomes]
15. 13 or 14
16. (randomized or randomly or double blind* or controlled trial? or controlled clinical trial?).ab,kf,ti.
17. (randomized controlled trial or controlled clinical trial).pt.
18. trial.ti.
19. or/16-18 [RCT's sensitive]
20. 15 and 19

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	Page 1, line 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐	N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	Page 3, line 58
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	Page 1, lines 3-33
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	Page 11, line 277
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☐	N/A
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	Page 11, lines 280-283
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	Page 10, lines 280-283
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	Page 10, lines 280-283
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	Page3, line 75 to Page 4, line 98

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	Page 4, lines 99-104
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	Page 5, line 109 to Page 6, line 133
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	Page 6, lines 135-140
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	Page 6, lines 142-145 and Appendix 1
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	Page 6, lines 148-152
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	Page 6, lines 148-152
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	Page 7, lines 153-154, Page 7 lines 158-159
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	Page 7, lines 154-158
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	Page 6, lines 130-133, Page 7, lines 163-176
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	Page 8, lines 179-188, Page 9 lines 210-211

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	Page 8, lines 197-198
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	Page 8, lines 197-203
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	Page 9, lines 204-212
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	Page 8, lines 192-195
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	Page 9, lines 214-215
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	Page 9, lines 223-225

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Primary Subject Heading:	Geriatric medicine
Secondary Subject Heading:	Pharmacology and therapeutics, Public health
Keywords:	GERIATRIC MEDICINE, PUBLIC HEALTH, Adverse events < THERAPEUTICS

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Protocol for a systematic review and meta-analysis assessing the effectiveness of deprescribing in falls prevention in older people

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Abstract

Introduction

One of the known risk factors for fall incidents is the use of specific medications, fall-risk-increasing drugs. However, to date, there is uncertainty related to the effectiveness of deprescribing as a single intervention in falls prevention. Thus, a comprehensive update of the literature focusing on all geriatric settings and all deprescribing interventions is warranted to enhance the current knowledge.

Methods and analysis

This systematic review protocol follows the PRISMA guidelines. A systematic search was performed in Cochrane Central Register of Controlled Trials, MEDLINE, Embase, and PsycINFO (2nd of November 2020). We will also search in trial registers. We will include Randomized Controlled Trials, in which any deprescribing intervention is compared to usual care and reports falls as an outcome. Both title and abstract screening and full-text screening will be done by two reviewers. The Cochrane Collaboration revised tool of Risk of Bias will be applied to perform risk of bias assessment. We will categorize the results separately for every setting. If a group of sufficiently comparable studies will be identified, we will perform a meta-analysis applying random effects model. We will investigate heterogeneity using a combination of visual inspection of the forest plot along with consideration of the Chi² test and the I^2 statistic results. We have pre-specified several subgroup and sensitivity analyses.

Ethics and dissemination

Ethics approval is not applicable for this study since no original data will be collected. The results will be disseminated through peer-reviewed publication and conference presentations. Furthermore, this systematic review will inform the recommendations of working group of polypharmacy and fall-risk-increasing drugs of the anticipated World's Falls Guidelines.

Registration: Registered in PROSPERO. Registration number: CRD42020218231

Key words: Medication withdrawal, deprescribing, older adults, accidental falls, falls prevention

Article summary

Strengths and limitations of this study

- we aim to create the most comprehensive systematic review of the effectiveness of deprescribing as a single intervention in falls prevention to date by focusing on all geriatric settings and all deprescribing interventions
- we will use rigorous methodology in accordance with the Cochrane handbook and the results will be reported as stated by PRISMA statement
- the search algorithm was developed by an experienced librarian and customized to four large databases
- no language restriction will be applied in the selection of the studies
- the certainty of the evidence of this systematic review may be limited by the limited number of studies available and the possible low quality of the individual studies

Background

Fall incidents are a growing major public health concern leading to associated morbidity, mortality and substantial healthcare costs (1). Of the community-dwelling older adults aged 65 years and older, approximately a third will sustain a fall each year (1). In long term care, residents are even at higher risk of falls; more than half of the residents will fall each year (2). One of the well-established risk factors for falls is the use of specific medications, so-called fall-risk-increasing drugs (FRIDs) (3-5). The prevalence of FRID use in older people with a fall-related injury is high, ranging from 65%-93% (6). Medication review is a common component of the multifactorial falls prevention intervention and the Cochrane review by Hopewell et al. 2018 concluded that multifactorial interventions may

reduce the rate of falls compared with usual care or attention control (7). However, to date, there is uncertainty related to the effectiveness of deprescribing as a single intervention in falls prevention.

Few systematic reviews and meta-analyses have aimed to summarize the evidence-related to deprescribing as a single intervention (6, 8-11). A comparison of the conclusions of these systematic reviews is difficult due to the variation in included trials in the different reviews. The trials performed in long-term care settings or hospitals were summarized by Cameron et al. in 2018 (9). They concluded that general medication review may make little or no difference to the rate of falls or risk of falling in long term care facilities. In addition, they identified only one deprescribing intervention study that was performed in a hospital. Furthermore, the Cochrane review by Gillespie et al. in 2012 assessing fall prevention approaches in community-dwelling older adults identified a total of five studies investigating medication withdrawal as a single intervention (8). Two of the five included studies found an effect of the intervention. Page et al. found in 2016 in their meta-analysis that deprescribing led to fewer falls overall but did not significantly improve the risk of experiencing at least one fall (11). However, very heterogeneous trials were pooled together from placebo-controlled psychotropics withdrawal in primary care to education program regarding appropriate medication use for physicians in nursing homes. Furthermore, Hart et al. concluded in 2020 that reducing FRIDs use as a stand-alone intervention may not be effective (6). However, only studies performed in older adults presenting with a fall-related injury or a history of falls were included in the review. The most recent meta-analysis on this topic by Lee et al. found no effect of FRIDs deprescribing on fall outcomes (10). However, all studies assessing medication reviews and management with a broader focus on reducing polypharmacy and potentially inappropriate prescribing were excluded.

Thus, a comprehensive update of the literature focusing all deprescribing interventions including medication reviews with broader focus is warranted to enhance current knowledge as important deprescribing trials have been published in recent years. Therefore, our aim is to perform a

systematic review concerning the effectiveness of deprescribing (e.g., including general medication reviews or FRIDs deprescribing) as a single intervention in falls prevention performed in any geriatric setting among older persons. Furthermore, we aim to report the results separately for each geriatric setting and perform a meta-analysis if sufficiently comparable studies will be identified.

Methods

This systematic review will be conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Eligibility criteria

Type of studies

Only Randomized Controlled Trials (RCTs), including quasi-randomized trials (for example, allocation by alternation), cluster-randomized trials and trials in which treatment allocations are inadequately concealed, will be included. We will include studies without language restriction.

Types of Participants

Trials will be considered for inclusion if they included participants aged ≥60 years or if the majority of participants are aged >65 years or the mean age is >65 years. We will include trials from all settings e.g., community, hospital ward, long term care facilities.

Type of interventions

The intervention can be any deprescribing intervention. “Deprescribing” has been described as “the process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes” (12). The interventions can be, for example, pharmacist-led medication reviews, physician-led interventions, prescriber education programs, multidisciplinary interventions or clinical decision support systems. The intervention can target specific drug classes (e.g., psychotropics) or general medication regimen (i.e. comprehensive

medication review). The intervention might target multiple medication issues in case of comprehensive medication review in addition to withdrawal such as polypharmacy, non-adherence, education, and starting medications. If deprescribing intervention is a part of a multi-modal intervention (e.g., including an exercise component in addition to deprescribing), the study will be excluded.

Type of Control

The comparison intervention will be usual care (i.e. no deprescribing or no change in usual activities of care).

Type of outcomes

We will include trials that report raw data or statistics related to falls outcomes. We will include any type of falls outcome: number of falls, number of fallers/non-fallers/frequent fallers, fall rate per person-year, and time to first fall. Our secondary outcome is injurious falls (for example fall-related fractures, fall-related hospital admissions or fall-related healthcare use).

Information sources

A systematic search was performed in Cochrane Central Register of Controlled Trials, MEDLINE, Embase, and PsycINFO to search for literature published from onset until 2nd of November 2020. A customized search strategy was conducted for each database. We will also search in trial registers. In the case that a relevant conference abstract is identified, we will contact the authors to obtain full text article. Reference lists of included studies, reviews (e.g., Cochrane reviews) and falls prevention guidelines will be reviewed to identify additional studies.

Search strategy

A search for Medline is provided as an example and is available in Appendix I.

The search terms used were:

1. Deprescription: inappropriate prescribing, medication errors, deprescriptions, drug prescriptions, drug utilization, dose in combination with reduction, polypharmacy or medication in combination with risk, management or review, harmful medication, medication reconciliation, appropriate in combination with prescribing or medicine or medication, prescribing problem, overprescribing, under prescribing, withdrawal or discontinuation or problem or alternative or change in combination with medicine, medication or drug or frid or polypharmacy, antidepressant or antipsychotic.
2. Falls or health care assessment: accidental falls, fall, fell, stumble, slip, trip, physical self-maintenance, ambulatory, health care outcome assessment
3. Geriatric: geriatric assessment, frail, elderly, aged, middle aged, nursing homes, homes for the aged, aging, older person, older patient, senior, elder, geriatric, frailty, postmenopausal women, community-dwelling, resident, old people, old client, old adult, older man, older woman
4. 1 AND 2 AND 3
5. Prescribing tools: e.g. STOPP, "Screening Tool of Older Person's Prescriptions"
6. 4 OR 5
7. RCT: randomized, randomly, double blind, controlled trial, controlled clinical trial
8. 6 AND 7

The search was built by an experienced clinical librarian. We used 30 potentially relevant test articles to test and build the search. These articles were a priori identified using the function similar articles in PubMed and by reading references of the selected articles. These test articles included also articles that were identified from systematic reviews on deprescribing and included falls as a secondary outcome and not as a main interest.

Data records and management

First, title and abstract screening will be done independently by two reviewers using Rayyan, a web-based systematic review program. In case of disagreement, a third reviewer will be consulted. Following the title and abstract screening, a full-text screening will be done using Rayyan by two independent reviewers. A third reviewer will be consulted in case of disagreement. Reasons for exclusion of studies will be collected during the full-text screening phase.

Two authors will independently extract data from each article using a structured data collection form. In case of disagreement, a third reviewer will be consulted. The following information will be collected: study design, country, setting, inclusion criteria, total number of participants and age (mean and standard deviation), intervention type, control type, all fall-related outcomes, and how collected, adjustment of outcomes if applicable, follow-up duration, compliance to the intervention and if the trials have reported possible adverse effects related to the intervention or economic outcomes. If data to be extracted are missing, incomplete or unclear, inquiries will be sent to the authors.

Effect measures

We will report the treatment effects between the intervention and control group as a Rate Ratio (RaR), a Risk Ratio (RR) and/or a Hazard Ratio (HR) and accompanying 95% confidence intervals (95% CI).

For rate of falls, we will use RaR as a treatment effect measure and the rate is the total number of falls per unit of person time that falls were monitored. We will use the unadjusted RaR, unless the adjustment is performed due to clustering. Furthermore, if needed due to missing reporting, we will calculate RaR from appropriate raw data if possible. For dichotomous outcomes e.g., fallers or frequent fallers, we will use RR as a treatment effect measure. We will use the unadjusted RR, unless the adjustment is performed due to clustering. Furthermore, if needed due to missing reporting or if Odds Ratio is reported, we will calculate RR from the raw data if possible. For survival time-to-event data,

we will use HR as a treatment effect measure. We will use the unadjusted HR, unless the adjustment is performed due to clustering.

Furthermore, we will adjust for clustering, if not already done in the published report using intra-cluster coefficient estimates and average cluster size.

Risk of bias

Two reviewers will assess the risk of bias independently by applying the Cochrane Collaboration revised tool of Risk of Bias (RoB 2.0) to all the included studies. In case of disagreement, a third reviewer will be consulted. The tool covers five domains: bias arising from randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of outcome, bias in selection of the reported result. In addition, an additional domain is available for cluster randomized trials; bias arising from identification or recruitment of individual participants within clusters. Each domain has signalling questions aiming to elicit relevant information. Responses to these questions are fed into algorithms to score each domain either low risk of bias, some concerns or high risk of bias. The scores of each domain are further mapped into overall risk-of-bias-judgement including categories of low risk of bias, some concerns and high risk of bias.

Data synthesis

We will categorize the results separately for every setting (e.g., community, hospital, or long term care facilities) due to different participant and environment characteristics.

First, a narrative synthesis will be provided in the text and tables to summarize the study characteristics and results.

If a group of studies with a sufficiently comparable intervention and outcome and performed in a same setting is identified, we will perform a meta-analysis applying the intention-to-treat principle. The results will be pooled using a random-effects model considering the expected heterogeneity between the studies. We will try to minimize the heterogeneity by grouping the trials per setting and similar intervention. We will investigate remaining heterogeneity within a pooled group of trials using a combination of visual inspection of the forest plot along with consideration of the Chi² test (with statistical significance set at $P < 0.10$), and the I^2 statistic results according to the recommendations from the Cochrane Handbook. We will explore heterogeneity by conducting a subgroup analysis based on 1) age, 2) whether the trial is targeted to known fallers (or recurrent fallers if applicable) or also non-fallers are included, 3) different possible healthcare professionals conducting the medication review e.g., by physician or pharmacist, 4) whether the medication review is done with the help of a prescribing tool e.g., STOPP/START or the Beers criteria and which tool is used and 5) population e.g. if the trial is conducted only in dementia patients in comparison to general nursing home population. We will perform a sensitivity analysis according to overall study quality; low risk of bias, some concerns and high risk of bias, by comparing random and fixed-effect model and by excluding possible outlying studies, if the visual inspection of the forest plot shows poorly overlapping confidence intervals.

We will explore the possibility of publication bias by constructing funnel plots and by conducting Eggers test for analyses that contain more than ten studies.

The software Review Manager (RevMan) will be used for all statistical tests (Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Confidence in cumulative evidence

The confidence in effect estimates for each reported outcome will be assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach by two reviewers and possible disagreement will be assessed by third reviewer.

Ethics and dissemination

Ethics approval is not applicable for this study since no original data will be collected. The results will be disseminated through peer-reviewed publication and conference presentations. Furthermore, this systematic review will inform the recommendations of working group of polypharmacy and fall-risk-increasing drugs of the anticipated World's Falls Guidelines.

Patient and Public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Discussion

Although FRIDs use is an important risk factor for falls, there is uncertainty regarding the effectiveness of deprescribing interventions as a single intervention in falls prevention in older people. Identifying effective falls prevention interventions is of importance, considering the burden-related to fall injuries to both individuals and society.

This systematic review will help update the knowledge on the effectiveness of deprescribing, since we aim to create the most comprehensive systematic review to date by focusing on all geriatric settings and all deprescribing interventions. In addition, we will use rigorous methodology in accordance with the Cochrane handbook and the results will be reported as stated by PRISMA

statement. Therefore, we will provide relevant knowledge that will be implemented into anticipated World's Falls Guidelines and may influence future clinical practice. However, the certainty of the evidence of this systematic review may be limited by the limited number of studies available and the possible low quality of the individual studies.

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Authors' contributions

L.S. and N.V. designed the protocol. L.S. and N.V. wrote the first draft of the protocol. N.K., J.R., T.M., J.G.D., M. M-O., S.H. and M.P. provided critical appraisal regarding the design of the systematic review and revised the manuscript. J.G.D. designed and performed the search. All the authors approved the final version of the protocol.

Funding

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Competing interests

The authors declare that they have no competing interests.

Word Count

Abstract: 265

Text: 2336

14

345

346

347

Appendix 1. Search strategy for Medline

1. inappropriate prescribing/ or exp medication errors/ or deprescriptions/ or exp drug prescriptions/ or exp drug utilization/
2. (deprescri* or ((antidepres* anti depress* or antipsychotic* or anti psychotic* or medicine or medication or drug? or frid? or polypharmac*) adj2 withdrawal) or ((dose or dosage) adj3 reduc*) or ((discontinu* or problem* or alternative?) adj3 (antidepres* anti depress* or antipsychotic* or anti psychotic* or medicine or medication or drug? or frid? or polypharmac*)) or (chang* adj5 (antidepres* anti depress* or antipsychotic* or anti psychotic* or medicine or medication or drug? or frid? or polypharmac*)) or ((polypharmac* or medication) adj2 (risk? or review)) or ((polypharmac* or medication) adj2 management) or prescribing problem? or overprescri* or underprescri* or under prescri* or over prescri* or (frid? and adverse) or medication errors or inappropriate prescri* or (appropriat* adj2 (prescri* or medicine or medication)) or harmful medic* or medication reconciliation).ab,kf,ti
3. or/1-2 [deprescription]
4. accidental falls/
5. (fall? or fell or falling or fallen or faller or stumble? or stumbling or stumbles or slip or slips or slipping or slipped or trip or tripped or physical self maintenance or ambulation or ambulatory).ab,kf,. ti.
6. "Outcome Assessment, Health Care"/
7. (assess* and health care).mp.
8. or/4-7 [Falls | health care assessment]
9. Geriatric assessment/ or frail elderly/ or exp aged/ or middle aged/ or exp nursing homes/ or "homes for the aged"/ or exp aging/
10. (older person? or older patient? or seniors or senior citiz* or elder or elders or elderly or geriatric* or frailty or postmenopausal women or community-dwelling or nursing home? or resident* or old* people or old* person? or old* patient? or old* client? or old* adult? or older m?n or older wom?n).ab,kf,ti.
11. (geriatr* or age or aging or elderl*).in,jw.
12. or/9-11 [Geriatric]
13. and/3,8,12
14. (Beers criteria or Stuck criteria or Beers-Fick criteria or McLeod criteria or Zhan criteria or Rancourt criteria or Lindblad criteria or HEDIS or "Healthcare Effectiveness Data and Information Set" or Japanese Beers or French criteria or Thailand criteria or STOPP or "Screening Tool of Older Person's Prescriptions" or NORGEP or "Norwegian General Practice criteria" or Italian Criteria or Priscus or Korean criteria or Taiwan criteria or Austrian Criteria or Australian Prescribing Indicators Tool or APIT or New Mexico criteria or Czech National criteria or Clyne criteria or Castillo-Paramo criteria or FORTA or "Fit fOR The Aged list" or Galan-Retamal criteria or "EU 7 PIM list" or "European list of potentially inappropriate medications for older people" or Kim criteria or GheOP3S or "Ghent Older People's Prescriptions community Pharmacy Screening" or Chilean criteria or Mazhar criteria or Khodyakov criteria or "Systematic Tool to Reduce Inappropriate Prescribing" or (STRIP adj2 criteria) or Medication Appropriateness Index or MAI or (Assessment of Underutilization adj2 index) or WWADR Profile or West Wales ADR or "lawton and brody").mp [specific tools | outcomes]
15. 13 or 14
16. (randomized or randomly or double blind* or controlled trial? or controlled clinical trial?).ab,kf,ti.
17. (randomized controlled trial or controlled clinical trial).pt.
18. trial.ti.
19. or/16-18 [RCT's sensitive]
20. 15 and 19

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	Page 1, line 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐	N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	Page 2, line 57
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	Page 1, lines 3-33
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	Page 12, line 317
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☐	N/A
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	Page 13, line 322
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	Page 13, lines 322
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	Page 13, lines 322
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	Page3, line 73 to Page 4, line 103

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	Page 4, lines 104-110
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	Page 5, line 114 to Page 6, line 142
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	Page 6, lines 144-149
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	Page 6 -7, lines 152-169 and Appendix 1
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	Page 8, lines 178-182
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	Page 8, lines 178-182
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	Page 8, lines 183-189
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	Page 8, lines 185-188
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	Page 6, lines 139-142 lines 193-206
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	Page 9, lines 209-218 Page 10 lines 240-214

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	Page 10, lines 227-228
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	Page 10, lines 229-234
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	Page 10, lines 234--242
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	Page 9, lines 222-225
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	Page 10, lines 244-254
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	Page 11, lines 253-255

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Protocol for a systematic review and meta-analysis assessing the effectiveness of deprescribing in falls prevention in older people

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Protocol for a systematic review and meta-analysis assessing the effectiveness of deprescribing in falls prevention in older people

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Abstract

Introduction

One of the known risk factors for fall incidents is the use of specific medications, fall-risk-increasing drugs. However, to date, there is uncertainty related to the effectiveness of deprescribing as a single intervention in falls prevention. Thus, a comprehensive update of the literature focusing on all settings in which older people receive health care and all deprescribing interventions is warranted to enhance the current knowledge.

Methods and analysis

This systematic review protocol follows the PRISMA guidelines. A systematic search was performed in Cochrane Central Register of Controlled Trials, MEDLINE, Embase, and PsycINFO (2nd of November 2020). We will also search in trial registers. We will include Randomized Controlled Trials, in which any deprescribing intervention is compared to usual care and reports falls as an outcome. Both title and abstract screening and full-text screening will be done by two reviewers. The Cochrane Collaboration revised tool of Risk of Bias will be applied to perform risk of bias assessment. We will categorize the results separately for every setting. If a group of sufficiently comparable studies will be identified, we will perform a meta-analysis applying random effects model. We will investigate heterogeneity using a combination of visual inspection of the forest plot along with consideration of the Chi^2 test and the I^2 statistic results. We have pre-specified several subgroup and sensitivity analyses.

Ethics and dissemination

Ethics approval is not applicable for this study since no original data will be collected. The results will be disseminated through peer-reviewed publication and conference presentations. Furthermore, this systematic review will inform the recommendations of working group of polypharmacy and fall-risk-increasing drugs of the anticipated World's Falls Guidelines.

Registration: Registered in PROSPERO. Registration number: CRD42020218231

Key words: Medication withdrawal, deprescribing, older adults, accidental falls, falls prevention

Article summary

Strengths and limitations of this study

- we aim to create the most comprehensive systematic review of the effectiveness of deprescribing as a single intervention in falls prevention to date by focusing on all settings in which older people receive health care and all deprescribing interventions
- we will use rigorous methodology in accordance with the Cochrane handbook and the results will be reported as stated by PRISMA statement
- the search algorithm was developed by an experienced librarian and customized to four large databases
- no language restriction will be applied in the selection of the studies
- the certainty of the evidence of this systematic review may be limited by the limited number of studies available and the possible low quality of the individual studies

Background

Fall incidents are a growing major public health concern leading to associated morbidity, mortality and substantial health care costs (1). Of the community-dwelling older adults aged 65 years and older, approximately a third will sustain a fall each year (1). In long term care, residents are even at higher risk of falls; more than half of the residents will fall each year (2). One of the well-established risk factors for falls is the use of specific medications, so-called fall-risk-increasing drugs (FRIDs) (3-5). The prevalence of FRID use in older people with a fall-related injury is high, ranging from 65%-93% (6). Medication review is a common component of the multifactorial falls prevention intervention and the Cochrane review by Hopewell et al. 2018 concluded that multifactorial interventions may

reduce the rate of falls compared with usual care or attention control (7). However, to date, there is uncertainty related to the effectiveness of deprescribing as a single intervention in falls prevention.

Few systematic reviews and meta-analyses have aimed to summarize the evidence-related to deprescribing as a single intervention (6, 8-11). A comparison of the conclusions of these systematic reviews is difficult due to the variation in included trials in the different reviews. The trials performed in long-term care settings or hospitals were summarized by Cameron et al. in 2018 (9). They concluded that general medication review may make little or no difference to the rate of falls or risk of falling in long term care facilities. In addition, they identified only one deprescribing intervention study that was performed in a hospital. Furthermore, the Cochrane review by Gillespie et al. in 2012 assessing fall prevention approaches in community-dwelling older adults identified a total of five studies investigating medication withdrawal as a single intervention (8). Two of the five included studies found an effect of the intervention. Page et al. found in 2016 in their meta-analysis that deprescribing led to fewer falls overall but did not significantly improve the risk of experiencing at least one fall (11). However, very heterogeneous trials were pooled together from placebo-controlled psychotropics withdrawal in primary care to education program regarding appropriate medication use for physicians in nursing homes. Furthermore, Hart et al. concluded in 2020 that reducing FRIDs use as a stand-alone intervention may not be effective (6). However, only studies performed in older adults presenting with a fall-related injury or a history of falls were included in the review. The most recent meta-analysis on this topic by Lee et al. found no effect of FRIDs deprescribing on fall outcomes (10). However, all studies assessing medication reviews and management with a broader focus on reducing polypharmacy and potentially inappropriate prescribing were excluded.

Thus, a comprehensive update of the literature focusing all deprescribing interventions including medication reviews with broader focus is warranted to enhance current knowledge as important deprescribing trials have been published in recent years. Therefore, our aim is to perform a

systematic review concerning the effectiveness of deprescribing (e.g., including general medication reviews or FRIDs deprescribing) as a single intervention in falls prevention performed in any setting in which older people receive health care. Furthermore, we aim to report the results separately for each setting and perform a meta-analysis if sufficiently comparable studies will be identified.

Methods

This systematic review will be conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Eligibility criteria

Type of studies

Only Randomized Controlled Trials (RCTs), including quasi-randomized trials (for example, allocation by alternation), cluster-randomized trials and trials in which treatment allocations are inadequately concealed, will be included. We will include studies without language restriction.

Types of Participants

Trials will be considered for inclusion if they included participants aged ≥60 years or if the majority of participants are aged >65 years or the mean age is >65 years. We will include trials from all settings e.g., community, hospital ward, long term care facilities.

Type of interventions

The intervention can be any deprescribing intervention. “Deprescribing” has been described as “the process of withdrawal of an (inappropriate) medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes” (12). The interventions can be, for example, pharmacist-led medication reviews, physician-led interventions, prescriber education programs, multidisciplinary interventions or clinical decision support systems. The intervention can target specific drug classes (e.g., psychotropics) or general medication regimen (i.e. comprehensive

medication review). The intervention might target multiple medication issues in case of comprehensive medication review in addition to withdrawal such as polypharmacy, non-adherence, education, and starting medications. If deprescribing intervention is a part of a multi-modal intervention (e.g., including an exercise component in addition to deprescribing), the study will be excluded.

Type of Control

The comparison intervention will be usual care (i.e. no deprescribing or no change in usual activities of care).

Type of outcomes

We will include trials that report raw data or statistics related to falls outcomes. We will include any type of falls outcome: number of falls, number of fallers/non-fallers/frequent fallers, fall rate per person-year, and time to first fall. Our secondary outcome is injurious falls (for example fall-related fractures, fall-related hospital admissions or fall-related health care use).

Information sources

A systematic search was performed in Cochrane Central Register of Controlled Trials, MEDLINE, Embase, and PsycINFO to search for literature published from onset until 2nd of November 2020 which will be updated to prior manuscript submission. A customized search strategy was conducted for each database. We will also search in trial registers. In the case that a relevant conference abstract is identified, we will contact the authors to obtain full text article. Reference lists of included studies, reviews (e.g., Cochrane reviews) and falls prevention guidelines will be reviewed to identify additional studies.

Search strategy

A search for Medline is provided as an example and is available in Appendix I.

The search terms used were:

1. Deprescription: inappropriate prescribing, medication errors, deprescriptions, drug prescriptions, drug utilization, dose in combination with reduction, polypharmacy or medication in combination with risk, management or review, harmful medication, medication reconciliation, appropriate in combination with prescribing or medicine or medication, prescribing problem, overprescribing, under prescribing, withdrawal or discontinuation or problem or alternative or change in combination with medicine, medication or drug or frid or polypharmacy, antidepressant or antipsychotic.

2. Falls or health care assessment: accidental falls, fall, fell, stumble, slip, trip, physical self-maintenance, ambulatory, health care outcome assessment

3. Geriatric: geriatric assessment, frail, elderly, aged, middle aged, nursing homes, homes for the aged, aging, older person, older patient, senior, elder, geriatric, frailty, postmenopausal women, community-dwelling, resident, old people, old client, old adult, older man, older woman

4. 1 AND 2 AND 3

5. Prescribing tools: e.g. STOPP, "Screening Tool of Older Person's Prescriptions"

6. 4 OR 5

7. RCT: randomized, randomly, double blind, controlled trial, controlled clinical trial

8. 6 AND 7

The search was built by an experienced clinical librarian. We used 30 potentially relevant test articles to test and build the search. These articles were a priori identified using the function similar articles in PubMed and by reading references of the selected articles. These test articles included also articles that were identified from systematic reviews on deprescribing and included falls as a secondary outcome and not as a main interest.

Data records and management

First, title and abstract screening will be done independently by two reviewers using Rayyan, a web-based systematic review program. In case of disagreement, a third reviewer will be consulted. Following the title and abstract screening, a full-text screening will be done using Rayyan by two independent reviewers. A third reviewer will be consulted in case of disagreement. Reasons for exclusion of studies will be collected during the full-text screening phase.

Two authors will independently extract data from each article using a structured data collection form. In case of disagreement, a third reviewer will be consulted. The following information will be collected: study design, country, setting, inclusion criteria, total number of participants and age (mean and standard deviation), intervention type, control type, all fall-related outcomes, and how collected, adjustment of outcomes if applicable, follow-up duration, compliance to the intervention and if the trials have reported possible adverse effects related to the intervention or economic outcomes. If data to be extracted are missing, incomplete or unclear, inquiries will be sent to the authors.

Effect measures

We will report the treatment effects between the intervention and control group as a Rate Ratio (RaR), a Risk Ratio (RR) and/or a Hazard Ratio (HR) and accompanying 95% confidence intervals (95% CI).

For rate of falls, we will use RaR as a treatment effect measure and the rate is the total number of falls per unit of person time that falls were monitored. We will use the unadjusted RaR, unless the adjustment is performed due to clustering. Furthermore, if needed due to missing reporting, we will calculate RaR from appropriate raw data if possible. For dichotomous outcomes e.g., fallers or frequent fallers, we will use RR as a treatment effect measure. We will use the unadjusted RR, unless the adjustment is performed due to clustering. Furthermore, if needed due to missing reporting or if Odds Ratio is reported, we will calculate RR from the raw data if possible. For survival time-to-event data,

we will use HR as a treatment effect measure. We will use the unadjusted HR, unless the adjustment is performed due to clustering.

Furthermore, we will adjust for clustering, if not already done in the published report using intra-cluster coefficient estimates and average cluster size.

Risk of bias

Two reviewers will assess the risk of bias independently by applying the Cochrane Collaboration revised tool of Risk of Bias (RoB 2.0) to all the included studies. In case of disagreement, a third reviewer will be consulted. The tool covers five domains: bias arising from randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of outcome, bias in selection of the reported result. In addition, an additional domain is available for cluster randomized trials; bias arising from identification or recruitment of individual participants within clusters. Each domain has signalling questions aiming to elicit relevant information. Responses to these questions are fed into algorithms to score each domain either low risk of bias, some concerns or high risk of bias. The scores of each domain are further mapped into overall risk-of-bias-judgement including categories of low risk of bias, some concerns and high risk of bias.

Data synthesis

We will categorize the results separately for every setting (e.g., community, hospital, or long term care facilities) due to different participant and environment characteristics.

First, a narrative synthesis will be provided in the text and tables to summarize the study characteristics and results.

If a group of studies with a sufficiently comparable intervention and outcome and performed in a same setting is identified, we will perform a meta-analysis applying the intention-to-treat principle. For example a study purely investigating antihypertensive withdrawal will not be pooled with a study purely investigating antidepressant withdrawal.

The results will be pooled using a random-effects model considering the expected heterogeneity between the studies. We will try to minimize the heterogeneity by grouping the trials by setting and similar intervention. We will investigate remaining heterogeneity within a pooled group of trials using a combination of visual inspection of the forest plot along with consideration of the Chi^2 test (with statistical significance set at $P < 0.10$), and the I^2 statistic results according to the recommendations from the Cochrane Handbook. We will explore heterogeneity by conducting a subgroup analysis based on the following: 1) age, 2) whether the trial is targeted to known fallers (or recurrent fallers if applicable) or also to non-fallers, 3) health care professionals conducting the medication review e.g., by physician or pharmacist, 4) whether the medication review is done with the help of a prescribing tool e.g., STOPP/START or the Beers criteria and which tool is used and 5) population e.g. if the trial is conducted only in dementia patients in comparison to general nursing home population. We will perform a sensitivity analysis according to overall study quality; low risk of bias, some concerns and high risk of bias, by comparing random and fixed-effect model and by excluding possible outlying studies, if the visual inspection of the forest plot shows poorly overlapping confidence intervals.

We will explore the possibility of publication bias by constructing funnel plots and by conducting Eggers test for analyses that contain more than ten studies.

The software Review Manager (RevMan) will be used for all statistical tests (Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Confidence in cumulative evidence

The confidence in effect estimates for each reported outcome will be assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach by two reviewers and possible disagreement will be assessed by third reviewer.

Ethics and dissemination

Ethics approval is not applicable for this study since no original data will be collected. The results will be disseminated through peer-reviewed publication and conference presentations. Furthermore, this systematic review will inform the recommendations of working group of polypharmacy and fall-risk-increasing drugs of the anticipated World's Falls Guidelines.

Patient and Public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Discussion

Although FRIDs use is an important risk factor for falls, there is uncertainty regarding the effectiveness of deprescribing interventions as a single intervention in falls prevention in older people. Identifying effective falls prevention interventions is of importance, considering the burden-related to fall injuries to both individuals and society.

This systematic review will help update the knowledge on the effectiveness of deprescribing, since we aim to create the most comprehensive systematic review to date by exploring all settings in

which older people receive health care and all deprescribing interventions. In addition, we will use rigorous methodology in accordance with the Cochrane handbook and the results will be reported as stated by PRISMA statement. Therefore, we will provide relevant knowledge that will be implemented into anticipated World's Falls Guidelines and may influence future clinical practice. However, the certainty of the evidence of this systematic review may be limited by the limited number of studies available and the possible low quality of the individual studies.

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Authors' contributions

L.S. and N.V. designed the protocol. L.S. and N.V. wrote the first draft of the protocol. N.K., J.R., T.M., J.G.D., M. M-O., S.H. and M.P. provided critical appraisal regarding the design of the systematic review and revised the manuscript. J.G.D. designed and performed the search. All the authors approved the final version of the protocol.

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Competing interests

The authors declare that they have no competing interests.

Word Count

Abstract: 265

Text: 2336

Appendix 1. Search strategy for Medline

1. inappropriate prescribing/ or exp medication errors/ or deprescriptions/ or exp drug prescriptions/ or exp drug utilization/
2. (deprescri* or ((antidepres* anti depress* or antipsychotic* or anti psychotic* or medicine or medication or drug? or frid? or polypharmac*) adj2 withdrawal) or ((dose or dosage) adj3 reduc*) or ((discontinu* or problem* or alternative?) adj3 (antidepres* anti depress* or antipsychotic* or anti psychotic* or medicine or medication or drug? or frid? or polypharmac*)) or (chang* adj5 (antidepres* anti depress* or antipsychotic* or anti psychotic* or medicine or medication or drug? or frid? or polypharmac*)) or ((polypharmac* or medication) adj2 (risk? or review)) or ((polypharmac* or medication) adj2 management) or prescribing problem? or overprescri* or underprescri* or under prescri* or over prescri* or (frid? and adverse) or medication errors or inappropriate prescri* or (appropriat* adj2 (prescri* or medicine or medication)) or harmful medic* or medication reconciliation).ab,kf,ti
3. or/1-2 [deprescription]
4. accidental falls/
5. (fall? or fell or falling or fallen or faller or stumble? or stumbling or stumbles or slip or slips or slipping or slipped or trip or tripped or physical self maintenance or ambulation or ambulatory).ab,kf,. ti.
6. "Outcome Assessment, Health Care"/
7. (assess* and health care).mp.
8. or/4-7 [Falls | health care assessment]
9. Geriatric assessment/ or frail elderly/ or exp aged/ or middle aged/ or exp nursing homes/ or "homes for the aged"/ or exp aging/
10. (older person? or older patient? or seniors or senior citiz* or elder or elders or elderly or geriatric* or frailty or postmenopausal women or community-dwelling or nursing home? or resident* or old* people or old* person? or old* patient? or old* client? or old* adult? or older m?n or older wom?n).ab,kf,ti.
11. (geriatr* or age or aging or elderl*).in,jw.
12. or/9-11 [Geriatric]
13. and/3,8,12
14. (Beers criteria or Stuck criteria or Beers-Fick criteria or McLeod criteria or Zhan criteria or Rancourt criteria or Lindblad criteria or HEDIS or "Healthcare Effectiveness Data and Information Set" or Japanese Beers or French criteria or Thailand criteria or STOPP or "Screening Tool of Older Person's Prescriptions" or NORGEP or "Norwegian General Practice criteria" or Italian Criteria or Priscus or Korean criteria or Taiwan criteria or Austrian Criteria or Australian Prescribing Indicators Tool or APIT or New Mexico criteria or Czech National criteria or Clyne criteria or Castillo-Paramo criteria or FORTA or "Fit fOR The Aged list" or Galan-Retamal criteria or "EU 7 PIM list" or "European list of potentially inappropriate medications for older people" or Kim criteria or GheOP3S or "Ghent Older People's Prescriptions community Pharmacy Screening" or Chilean criteria or Mazhar criteria or Khodyakov criteria or "Systematic Tool to Reduce Inappropriate Prescribing" or (STRIP adj2 criteria) or Medication Appropriateness Index or MAI or (Assessment of Underutilization adj2 index) or WWADR Profile or West Wales ADR or "lawton and brody").mp [specific tools | outcomes]
15. 13 or 14
16. (randomized or randomly or double blind* or controlled trial? or controlled clinical trial?).ab,kf,ti.
17. (randomized controlled trial or controlled clinical trial).pt.
18. trial.ti.
19. or/16-18 [RCT's sensitive]
20. 15 and 19

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	Page 1, line 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐	N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	Page 2, line 57
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	Page 1, lines 3-33
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	Page 12, line 317
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☐	N/A
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	Page 13, line 322
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	Page 13, lines 322
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	Page 13, lines 322
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	Page3, line 73 to Page 4, line 103

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	Page 4, lines 104-110
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	Page 5, line 114 to Page 6, line 142
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	Page 6, lines 144-149
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	Page 6 -7, lines 152-169 and Appendix 1
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	Page 8, lines 178-182
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	Page 8, lines 178-182
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	Page 8, lines 183-189
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	Page 8, lines 185-188
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	Page 6, lines 139-142 lines 193-206
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	Page 9, lines 209-218 Page 10 lines 240-214

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	Page 10, lines 227-228
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	Page 10, lines 229-234
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	Page 10, lines 234--242
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	Page 9, lines 222-225
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	Page 10, lines 244-254
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	Page 11, lines 253-255