

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Protocol for a systematic review and meta-analysis assessing the effectiveness of deprescribing in falls prevention in older people
<b>AUTHORS</b>	Seppala, Lotta; Kamkar, Nellie; Ryg, Jesper; Masud, Tahir; Daams, Joost; Montero-Odasso, Manuel; Hartikainen, Sirpa; Petrovic, Mirko; van der Velde, Nathalie

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Lord, Stephen University of New South Wales, Neuroscience Research Australia
<b>REVIEW RETURNED</b>	11-Jan-2021

<b>GENERAL COMMENTS</b>	<p>The proposed review will be conducted according to best practice guidelines It includes an assessment of quality of evidence using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Framework, the conduct of the review following the Cochrane Handbook, the reporting of the findings in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and the registration of the protocol in PROSPERO.</p> <p>I have only one main comment and some minor suggestions.</p> <p>Main comment The systematic review on this topic by Lee et al from 2017 has not been cited. I suggest this review be included in the introduction along with a brief discussion as to what the proposed review will add to this. [Lee J, Negm A, Wong E et al. Does deprescribing fall-associated drugs reduce falls and its complications?: a systematic review. Innovation in Aging 2017; (Suppl 1): 268. doi: 10.1093/geroni/igx004.981].</p> <p>Minor suggestions Line 58: Explicitly state in the document that the review is registered with Prospero. Line 79 – change “fall incidents” to “falls”. Line 80: change “person” to “people”. Line 169: delete “the” after “appropriate”. Line 198: change “will be” to “is”.</p>
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<b>REVIEWER</b>	Naganathan, Vasi University of Sydney, Concord Hospital
<b>REVIEW RETURNED</b>	15-Feb-2021

## GENERAL COMMENTS

In my view there is a strong rationale for conducting a systematic review to assess the effectiveness of deprescribing to prevent falls. The protocol meets the PRISMA guidelines for reporting a SR. There have been a number of major deprescribing trials in the last few years which in my mind is the strongest rationale for conducting this SR

The following are some suggestions that may improve the final manuscript.  
See attached PDF

See minor edit of abstract methods

The title implies deprescribing in general but the abstract implies the deprescribing of FRIDs specifically, as does the introduction...this should be clarified. The search strategy suggest the focus is not just on FRIDs

## INTRODUCTION

It would not be correct to suggest that the fact that previous systematic reviews found variation in included trials and heterogenous results is a good rationale for why another SR needs to be done especially as this is a likely finding in this SR

There is a more recent Cochrane review (Hopewell et al 2018) that should be mentioned even if they did not report much about deprescribing

The following SR should be talked about:

Page AT, Clifford RM, Potter K, Schwartz D, Etherton-Beer CD. The feasibility and effect of deprescribing in older adults on mortality and health: a systematic review and meta-analysis. *Br J Clin Pharmacol*. 2016 Sep;82(3):583-623. doi: 10.1111/bcp.12975. Epub 2016 Jun 13. PMID: 27077231; PMCID: PMC5338123.

They report the following: Deprescribing did not significantly improve the risk of experiencing at least one fall (OR 0.65, 95% CI 0.40–1.05; participants = 2173; studies = 5) (Figure S2). However, participants who did fall had significantly fewer falls overall in the deprescribing group compared to those in the control group (MD 0.11, 95% CI 0.21–0.02; participants = 844; studies = 3) (Figure S3)

The rationale for conducting this SR could be stronger. Isn't the strongest argument that in the last 5 odd years the results of some major deprescribing trials have been published and therefore now is the time to do updated SR?

## METHODS

See minor suggestions on section on information sources

Search strategy: the description of the search strategy does not do justice to the search strategy described in the appendix. See

	<p>Page et al article which is a good example of trying to summarise the search strategy. I am not sure the strategy to look for studies under the theme of health care assessment will capture studies that had falls as a secondary outcome. Capturing studies where falls was not the main outcomes of interest but is reported is going to be a challenge and it may be worth explaining this in more detail in the search strategy</p> <p>Could you clarify this please: does the intervention have to be part of clear deprescribing intervention? ie: for older trials in particular will terms such as deprescribing/withdrawal etc capture them. Page et al in their 2016 SR used a search strategy that included the individual name of medications (see their supplement).</p>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Prof. Stephen Lord, University of New South Wales

#### 1. Main comment

The systematic review on this topic by Lee et al from 2017 has not been cited. I suggest this review be included in the introduction along with a brief discussion as to what the proposed review will add to this. [Lee J, Negm A, Wong E et al. Does deprescribing fall-associated drugs reduce falls and its complications?: a systematic review. *Innovation in Aging* 2017; (Suppl 1): 268. doi: 10.1093/geroni/igx004.981].

*We thank the reviewer pointing this out. The review by Lee et al. found no effect of FRIDs deprescribing on fall outcomes. However, all studies assessing medication reviews and management with a broader focus on reducing polypharmacy and potentially inappropriate prescribing were excluded. In contrast, we plan to include these studies with a broader focus. The following have been added to the manuscript (page 4, line 104):*

*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.*

#### Minor suggestions

1. Line 58: Explicitly state in the document that the review is registered with Prospero.

*We have added the following (page 3, line 59): **Registered in PROSPERO. Registration number: CRD42020218231***

2. Line 79 – change “fall incidents” to “falls.

*We have changed the fall incidents to falls (page 3, line 80).*

3. Line 80: change “person” to “people”.

*We have changed the person to people (page 3, line 81).*

4. Line 169: delete “the” after “appropriate”.

*We have deleted the word the (page 9, line 209)*

5. Line 198: change “will be” to “is”.

*We have changed the will be to is (page 10, line 238).*

## **Reviewer: 2**

Prof. Vasi Naganathan, University of Sydney Comments to the Author:

In my view there is a strong rationale for conducting a systematic review to assess the effectiveness of deprescribing to prevent falls. The protocol meets the PRISMA guidelines for reporting a SR. There have been a number of major deprescribing trials in the last few years which in my mind is the strongest rationale for conducting this SR

The following are some suggestions that may improve the final manuscript.  
See attached PDF

2. See minor edit of abstract methods

*We have adjusted the abstract according to the suggested minor edits. Please see the following sentences in the abstract:*

*Page 2, line 42: This systematic review protocol follows the PRISMA guidelines*

*Page 2, line 46: We will include Randomized Controlled Trials, in which any deprescribing intervention is compared to usual care and reports falls as an outcome.*

3. The title implies deprescribing in general but the abstract implies the deprescribing of FRIDs specifically, as does the introduction. this should be clarified. The search strategy suggest the focus is not just on FRIDs

*We thank the reviewer pointing this out. The focus is not only on FRIDs but also on medication reviews targeting the whole medication regimen. Therefore, we have adjusted the abstract and the introduction and excluded the terms FRIDs deprescribing.*

*Please see the following sentences in the abstract:*

*Page 2, line 38: 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.*

*Please see the following sentences in the introduction:*

*Page 4, line 85: However, to date, there is uncertainty related to the effectiveness of deprescribing as a single intervention in falls prevention.*

*Page 4, line 87: Few systematic reviews and meta-analyses have aimed to summarize the evidence-related to deprescribing as a single intervention.*

## INTRODUCTION

4. It would not be correct to suggest that the fact that previous systematic reviews found variation in included trials and heterogenous results is a good rationale for why another SR needs to be done especially as this is a likely finding in this SR

*We agree with the reviewer that the heterogeneous results of the individual studies or a heterogeneity found in a previous meta-analysis is not an appropriate rationale to conduct another systematic review. Therefore, we do not mention this anymore in the introduction. However, the inclusion of different trials in the different systematic reviews may explain the varying conclusion of these reviews. Thus, this explanation is still included in the introduction. Please see the following sentence;*

*Page 4, line 88: A comparison of the conclusions of these systematic reviews is difficult due to the variation in included trials in the different reviews*

5. There is a more recent Cochrane review (Hopewell et al 2018) that should be mentioned even if they did not report much about deprescribing

*We thank the reviewer for pointing this out. The review by Hopewell et al. (2018) assessed the effects of multifactorial interventions and multiple component interventions for preventing falls in older people living in the community. Medication review was a common component of the multifactorial intervention. They concluded that multifactorial interventions may reduce the rate of falls compared with usual care or attention control. We have added the following sentence;*

*Page 3, line 82: 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).*

6. The following SR should be talked about:

Page AT, Clifford RM, Potter K, Schwartz D, Etherton-Beer CD. The feasibility and effect of deprescribing in older adults on mortality and health: a systematic review and meta-analysis. *Br J Clin Pharmacol.* 2016 Sep;82(3):583-623. doi: 10.1111/bcp.12975. Epub 2016 Jun 13. PMID: 27077231; PMCID: PMC5338123.

They report the following: Deprescribing did not significantly improve the risk of experiencing at least one fall (OR 0.65, 95% CI 0.40–1.05; participants = 2173; studies = 5) (Figure S2). However, participants who did fall had significantly fewer falls overall in the deprescribing group compared to those in the control group (MD 0.11, 95% CI 0.21–0.02; participants = 844; studies = 3) (Figure S3)

*We thank the reviewer mentioning this review and have covered it now in the introduction. Please see the following:*

*Page 4, line 98: 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. However, very heterogeneous interventions were pooled together from placebo-controlled psychotropics withdrawal in primary care to education program regarding appropriate medication use for physicians in nursing homes.*

7. The rationale for conducting this SR could be stronger. Isn't the strongest argument that in the last 5 odd years the results of some major deprescribing trials have been published and therefore now is the time to do updated SR?

*We have clarified the rationale for conducting this review. In addition to the major rationale that there has been some major deprescribing trials in the past years, we believe that there are two important reasons to*

conduct this review. First, we will focus on the different geriatric setting separately (community, hospital, long term care) to minimize the heterogeneity. Secondly, we will include also studies assessing medication reviews and management with a broader focus on reducing polypharmacy and potentially inappropriate prescribing. As there has been a systematic review and meta-analysis by Lee et al. (2021) but only studies focusing on pure FRIDs deprescribing were included.

We have adjusted the following in the manuscript:

Page 5, line 110: 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.

Page 5, line 115: 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

8. See minor suggestions on section on information sources

We have adjusted the sentence by adding the year. Please see the following:

Page 6, line 152: A systematic search was performed in Cochrane Central Register of Controlled Trials, MEDLINE, Embase, and PsycINFO to search for literature published from onset until 2<sup>nd</sup> of November 2020.

9. Search strategy: the description of the search strategy does not do justice to the search strategy described in the appendix. See Page et al article which is a good example of trying to summarise the search strategy.

We have adjusted the description of the search in the manuscript. Please see the following:

Page 7, line 161:

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

10. I am not sure the strategy to look for studies under the theme of health care assessment will capture studies that had falls as a secondary outcome. Capturing studies where falls was not the main outcomes of interest but is reported is going to be a challenge and it may be worth explaining this in more detail in the search strategy

*We thank the reviewer pointing this out.*

*The search was built by an experienced clinical librarian. We used 30 potentially relevant test articles to test that the final search captures all the test articles. 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. This led to inclusion of the search concept health care assessment to the search as this was term indexed to some of the articles which did not mention falls in the abstract or title. Moreover, the search concept “prescribing tools” such as STOPP/START was combined only with the concept “RCTs”.*

*We have added the following to the manuscript (page 7, line 180) :*

*The search was built by an experienced clinical librarian. We used 30 potentially relevant test articles to build and test 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.*

11. Could you clarify this please: does the intervention have to be part of clear deprescribing intervention? ie: for older trials in particular will terms such as deprescribing/withdrawal etc capture them.

Page et al in their 2016 SR used a search strategy that included the individual name of medications (see their supplement).

*The intervention needs to be part of deprescribing intervention but also interventions targeting multiple medication issues will be included. The used search was broad with several terms for deprescribing/medication management and the search was tested appropriately.*

*The type of interventions that we will include are described under subheading type of interventions. We have added the sentence underlined to clarify the interventions included indicating that also comprehensive medication review interventions will be included. Please see the following (page 5, line 131):*

*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” (11). 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.*

*We believe that the search captures relevant studies as it was built by an experienced clinical librarian and we have tested and built the search as described above. As described, 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. The search by Page et al. contains a comprehensive list of individual*

medications but these were combined with the operator AND with search terms regarding deprescribing. Our search contained several terms for deprescribing which were not restricted by combining them with the names of individual medications.

We have added the following to the manuscript as described above in the answer to the point 10 (page 7, line 181):

The search was built by an experienced clinical librarian. We used 30 potentially relevant test articles to build and test the search. These articles were a prior 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.

### VERSION 2 – REVIEW

<b>REVIEWER</b>	Naganathan, Vasi University of Sydney, Concord Hospital
<b>REVIEW RETURNED</b>	16-May-2021

<b>GENERAL COMMENTS</b>	<p>thank you for considering the suggestions from my original review the protocol is now even better and up to date with regards to literature. The rational for the SR is now stronger.</p> <p>Please see attached PDF place cursor on symbols to see comments</p> <p>I have two minor comment what you might like to consider (that I did not think about on the original review)</p> <ol style="list-style-type: none"> <li>1. I wonder if there is way to avoid the phrase "Geriatric settings" it could be seen as ageist. I think the message you want to get out is that this evidence is applicable to anyone looking after older people in the variety of setting that they receive health care. ie applicable to most health care workers rather than only people with a "Geriatric interest". I have done some editing to remove this phrase at 3 places.</li> <li>2. A subgroup analysis has to be done by type of medication class doesn't it? Current literature would suggest that it more likely that an effect will be seen in the withdrawal of psychotropic medications. Literature would also suggest that interventions that target polypharmacy specifically might be more effective but I think you could argue that this implied if it a deprescribing trial.</li> </ol> <p>Other comments</p> <p>page 7, line 125: deprescribing does not always have to be on a strictly of "inappropriate" medication - suggest remove this term</p> <p>page 8, line 145: suggest update the literature review prior to manuscript submission</p>
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	<p>really like the description of the use of 30 test articles. I think readers will find this interesting it is not "officially" reported in most SR publications even though something similar is probably often done.</p> <p>All the best with this very important piece of work</p>
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## VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Prof. Vasi Naganathan, University of Sydney

Thank you for reviewing our manuscript.

1. I wonder if there is way to avoid the phrase "Geriatric settings" it could be seen as ageist. I think the message you want to get out is that this evidence is applicable to anyone looking after older people in the variety of setting that they receive health care. ie applicable to most health care workers rather than only people with a "Geriatric interest". I have done some editing to remove this phrase at 3 places.

Thank you for pointing this out. We have changed the term geriatric to "setting in which older people receive health care". Please see the following changes:

page 2, line 40:

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.

page 3, line 63:

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

page 5, line 110:

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 among older person sin 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.

page 11, line 274:

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 settings in which older people receive health care and all deprescribing interventions.

2. A subgroup analysis has to be done by type of medication class doesn't it? Current literature would suggest that it more likely that an effect will be seen in the withdrawal of psychotropic medications. Literature would also suggest that interventions that target polypharmacy specifically might be more effective but I think you could argue that this implied if it a deprescribing trial.

We thank the reviewer for mentioning this. In our study we want to pool only studies with a sufficiently comparable intervention to minimize the heterogeneity. Thus, for example study evaluating antidepressant withdrawal will not be pooled study investigating antihypertensive withdrawal as we consider these interventions not similar enough. We have clarified this in the manuscript (please see page 10, line 230):

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.

Other comments

page 7, line 125: deprescribing does not always have to be on a strictly of "inappropriate" medication - suggest remove this term

We thank you for mentioning this. We have changed this by placing the word inappropriate in brackets. Please see the following (page 5, line 126):

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).

page 8, line 145: suggest update the literature review prior to manuscript submission

We thank you for pointing this out. We have added the following (page 6, line 147):

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.