PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Deprescribing Fall-Risk-Increasing Drugs (FRIDs) for the Prevention of Falls and Fall-related Complications: A Systematic Review and Meta-analysis
AUTHORS	Lee, Justin; Negm, AM; Peters, Ryan; Wong, Eric; Holbrook, Anne

VERSION 1 – REVIEW

REVIEWER	Slavko Rogan Bern University of Applied Sciences Department of Health Faculty of Physiotherapy Switzerland
REVIEW RETURNED	07-Jan-2020

GENERAL COMMENTS	Thank you for the opportunity to read and review this manuscript. This article deals with medical intervention in elderly persons. It was refreshing to see the use of reporting guideline PRISMA and PROSPERO registration. Introduction Page 6: Please specify how drugs work that trigger such physiological reaction as anti-arrhythmic in elderly individuals Page 6: The study aim is not clear formulated. Specify the aims Page 6: A research question should be formulated. Method Page 7 Line 7-8: the last search was 7 March2019 – please do an update search Discussion Discussion section should be revised. Start the discussion with the research question and answer it in two—three sentences. Please discusses more in detail the RoB, e.g. What are problems of missing random sequence generation and allocation concealment… Discuss more in detail your aims of the study (deprescribing of FRIDs) relating - the detail deprescribing of FRIDs in the studies and the differences with other articles - the results and conclusion of the current e.g. deprescribing FRIDs did not reduce the incidence of falls; explain the reason of this situation and compare this Gillespie et al. Cochrane review. - and not what is missing- Page 18 Line 45-54

REVIEWER	Stephen Lord

	NeuRA, UNSW, Australia
REVIEW RETURNED	15-Jan-2020

GENERAL COMMENTS	This manuscript presents a systematic review that examined the efficacy de-prescribing fall risk increasing drugs (FRIDs) in preventing falls and fall-related complications. Five trials involving 1305 participants met the eligibility criteria. The main findings were that de-prescribing FRIDs did not change the rate of falls, the incidence of falls or rate of fall-related injuries in follow-up periods of 6 to 12 months. Strengths of the study were the 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. I have the following comments. 1. The review does not include at least two highly relevant papers (Refs 1-2). If excluded for some reason, I suggest the eligibility criteria be altered to include these papers that are directly on the topic and will influence the review findings substantially. This would go part way to addressing the authors' conclusion that additional studies are needed to reach the optimal information size to reduce uncertainty about this intervention and establish its relative importance in the range of possible fall prevention interventions. 2. The sub-group and sensitivity analysis are of marginal value given so few studies are included in the review. The Campbell et al study is very different to the studies that addressed multiple FRIDS, as is the study conducted in residential care to those conducted in community settings. Even though these were outlined in the review registration, I feel they are unhelpful and should be omitted. 3. The statement that the evidence for medications increasing fall risk is based primarily on retrospective observational data with limited adjustment for confounders, dosage or duration of therapy is not correct. Many of these studies have been conducted in well deigned prospective cohort studies. The reviews describing FRID risk factors and falls by Leipzig et al and Woolcott et al should also be replaced by the more recent and comprehensive systematic reviews in this topic (Refs 3-5). 4. The authors report that several key confounders were not reported in the studies including baseline number and types of FRIDs, baseline number of medications, and baseline number and types of co-morbidities. Even though these factors may modify falls risk, this does not represent a major issues for the included studies as they were all randomised controlled trials. 5. The statement that the author's search found no trials measuring the impact on fall-related fractures, fall-related hospitalizations or adverse effects related to a FRID de-prescribing strategy is not surprising, as none of the included studies were powered for such outcomes, and thus not meaningful or relevant

	outcome measures. This important issue should be stated in the discussion. References 1. Pit SW, Byles JE, Henry DA, Holt L, Hansen V, Bowman DA. A Quality Use of Medicines program for general practitioners and older people: a cluster randomised controlled trial. Med J Aust 2007;187:23–30. 2. Zermansky AG, Alldred DP, Petty DR, Raynor DK, Freemantle N, Eastaugh J, et al. Clinical medication review by a pharmacist of elderly people living in care homes—randomized controlled trial. Age Ageing 2006;35:586–591. 3. Seppala LJ, Wermelink AMAT, de Vries M, Ploegmakers KJ, van de Glind EMM, Daams JG, van der Velde N, on behalf of the EUGMS Task and Finish Group on Fall-Risk-Increasing Drugs. Fall-Risk-Increasing Drugs: A Systematic Review and Meta-Analysis: II. Psychotropics. Journal of the American Medical Directors Association 2018; 19;371:e11-e17. 4. Seppala LJ, van de Glind EMM, Daams JG, Ploegmakers KJ, de Vries M, Wermelink, van der Velde N, on behalf of the EUGMS Task and Finish Group on Fall-Risk-Increasing Drugs. Fall-Risk-Increasing Drugs: A Systematic Review and Meta-analysis: III. Others. Journal of the American Medical Directors Association 2018;19:372: e1-e8. 5. de Vries M, Seppala LJ, Daams JG, van de Glind EMM, Masud T, van der Velde N on behalf of the EUGMS Task and Finish Group on Fall-Risk-Increasing Drugs. Fall-Risk-Increasing Drugs: A Systematic Review and Meta-Analysis: I. Cardiovascular Drugs. Journal of the American Medical Directors Association 2018;19;71:e1-e9.

REVIEWER	Nathalie van der Velde Amsterdam UMC, The Netherlands
REVIEW RETURNED	10-Feb-2020

GENERAL COMMENTS	Review BMJ open FRID withdrawal by Nathalie van der Velde Major revision The topic of the paper, eg falls prevention is a clinically very relevant topic. Specifically FRID withdrawal is an area that direly needs further research. The paper is well written and methodology is sound. The paper selection is however too rigorous in my opinion. Given the exclusion criteria in the methods section, it remained unclear to me why several relevant papers were not included. Although it can be found in the flow chart and appendix that a very strict definition of FRID withdrawal was chosen. Nevertheless this does not rule out heterogeneity, as the definition of FRID still differs between papers. Moreover, both in international literature and in guidelines there are different definitions of FRID varying between any drug that has side effects that may lead to falls, to a small selection of usually psychotropic drugs. And it is conceivable that general medication withdrawal tools better handle/include the actual culprit drugs that result in falls. Thus in my opinion the stringent definition of FRID withdrawal reduces the clinical relevance of the review. Therefore either a revision including all relevant papers is needed or a clear and convincing explanation of why these papers should be left out together with a very prudent translation and interpretation of the outcome in the discussion and conclusion section is warranted. 1. Pit SW, Byles JE, Henry DA, Holt L, Hansen V, Bowman DA. A Quality Use of Medicines program for general

	practitioners and older people: a cluster randomised controlled trial. Medical Journal of Australia 2007;187(1): 23–30. 2. Weber V, White A, McIlvried R. An electronic medical record (EMR)-based intervention to reduce polypharmacy and falls in an ambulatory rural elderly population. Journal of General Internal Medicine 2008;23(4):399–404. 3. Michalek C, Wehling M, Schlitzer J, Frohnhofen H. Effects of "Fit fOR The Aged" (FORTA) on pharmacotherapy and clinical endpoints–a pilot randomized controlled study. Eur J Clin Pharmacol. 2014;70:1261–7. 4. Frankenthal D, Lerman Y, Kalendaryev E, Lerman Y. Intervention with the screening tool of older persons potentially inappropriate prescriptions/screening tool to alert doctors to right treatment criteria in elderly residents of a chronic geriatric facility: a randomized clinical trial. J Am Geriatr Soc. 2014;62:1658–65. ... and thus besides papers earlier included in the Cochrane review of Gillespie et all also other papers that addressed the effectiveness general deprescribing tools (including FRIDs) on fall risk are lacking in the current review. In my opinion those papers need to be included as they address the effectiveness of deprescribing on fall risk eg with the goals lowering ADEs. Since there is reasonable uncertainty on which drugs do or do not lead to falls, a stringent definition of FRIDs is counterproductive in this point in time. Discussion Page 18 row 42. Review that is referred to with regard to general medication withdrawal is outdated. Please rephrase and refer to recent studies page 19 row 31. Please rephrase and include other effective RCT data, given among others the references mentioned above. Introduction page 6, row 44. remove belief. The increased risk eg associations have been clearly shown. The uncertainty is about effectiveness of withdrawal and thus causality has not yet been proven. Please include recent systematic reviews of FRIDs in the introduction, e.g. papers of the EuGMS Task and Finish group on FRID by Lotta Seppala et al (JAMDA 2018).

VERSION 1 – AUTHOR RESPONSE

Response to Reviewers - Manuscript ID: bmjopen-2019-035978

#	Reviewer 1 Comments	Revisions to Manuscript in Response
	Introduction	

1	Page 6: Please specify how drugs work that trigger such physiological reaction as anti-arrhythmic in elderly individuals.	Thank you for the suggestion. We have added the following: *"Although the mechanisms are not fully understood, these drugs may influence falls risk by adversely affecting the cardiovascular or central nervous system (e.g. orthostatic hypotension, bradycardia, sedation, sleep disturbance, confusion, dizziness)."*
2	Page 6: The study aim is not clear formulated. Specify the aims.	We have revised the introduction to provider greater clarity on the study aim and research question: *"With the aim of evaluating its effectiveness as a falls prevention strategy, we conducted this systematic review to determine whether deprescribing FRIDs decreases the risk of falls compared to usual care in older adults."*
3	Page 6: A research question should be formulated.	See above response to Comment #2
	Methods	
4	Page 7 Line 7-8: the last search was 7 March2019 – please do an update search	We have updated the citation search through to August 1, 2020 and revised the paper accordingly.
	Discussion	
5	Discussion section should be revised. Start the discussion with the research question and answer it in two—three sentences.	We have revised the discussion based on the feedback: *"This systematic review sought to determine whether deprescribing FRIDs decreased the risk of falls in older adults and found that there is a lack of robust high-quality evidence to support or refute the deprescribing of FRIDs as an effective fall prevention strategy. Incorporating data from 5 RCTs involving 1305 participants aged ≥65 years, our meta-analyses indicate that a FRID deprescribing strategy did not significantly change the rate*

		of falls (RaR 0.98, 95% CI 0.63 to 1.51) nor the risk of falling (RD 0.01, 95% CI -0.06 to 0.09) over a 6 to 12-month follow-up period."
6	Please discusses more in detail the RoB, e.g. What are problems of missing random sequence generation and allocation concealment…	Based on the feedback, we have added the following to the Risk of Bias section: *"For falls rate and incidence, all studies except one[24] were judged at high risk of bias for lack of blinding of participants, personnel and outcome assessors. It is unclear whether blinding could have impacted behaviour or perceptions (e.g. activity risk-level, nocebo effect). Risk of ascertainment bias was high in one study[26] (i.e. no standardized falls definition was used), but all other studies used methods accepted to be low risk of bias (i.e. falls recorded daily on postcards or calendars). Risk of attrition bias was deemed high in three studies based on high or unbalanced lost to follow-up rates.[23,24,27]"*
7	Discuss more in detail your aims of the study (deprescribing of FRIDs) relating - the detail deprescribing of FRIDs in the studies and the differences with other articles - the results and conclusion of the current e.g. deprescribing FRIDs did not reduce the incidence of falls; explain the reason of this situation and compare this Gillespie et al. Cochrane review. - and not what is missing- Page 18 Line 45-54	Based on the feedback, we have added the following in various sections of the discussion: *"Although this intervention focuses on those medications thought to be associated with falls, the conclusions are similar to previous systematic reviews evaluating the effectiveness of medication reviews that had a broader focus on reducing polypharmacy and potentially inappropriate prescribing (i.e. not focused solely on FRIDs).[35,36]"* *"Our findings likely reflect the multi-factorial nature of falls and the varying risk of different FRIDs. It is unclear as to what degree a particular risk factor or combination of risk factors (e.g. specific FRIDs) must be reduced to produce an appreciable change in falls. Medications may only have conditional or contributory causality to falls. It may be that medication-related interventions work best in*

		combination with other interventions or only in specific contexts." *"It is also unclear whether medication review and management with a broader focus on reducing polypharmacy and potentially inappropriate prescribing in older adults may be beneficial in preventing falls."*

#	**Reviewer 2 Comments**	**Revisions to Manuscript in Response**
8	This manuscript presents a systematic review that examined the efficacy de-prescribing fall risk increasing drugs (FRIDs) in preventing falls and fall-related complications. Five trials involving 1305 participants met the eligibility criteria. The main findings were that de-prescribing FRIDs did not change the rate of falls, the incidence of falls or rate of fall-related injuries in follow-up periods of 6 to 12 months. Strengths of the study were the 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.	Thank you for the feedback.

9	I have the following comments. 1. The review does not include at least two highly relevant papers (Refs 1-2). If excluded for some reason, I suggest the eligibility criteria be altered to include these papers that are directly on the topic and will influence the review findings substantially. This would go part way to addressing the authors' conclusion that additional studies are needed to reach the optimal information size to reduce uncertainty about this intervention and establish its relative importance in the range of possible fall prevention interventions. References 1. Pit SW, Byles JE, Henry DA, Holt L, Hansen V, Bowman DA. A Quality Use of Medicines program for general practitioners and older people: a cluster randomised controlled trial. Med J Aust 2007;187:23–30. 2. Zermansky AG, Alldred DP, Petty DR, Raynor DK, Freemantle N, Eastaugh J, et al. Clinical medication review by a pharmacist of elderly people living in care homes—randomized controlled trial. Age Ageing 2006;35:586–591.	Thank you for the feedback. Our eligibility criteria have been registered on PROSPERO and published in a peer-reviewed protocol paper. We do not feel it would be appropriate to modify the eligibility criteria post-hoc. We reviewed the 2 papers mentioned by the peer reviewer. They do not meet this review's eligibility criteria. Both studies involve mixed interventions where it is not possible to isolate the effect of deprescribing FRIDs. They intervened on multiple medication issues that could influence several health-related outcomes including falls (e.g. polypharmacy, non-adherence, education, and medications changes that may have included the starting or stopping both FRIDs and non-FRIDs). In Zermansky 2006, for example, only 13% of recommendations were to deprescribe medications. These studies are interesting, but provide data for a different research question (e.g. does general medication review and polypharmacy reduction affect the rate of falls). We have also revised the manuscript to provide more clarity on the differences of the intervention of our systematic review compared to others: *"Although this intervention focuses on those medications thought to be associated with falls, the conclusions are similar to previous systematic reviews evaluating the effectiveness of medication reviews that had a broader focus on reducing polypharmacy and potentially inappropriate prescribing (i.e. not focused solely on FRIDs).[35,36]"*

10	2. The sub-group and sensitivity analysis are of marginal value given so few studies are included in the review. The Campbell et al study is very different to the studies that addressed multiple FRIDS, as is the study conducted in residential care to those conducted in community settings. Even though these were outlined in the review registration, I feel they are unhelpful and should be omitted.	Thank you for the feedback. The sub-group and sensitivity analyses were pre-specified and published both in a peer-reviewed protocol paper and PROSPERO registration. Thus, we have elected to keep them in the manuscript for reporting transparency. We agree with the reviewer that there are a small number of studies/participants available for these analyses. As such, we have emphasized in the manuscript text that these analyses need to be interpreted cautiously. We highlight that subgroup credibility criteria (as outlined in Cochrane Handbook) suggest that there is lack of certainty in the subgroup effects as follows: *"… in both analyses, only 6 of 11 subgroup credibility criteria were met and each subgroup was limited to one trial with less than 100 participants (Supplementary Table S2). We, therefore, judged the credibility that these subgroup effects are real as poor and uncertain."*
11	3. The statement that the evidence for medications increasing fall risk is based primarily on retrospective observational data with limited adjustment for confounders, dosage or	Based on the feedback, we have added the citations suggested by the reviewer and revised the text as follows:

	duration of therapy is not correct. Many of these studies have been conducted in well deigned prospective cohort studies. The reviews describing FRID risk factors and falls by Leipzig et al and Woolcott et al should also be replaced by the more recent and comprehensive systematic reviews in this topic (Refs 3-5). References: 3. Seppala LJ, Wermelink AMAT, de Vries M, Ploegmakers KJ, van de Glind EMM, Daams JG, van der Velde N, on behalf of the EUGMS Task and Finish Group on Fall-Risk-Increasing Drugs. Fall-Risk-Increasing Drugs: A Systematic Review and Meta-Analysis: II. Psychotropics. Journal of the American Medical Directors Association 2018; 19;371:e11-e17. 4. Seppala LJ, van de Glind EMM, Daams JG, Ploegmakers KJ, de Vries M, Wermelink, van der Velde N, on behalf of the EUGMS Task and Finish Group on Fall-Risk-Increasing Drugs. Fall-Risk-Increasing Drugs: A Systematic Review and Meta-analysis: III. Others. Journal of the American Medical Directors Association 2018;19:372: e1-e8. 5. de Vries M, Seppala LJ, Daams JG, van de Glind EMM, Masud T, van der Velde N on behalf of the EUGMS Task and Finish Group on Fall-Risk-Increasing Drugs. Fall-Risk-Increasing Drugs: A Systematic Review and Meta-Analysis: I. Cardiovascular Drugs. Journal of the American Medical Directors Association 2018;19;71:e1-e9.	*Although there is limited evidence of effectiveness, deprescribing medications known as "fall-risk increasing drugs" (FRIDs) is common practice and typically included in both multifactorial and single intervention strategies. The justification is based primarily on observational studies that suggest certain medications are associated with increased falls risk… Key issues affecting the quality of this observational evidence and certainty of a causal relationship include: (1) variable adjustment for confounders, dosage or duration of therapy, (2) medication use confirmed only at baseline (but not throughout follow-up), and (3) potential prescribing bias associated with specific medication classes. Most meta-analyses have also been based on the pooling of unadjusted estimates and thus susceptible to bias including confounding by indication. As a result, it is unclear whether the observed increase in falls is causally related to such drug use versus the underlying conditions or patients for which the drugs are treating."*
12	4. The authors report that several key confounders were not reported in the studies including baseline number and types of FRIDs, baseline number of medications, and baseline number and types of co-morbidities. Even though these factors may modify falls risk, this does not represent a major issues for the included studies as they were all randomised controlled trials.	We agree that these baseline factors do not represent a major risk of bias in properly conducted RCTs. Their reporting is important to our interpretation, understanding and application of their results (e.g. potential reasons for variable effectiveness and inconsistency in results between trials). Based on the feedback, we have revised the text as follows: *"Greater attention to optimal design and reporting is needed to minimize risk of bias and enhance our interpretation of the results. Examples include improved reporting of confounding baseline characteristics and*

		intervention fidelity (e.g. number and types of FRIDs, degree and duration of dose reduction). Deprescribing is challenging and extra measures are likely needed to improve successful intervention adherence and follow-up."
13	5. The statement that the author's search found no trials measuring the impact on fall-related fractures, fall-related hospitalizations or adverse effects related to a FRID de-prescribing strategy is not surprising, as none of the included studies were powered for such outcomes, and thus not meaningful or relevant outcome measures. This important issue should be stated in the discussion.	We disagree that these outcomes are not meaningful or relevant outcome measures. Although the studies may not be powered for these outcomes, their reporting becomes relevant in systematic review and meta-analysis (which may lead to sufficient statistical power to evaluate these outcomes). Based on the feedback, we have revised the discussion as follows: *"Our search found no trials measuring the impact on fall-related fractures, fall-related hospitalizations or adverse effects related to a FRID deprescribing strategy. Although this may be rooted in the difficulty of conducting RCTs powered for such outcomes, their measurement and reporting are still important to inform systematic review meta-analyses that could lead to more precise estimates."*

#	**Reviewer 3 Comments**	**Revisions to Manuscript in Response**
14	The topic of the paper, eg falls prevention is a clinically very relevant topic. Specifically FRID withdrawal is an area that direly needs further research. The paper is well written and methodology is sound. The paper selection is however too rigorous in my opinion. Given the exclusion criteria in the methods section, it remained unclear to me why several relevant papers were not included. Although it can be found in the flow chart and	Thank you for the feedback. There is general consensus that several medications appear to influence falls risk (e.g. sedative-hypnotics, antipsychotics, opioids, antidepressants). These informed our search strategy. However, given that there is debate on the exact definition of a FRID, we did not limit study eligibility to a strict pre-defined list of drug classes. Our screening also permitted studies that deprescribed any drug(s) that its investigators identified as increasing falls risk.

	appendix that a very strict definition of FRID withdrawal was chosen. Nevertheless this does not rule out heterogeneity, as the definition of FRID still differs between papers. Moreover, both in international literature and in guidelines there are different definitions of FRID varying between any drug that has side effects that may lead to falls, to a small selection of usually psychotropic drugs. And it is conceivable that general medication withdrawal tools better handle/include the actual culprit drugs that result in falls. Thus in my opinion the stringent definition of FRID withdrawal reduces the clinical relevance of the review. Therefore either a revision including all relevant papers is needed or a clear and convincing explanation of why these papers should be left out together with a very prudent translation and interpretation of the outcome in the discussion and conclusion section is warranted. ... and thus besides papers earlier included in the Cochrane review of Gillespie et all also other papers that addressed the effectiveness general deprescribing tools (including FRIDs) on fall risk are lacking in the current review. In my opinion those papers need to be included as they address the effectiveness of deprescribing on fall risk eg with the goals lowering ADEs. Since there is reasonable uncertainty on which drugs do or do not lead to falls, a stringent definition of FRIDs is counterproductive in this point in time. 1. Pit SW, Byles JE, Henry DA, Holt L, Hansen V, Bowman DA. A Quality Use of Medicines program for general practitioners and older people: a cluster randomised controlled trial. Medical Journal of Australia 2007;187(1): 23–30. 2. Weber V, White A, McIlvried R. An electronic	We reviewed the papers mentioned by the peer reviewer. They do not meet this review's eligibility criteria. All of the studies involve mixed interventions where it is not possible to isolate the effect of deprescribing FRIDs. They intervened on multiple medication issues that could influence several health-related outcomes including falls (e.g. polypharmacy, non-adherence, education, and medications changes that may have included the stopping of potentially inappropriate medications **and** the starting medically indicated medications [e.g. application of STOPP and START criteria]). The scope of potential medications changes extended beyond the deprescribing of FRIDs. These studies are interesting, but provide data for a different research question (e.g. does general medication review and polypharmacy reduction affect the rate of falls). This may be the reason that the Cochrane review by Gillespie differentiated studies that carried out "medication withdrawal" vs. those conducted "medication review and modification". Based on the reviewer's feedback, we have added the following to the discussion for clarity: *"Despite insufficient evidence to support or refute the deprescribing of FRIDs for falls prevention, our results do not mean that clinicians should avoid deprescribing FRIDs. There may be many other reasons to deprescribe these medications. These include avoidance of adverse drug events, improvements in cognition, increased medication adherence and drug costs savings. It is also unclear whether medication review and management with a broader focus on reducing polypharmacy and potentially*

	medical record (EMR)-based intervention to reduce polypharmacy and falls in an ambulatory rural elderly population. Journal of General Internal Medicine 2008;23(4):399–404. 3. Michalek C, Wehling M, Schlitzer J, Frohnhofen H. Effects of "Fit fOR The Aged" (FORTA) on pharmacotherapy and clinical endpoints–a pilot randomized controlled study. Eur J Clin Pharmacol. 2014;70:1261–7. 4. Frankenthal D, Lerman Y, Kalendaryev E, Lerman Y. Intervention with the screening tool of older persons potentially inappropriate prescriptions/screening tool to alert doctors to right treatment criteria in elderly residents of a chronic geriatric facility: a randomized clinical trial. J Am Geriatr Soc. 2014;62:1658–65.	*inappropriate prescribing in older adults may be beneficial in preventing falls.*
	Discussion	
15	Page 18 row 42. Review that is referred to with regard to general medication withdrawal is outdated. Please rephrase and refer to recent studies	Based on the feedback, we have added a reference to the 2018 United States Preventative Task Force systematic review and modified the text as follows: *"Although this intervention focuses on those medications thought to be associated with falls, the conclusions are similar to previous systematic reviews evaluating the effectiveness of medication reviews that had a broader focus on reducing polypharmacy and potentially inappropriate prescribing (i.e. not focused solely on FRIDs).[35,36]"*
16	page 19 row 31. Please rephrase and include other effective RCT data, given among others the references mentioned above.	After the updated citation search, we did not find any additional RCTs with results demonstrating reduced falls. Please refer to responses to comments #9 and #14 for the reasons that the studies listed by the reviewer were not eligible and did not provide data for this research question.
17	Introduction page 6, row 44. remove belief. The increased risk eg associations have been clearly shown. The uncertainty is about effectiveness of withdrawal and thus causality has not yet been proven. Please include recent systematic reviews of FRIDs in the	Please refer to response for comment #11.

	introduction, e.g. papers of the EuGMS Task and Finish group on FRID by Lotta Seppala et al (JAMDA 2018).	

VERSION 2 – REVIEW

REVIEWER	Slavko Rogan Bern University of Applied Sciences, Department of Health Professions, Switzerland
REVIEW RETURNED	30-Aug-2020

GENERAL COMMENTS	Dear authors, congratulation to the nice work. I've read the manuscript with pleasure. In order to improve the quality of this manuscript, I will make few remarks. Introduction: Please describe the terms multifactorial intervention and multicomponent intervention more in detail and the link to the medication is still unlcear to me. In the end it's all about FRIDs. The research question is missing. I found in PROSPERO the following one: In older adults aged >= 65 years, does the withdrawal of fall-risk-increasing drugs (FRIDs) decrease the risk of falls compared to usual care and continuation of these drugs? Method The statistical analysis has weaknesses: On the one hand, a pilot study was included (Mott et al.), because the goal of a pilot study is not the presentation of statistics On the other hand, one study was conducted over 14 days and another over 12 months (Pattersson et al.).Which types of medication were used (this should be listed in the table). In my view, a meta-analysis with these data is not possible. Discussion A discussion on the risk of bias should occur.

REVIEWER	Stephen Lord NeuRA, UNSW, Australia
REVIEW RETURNED	18-Aug-2020

GENERAL COMMENTS	The authors have addressed most of my comments. I have only one remaining: The authors included the following with regard to previous research that has addressed a similar topic. i.e. medication review for fall prevention, that relates to my concern that the restricted focus of the review misses some of the clinical implications for such interventions:

	"Despite insufficient evidence to support or refute the deprescribing of FRIDs for falls prevention, our results do not mean that clinicians should avoid deprescribing FRIDs. There may be many other reasons to deprescribe these medications. These include avoidance of adverse drug events, improvements in cognition, increased medication adherence and drug costs savings. It is also unclear whether medication review and management with a broader focus on reducing polypharmacy and potentially inappropriate prescribing in older adults may be beneficial in preventing falls. To better reflect this related work, i suggest the final sentence in the above paragraph be amended to indicate some such broader fall prevention initiatives with de-prescribing FRIDS as a component have been effective in preventing falls (along with references to some of the papers suggested by reviewer 3 and me).

REVIEWER	Nathalie van der Velde Amsterdam UMC, The Netherlands
REVIEW RETURNED	02-Sep-2020

GENERAL COMMENTS	Although I fully understand and respect the choice of the authors not to defer from their pre-registered search criteria, the chosen approach does seriously limit the clinical relevance of the results and conclusions of the SR and meta-analyses and thus the paper. I fully agree with their general conclusion however, that given the paucity of high quality evidence it can neither be supported or refuted that FRID withdrawal as an isolated intervention for falls prevention is or is not effective. And in any case a multifactorial falls preventive intervention would be the best approach. The authors have now partly tackled this in their paper by reflecting on their chosen scope more clearly in the different parts of the manuscript. Nevertheless, this was inconsistently done (see below for details) and several adjustments are put quite strongly. Some more nuance is still essential and especially in the introduction and discussion references need to be added. Abstract Introduction please rephrase. Although scarse, there are intervention studies, including several RCTs available, as mentioned in the Cochrane review a.o., not solely on observational studies. Conclusion, please also add in the first sentence of the conclusion 'as a single intervention strategy' as this is what was reviewed in your SR. Introduction Please rephrase paragraph one and two on page 6. Justification of FRID withdrawal as part of the multifactorial intervention is not solely based on observational studies as mentioned above. The Cochrane SR needs to be cited instead. Page 6 last paragraph: please add to the aim that only effectiveness of FRID withdrawal as a single/isolated intervention was studied Discussion First sentence, first paragraph page 18: again, please add that only the isolated intervention strategy was assessed Page 18, row 40-49: please rephrase. Although I agree that also with regard of studies on the effectiveness general deprescribing interventions studies are scarce, it cannot be concluded that these studies did not positively affect fall risk, including the refs

	mentioned in the previous review. Does the statement needs to be adjusted accordingly.

VERSION 2 – AUTHOR RESPONSE

Response to Reviewers - Manuscript ID: bmjopen-2019-035978.R1

#	Reviewer 1 Comments	Revisions to Manuscript in Response
1	Dear authors, congratulation to the nice work. I've read the manuscript with pleasure. In order to improve the quality of this manuscript, I will make few remarks. Introduction: Please describe the terms multifactorial intervention and multicomponent intervention more in detail and the link to the medication is still unlcear to me. In the end it's all about FRIDs.	Based on the feedback, we have added the following for clarity: *"Since the majority of falls result from multiple factors (e.g. poor strength and balance, visual and cognitive impairment), current practice guidelines and accreditation standards focus on multi-factorial assessment and intervention strategies.[5]* ***These strategies involve the combination of two or more interventions (e.g. exercise, home or environmental modification, vision assessment, education, medication management, vitamin D supplementation)."***
2	The research question is missing. I found in PROSPERO the following one: In older adults aged >= 65 years, does the withdrawal of fall-risk-increasing drugs (FRIDs) decrease the risk of falls compared to usual care and continuation of these drugs?	The research question can be found in the last paragraph of the introduction. However, we have revised for greater clarity based on the feedback: *"We conducted this systematic review to determine whether deprescribing FRIDs alone, decreases the risk of falls compared to usual care in older adults* ***aged ≥ 65 years****. To the best of our knowledge, no previous systematic review has addressed this specific research question."*
3	Method The statistical analysis has weaknesses: On the one hand, a pilot study was included (Mott et al.), because the goal of a pilot study is not the presentation of statistics On the other hand, one study was conducted over 14 days and another over 12 months (Pattersson et al.).Which types of medication were used (this should	As per the reviewer's suggestion, we have added a column entitled "Targeted FRIDs" into Table 1: Characteristics of Included Studies to provide greater details on the medications. We believe that it is appropriate to conduct meta-analysis. Although the pilot RCT by Mott et al was not powered for our primary outcomes, its reported data is relevant to our systematic review and meta-analysis because it increases our statistical power to evaluate

	be listed in the table). In my view, a meta-analysis with these data is not possible.	these outcomes and increases the precision of our effect estimates. See Thabane et al. A tutorial on pilot studies: the what, why and how. BMC Med Res Methodol 2010. There were no studies with a 14 day follow-up period. One study had a 6 month follow-up period and all other studies have a 12 month follow-up period. These follow-up periods are similar enough clinically and methodologically for meta-analysis. This follows our a priori plan in our published protocol. We intended to pool data at various follow-up time intervals (i.e. < 3 months, 3-6 months, 6-12 months, > 12 months), but all included studies had follow-up between 6-12 months.
4	Discussion A discussion on the risk of bias should occur.	A dedicated discussion of risk of bias is found in a dedicated "Risk of Bias" section on pages 13-14 of the manuscript. Based on the feedback, we have revised the relevant section of the discussion as follows: *"Only one trial[25] included in our review demonstrated a statistically significant benefit with deprescribing FRIDs. This was also the only trial to use study capsules to operationalize blinded deprescribing of FRIDs in participants, research personnel and outcome assessors. Its results might be more reflective of the true potential physiological effect of deprescribing FRIDs because it minimized the risk of performance bias. However, the magnitude of benefit achievable in the non-research setting at this time may be closer to those seen in the unblinded trials due to the strong psychological and behavioural factors (e.g. nocebo effect) that may hinder successful deprescribing. Further advances in implementation science and behavioural change strategies are likely needed to facilitate medication optimization.*"

#	**Reviewer 2 Comments**	**Revisions to Manuscript in Response**
8	The authors have addressed most of my comments. I have only one remaining:	Thank you for the feedback. We have added the following sentence for clarity and included some references as per the reviewer's suggestions: *"It is also unclear whether medication review and management with a broader focus on reducing*

	The authors included the following with regard to previous research that has addressed a similar topic. i.e. medication review for fall prevention, that relates to my concern that the restricted focus of the review misses some of the clinical implications for such interventions: "Despite insufficient evidence to support or refute the deprescribing of FRIDs for falls prevention, our results do not mean that clinicians should avoid deprescribing FRIDs. There may be many other reasons to deprescribe these medications. These include avoidance of adverse drug events, improvements in cognition, increased medication adherence and drug costs savings. It is also unclear whether medication review and management with a broader focus on reducing polypharmacy and potentially inappropriate prescribing in older adults may be beneficial in preventing falls. To better reflect this related work, i suggest the final sentence in the above paragraph be amended to indicate some such broader fall prevention initiatives with de-prescribing FRIDS as a component have been effective in preventing falls (along with references to some of the papers suggested by reviewer 3 and me).	*polypharmacy and potentially inappropriate prescribing in older adults may be beneficial in preventing falls. RCTs with such interventions have shown mixed results on falls risk.[40–46]"* *"It is also unclear whether medication review and management with a broader focus on reducing polypharmacy and potentially inappropriate prescribing in older adults may be beneficial in preventing falls. Some RCTs with such interventions have shown a reduction of falls risk, while others have not demonstrated a significant difference.[40–46]"*

#	**Reviewer 3 Comments**	**Revisions to Manuscript in Response**
14	Although I fully understand and respect the choice of the authors not to defer from their pre-registered search criteria, the chosen approach does seriously limit the clinical relevance of the results and conclusions of the SR and meta-analyses and thus the paper. I fully agree with their general conclusion	Based on the reviewer's suggestions, we deleted the comment on observational studies and the conclusion has been amended as follows: *"There is a paucity of robust high-quality evidence to support or refute that a FRID deprescribing strategy*

	however, that given the paucity of high quality evidence it can neither be supported or refuted that FRID withdrawal as an isolated intervention for falls prevention is or is not effective. And in any case a multifactorial falls preventive intervention would be the best approach. The authors have now partly tackled this in their paper by reflecting on their chosen scope more clearly in the different parts of the manuscript. Nevertheless, this was inconsistently done (see below for details) and several adjustments are put quite strongly. Some more nuance is still essential and especially in the introduction and discussion references need to be added. Abstract Introduction please rephrase. Although scarse, there are intervention studies, including several RCTs available, as mentioned in the Cochrane review a.o., not solely on observational studies. Conclusion, please also add in the first sentence of the conclusion 'as a single intervention strategy' as this is what was reviewed in your SR.	***alone** is effective at preventing falls or falls-related injury in older adults."*
	Introduction Please rephrase paragraph one and two on page 6. Justification of FRID withdrawal as part of the multifactorial intervention is not solely based on observational studies as mentioned above. The Cochrane SR needs to be cited instead.	As per the reviewer's suggestion, we have the revised this section and cited the Cochrane SR as follows: *"The justification is based on observational studies that suggest certain medications are associated with increased falls risk **as well as some randomized controlled trials (RCTs) that have shown that medication management interventions (including those with a broader focus of reducing polypharmacy and/or potentially inappropriate prescribing) may reduce the risk of falls**.[9]"*

	Page 6 last paragraph: please add to the aim that only effectiveness of FRID withdrawal as a single/isolated intervention was studied *falls prevention strategy*	We have revised the last paragraph for clarity as per the reviewer's suggestion: *"With the aim of evaluating its effectiveness as an **single** …"*
15	Discussion First sentence, first paragraph page 18: again, please add that only the isolated intervention strategy was assessed	We have revised based the feedback: "… there is a lack of robust high-quality evidence to support or refute the deprescribing of FRIDs alone as an effective fall prevention strategy."
16	Page 18, row 40-49: please rephrase. Although I agree that also with regard of studies on the effectiveness general deprescribing interventions studies are scarce, it cannot be concluded that these studies did not positively affect fall risk, including the refs mentioned in the previous review. Does the statement needs to be adjusted accordingly.	Based on the feedback, we have revised the sentence for clarity: *Although this intervention focuses on those medications thought to be associated with falls,* *the uncertainty of its effect on falls and conclusions of current lack of evidence of effectiveness are similar to previous systematic reviews evaluating the effectiveness of medication reviews that had a broader focus on reducing polypharmacy and potentially inappropriate prescribing (i.e. not focused solely on FRIDs).[9,36]* This is based on the following evidence syntheses that were referenced: • In the Cochrane systematic review (Gillespie et al, 2012) referenced by the reviewer, the authors concluded that: ○ *"Three trials in this review failed to reduce the number of falls by reviewing and adjusting medications. A fourth trial involving family physicians and their patients in medication review was effective in reducing falls."* • In the 2018 Systematic Review for the U.S. Preventive Services Task Force, the authors concluded that: ○ *"Evidence is limited to two underpowered RCTs (n=266). There was no difference in falls, people experiencing a fall, injuries or mortality seen in high-risk older adults*

		receiving medication management interventions"

VERSION 3 – REVIEW

REVIEWER	Slavko Rogan Bern University and Applied Sciences, Department of Health Professions, Switzerland
REVIEW RETURNED	10-Oct-2020

GENERAL COMMENTS	The authors have addressed most of my remarks. A note, i cannot find a research question in the last paragraph of the introduction, but rather a formulation of the study goal. On the one hand, questions always end with a question mark, and on the other hand, the written text is not identical to that on PROSPERO and the published study protocol: In older adults age ≥65 years, does the withdrawal of fall-risk increasing drugs (FRIDs) decrease the risk of falls compared to usual care and continuation of these drugs?

REVIEWER	Nathalie van der Velde Amsterdam UMC, The Netherlands
REVIEW RETURNED	30-Oct-2020

GENERAL COMMENTS	The authors have addressed the earlier raised concerns and comments appropriately.

VERSION 3 – AUTHOR RESPONSE

Response to Reviewers - Manuscript ID: bmjopen-2019-035978.R2

#	Reviewer 1 Comments	Revisions to Manuscript in Response
1	The authors have addressed most of my remarks. A note, i cannot find a research question in the last paragraph of the introduction, but rather a formulation of the study goal. On the one hand, questions always end with a question mark, and on the other hand, the written text is not identical to that on PROSPERO and the published study protocol: In older adults age ≥65 years, does the withdrawal of fall-risk increasing drugs (FRIDs) decrease the risk of falls compared to usual care and continuation of these drugs?	Based on the feedback, we have modified the text as follows: *With the aim of evaluating its effectiveness as a single falls prevention strategy, we conducted this systematic review to answer the following: "In older adults aged 65 years or older, does deprescribing and the withdrawal of fall-risk increasing drugs (FRIDs) decrease the risk of falls compared to usual care and continuation of these drugs?" To the best of our knowledge, no previous systematic review has addressed this specific research question.*

#	**Reviewer 3 Comments**	**Revisions to Manuscript in Response**
2	The authors have addressed the earlier raised concerns and comments appropriately.	Thank you for the careful review and feedback.