PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Deprescribing anticholinergic and sedative medicines: protocol for a Feasibility Trial (DEFEAT-polypharmacy) in residential aged care facilities
AUTHORS	Ailabouni, Nagham; Mangin, Dee; Nishtala, Prasad

VERSION 1 - REVIEW

REVIEWER	Sverre Bergh Center for old age psychiatry research, Innlandet Hospital trust. Ottestad, Norway
REVIEW RETURNED	30-Aug-2016

GENERAL COMMENTS	Review, Ailabouni PROTOCOL: Deprescribing anticholinergic and sedative medicines: A Feasibility Trial (DEFEAT-polypharmacy) in residential aged care facilities Thank you for the ability to review the manuscript. The manuscript describes the protocol for a study assessing the feasibility of using a peer-reviewed deprescribing guidelines to deprescribe anticholinergic and sedative medicines. The manuscript describes a pilot-study that eventually will lead to a RCT. Medication reviews and safe reducing or stopping medication with potential adverse effects or drug-drug interaction are important for patients with dementia, and I welcome the initiative and the study. The intervention is well described, and reasonable. The ethics are described in a good way, and the study is approved be the Human Disability and Ethics Committee of New Zealand. I do have some comments to the authors about the method and the research questions, but as the study already have started recruiting I am not sure how appropriate they are. 1. Abstract: a. Falls should be included in the text as one of the secondary outcomes. Funding is not stated in the abstract. 2. In-/exclusion criteria: a. Residents with severe dementia will be excluded from the study. Why? Persons with severe dementia have severe neurocognitive disorder, and they are sensitive to drugs. The advantage of reducing medication in this group of patients should be great. b. Exclusion criteria no. 4 should be omitted, as the criteria logically follows the inclusion criteria. 3. Recruitment procedure: a. The authors describe that patients unable to provide informed consent should be included if the GP believes that a deprescribing could result in an improvement in QoL. Why? How is it possible to assess the feasibility of deprescribing in an objective manner if you

	will include participants that in advance are judged to have an advantage of deprescribing? b. Following the same idea, p. 4 line 51-52: “The decision to enrol those patients….be the decision of the GP”. So the GP should decide if the participants could be deprescribe the medication, and if yes, they should be recruited and the study should answer if the intervention reduce the DBI? c. The same goes for reconsidering the consent after 3 months. Again, the GP should decide whether if not the participants should continue in the study if the EPOAs are not responding. 4. Data collection: a. The data collection is described in detail, and is reasonable. Nevertheless, assessing adverse drug effects three months after deprescribing seems odd as the adverse effect may be present only a few weeks after deprescribing. The pharmacist will assess the participants twice a week the weeks after deprescribing. Could a standardized assessment tool like UKU-SERS been applied during these visits? 5. Outcomes: a. On page 8, number of falls are described as a secondary outcome, which I find reasonable. Could this information be included in the tables as well? b. GDS is described as an assessment tool used for data collection, but is not one of the outcomes. Why not? I would also suggest that you assessed NPS at baseline and follow up, e.g. using the NPI, to assess how deprescribing medication interfere with the NPS. 6. Power, sample size and analyses: a. According to the power calculation 150 participants should be included, but the text on page 8 indicate that a smaller number of participants or a higher number may be necessary. I assume that you will include 150 participants but it is a bit unclear for me. Please clarify. b. Table 3 states that the four primary and secondary outcomes should be analysed with t-test. What if the results are not-normally distributed? In the text you say that M-W-U test may be used, should this be written in the table as well? 7. Limitations: a. The limitation of the recruitment procedure is not fully discussed in the limitations section 8. Funding a. I can’t see that the manuscript includes information about funding of the study, but I may be wrong? Minor comments: 1. P. 7, line 31-32: …as detailed in Table 1. – Should be table 2? 2. P. 7, line 57: ….in the intervention group…. – As there is only one group of patients, the term intervention group could be rephrased 3. P. 8, line 1: DSMB should be written out fully 4. P. 8, line 8: …DBI tool at baseline 6 months post-intervention. – Unclear sentence, please rephrase 5. P.8 line 52: A sample size of 150 participants…..– Unclear sentence, please rephrase 6. P. 8, line 53-54: …., so smaller numbers may suffice…. – Unclear sentence, please rephrase 7.

REVIEWER	Noll Campbell Purdue University, United States
REVIEW RETURNED	10-Nov-2016

GENERAL COMMENTS	This study is of high importance given the questions that have yet to be answered regarding the safety and efficacy of de-prescribing interventions. The protocol is well written, however a few comments are offered to improve the clarity of the manuscript. Abstract: 1. The last sentence of the introduction and first of the methods duplicate each other; suggest removing the first sentence of the methods. 2. In the methods section of the abstract, I suggest revising the description of the intervention - it starts with the outcome rather than a description of the intervention, which is a pharmacist consult and clinical service. Methods: 1. How many pharmacists will serve as interventionists? Will this be one person or multiple people? What level of training is required? Although the intervention is designed to follow an algorithm, this is still a clinical intervention, and the pragmatism of such could result in variable rates of success and tolerability. Some discussion to the attempts to standardize the approach would be helpful. 2. The authors could comment on likelihood of success, or difference in expected outcomes based on stage of disease or chronic illness. Are palliative care participants more likely to succeed in de-prescribing? Are less severely ill participants more likely to receive benefit in QOL? This is designed as a pilot study, but this stratification may be of interest for future studies. 3. The authors should clarify how the DBI scoring will be executed. Can the DBI accurately account for dose reductions, if discontinuation is not achieved? Similarly, if an as needed medication is used less frequently, will that be accounted for in the outcome measure? Such scenarios would be a success of the intervention, but if not accommodated for in the outcome measure may go unnoticed. 4. More detail in psychometric properties of the secondary outcomes would be worthwhile. For example, what domains of cognitive function are included? Similarly, how long will it take to complete the assessment? The adverse event scale is reported as 48 questions alone, this introduces the concern that a number of these data points may go missing, and as such appropriate statistical repair may be introduced. 5. In appendix 6, page 43 of the submitted pdf, advice is given to de-prescribing SSRI's. However, not all SSRI's are considered anticholinergic. It should be clarified if the targets for this trial include all psychotropics, or just those with anticholinergic or sedative properties. The intervention GP's may be confused by this as well, leading them to discontinue a greater number of antidepressants than the intervention may have intended. 6. The limitations section should address the lack of prevention

	approach after the de-prescribing intervention. For participants who may be using 1 DBI medication, it is plausible that a 2-4 week observation is sufficient, leaving 5 months without intervention until primary outcomes are assessed. It is plausible that other providers, hospitalists or specialists may prescribe a medication in that time. If no preventative component is included in this time period, new medication may complicate the efficacy of the intervention. 7. The clinical observation of ADWE's appears subjective. For example, staff is instructed to call the interventionist and GP if "increased agitation" is noticed. An objective measure would be preferred. Since this study is ongoing, it may be appropriate to list this in the limitations as a subjective assessment open to clinical interpretation rather than apply clinical criteria at this point in the study.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Reviewer Name: Sverre Bergh
Institution and Country: Center for old age psychiatry research, Innlandet Hospital trust, Ottestad, Norway

Thank you for the ability to review the manuscript. The manuscript describes the protocol for a study assessing the feasibility of using a peer-reviewed deprescribing guidelines to deprescribe anticholinergic and sedative medicines. The manuscript describes a pilot-study that eventually will lead to a RCT. Medication reviews and safe reducing or stopping medication with potential adverse effects or drug-drug interaction are important for patients with dementia, and I welcome the initiative and the study. The intervention is well described, and reasonable. The ethics are described in a good way, and the study is approved be the Human Disability and Ethics Committee of New Zealand.

I do have some comments to the authors about the method and the research questions, but as the study already have started recruiting I am not sure how appropriate they are.

1. Abstract:
a. Falls should be included in the text as one of the secondary outcomes. Funding is not stated in the abstract.

Falls as a secondary study outcome has been included in the text of the revised manuscript (Page 2; line 16). Funding details have been appended (Page 2; lines 24-26) in the revised manuscript.

2. In-/exclusion criteria:
a. Residents with severe dementia will be excluded from the study. Why? Persons with severe dementia have severe neurocognitive disorder, and they are sensitive to drugs. The advantage of reducing medication in this group of patients should be great.

We agree with the reviewer and the decision to include all eligible participants with enduring power of attorney provided by their relative/friend to take part in the study. This has been clarified in the revised manuscript. Page 4; line 15.

b. Exclusion criteria no. 4 should be omitted, as the criteria logically follows the inclusion criteria.

This has been deleted. Page 4; line 16

3. Recruitment procedure:
a. The authors describe that patients unable to provide informed consent should be included if the GP believes that a deprescribing could result in an improvement in QoL. Why? How is it possible to assess the feasibility of deprescribing in an objective manner if you will include participants that in advance are judged to have an advantage of deprescribing?
b. Following the same idea, p. 4 line 51-52: "The decision to enrol those patients….be the decision of the GP". So the GP should decide if the participants could be deprescribe the medication, and if yes, they should be recruited and the study should answer if the intervention reduce the DBI?
c. The same goes for reconsidering the consent after 3 months. Again, the GP should decide whether if not the participants should continue in the study if the EPOAs are not responding.

We understand the issues surrounding informed consent and appreciate the reviewer's comments. In the revised manuscript, we have clarified that participants will be enrolled in the study as per the inclusion and exclusion criteria outlined in the protocol only, and not based on perceptions of whether or not the intervention will improve their quality of life. The sentence has been amended appropriately (Page 4; line 28).

In regards to enrolment (Page 4; paragraph 4), due to ethical and legal considerations in New Zealand, enduring power of attorneys (EpoAs) are legally not able to 'consent' for their resident to take part in the study. The Health and Disability Ethics Committee (HDEC) of New Zealand have requested that we amend our application so that EpoAs can sign a 'declaration' form to state that they approve of their relative/friend to take part in the study. They also suggested that in the case of there being no response from EpoAs upon follow up; that the GP of the resident can enrol the resident in the study if he/she believes that it is in the best interest of the resident (i.e. they are prescribed many sedative/anticholinergic medicines that are thought to be harmful or un-necessary). This is to minimise the number of residents who could miss out on a potentially beneficial intervention; due to their EpoAs being difficult to reach.

During the study; we have found that most EpoAs have responded well to the request of enrolling their relatives/friends to the study. Therefore, we have not had a GP enrol any resident in the case of the EpoA not responding at the beginning of the study or at the three-month time point, when re-consideration of participant consent has occurred. However, we are bound to include this statement in our protocol as this is what has been recommended to us, by HDEC.

4. Data collection:
a. The data collection is described in detail, and is reasonable. Nevertheless, assessing adverse drug effects three months after deprescribing seems odd as the adverse effect may be present only a few weeks after deprescribing. The pharmacist will assess the participants twice a week the weeks after deprescribing. Could a standardized assessment tool like UKU-SERS been applied during these visits?

We agree with the reviewer that assessment of adverse effects that appear immediately after a deprescribing intervention is important. The principal investigator (NA) has been visiting participants who have had medicine(s) deprescribed twice a week to make sure they are not experiencing any adverse drug withdrawal effects (ADWEs) from stopping these medicines.

No specific objective measure has been used in the study to measure ADWEs. This has been added as a study limitation, as ADWEs have been monitored subjectively by the principal investigator and nurses (Page 9; study limitations, lines 4-5).

5. Outcomes:
a. On page 8, number of falls are described as a secondary outcome, which I find reasonable. Could this information be included in the tables as well?

We agree with the reviewer and included 'falls' as a secondary outcome in Table 3.

b. GDS is described as an assessment tool used for data collection, but is not one of the outcomes. Why not? I would also suggest that you assessed NPS at baseline and follow up, e.g. using the NPI, to assess how deprescribing medication interfere with the NPS.

We have taken the reviewer's suggestion on board and included GDS as a secondary outcome in the revised manuscript has been updated (Page 8; Secondary outcomes; bullet point 8).

We agree with the reviewer that inclusion of NPI is important. However, this is not feasible at this point as the study has already progressed to a substantial degree.

6. Power, sample size and analyses:
a. According to the power calculation 150 participants should be included, but the text on page 8 indicate that a smaller number of participants or a higher number may be necessary. I assume that you will include 150 participants but it is a bit unclear for me. Please clarify.

We thank the reviewer for pointing this out. The power sample size has been recalculated, and we in fact need 72 participants. We apologise for the confusion caused. This paragraph has been amended (Page 9; paragraph 1)

b. Table 3 states that the four primary and secondary outcomes should be analysed with t-test. What if the results are not-normally distributed? In the text you say that M-W-U test may be used, should this be written in the table as well?

The Wilcoxon Signed Rank statistical test will be used in the case of the data not being normally distributed. This has been updated in the revised manuscript (Page 9; statistical methods and analysis; line 3). This has also been updated accordingly in Table 3.

7. Limitations:
a. The limitation of the recruitment procedure is not fully discussed in the limitations section

This has now been included in this section (Page 9; study limitations).

8. Funding:
a. I can't see that the manuscript includes information about funding of the study, but I may be wrong?

Information regarding funding has been included at the end of the manuscript (Page 10; funding statement).

Minor comments:
1. P. 7, line 31-32: …as detailed in Table 1. – Should be table 2?

The error has been fixed (Page 7; line 25) in the revised manuscript.

2. P. 7, line 57: ….in the intervention group…. – As there is only one group of patients, the term

intervention group could be rephrased.

The sentence has been rephrased and the term ‘intervention group’ has been omitted (Page 8; paragraph ; lines 5-6) in the revised manuscript.

3. P. 8, line 1: DSMB should be written out fully

This has been written in full (Page 8; paragraph 1; line 8)

4. P. 8, line 8: …DBI tool at baseline 6 months’ post-intervention. – Unclear sentence, please rephrase

This has been rephrased and amended (Page 8; paragraph 2; lines 1-2)

5. P.8 line 52: A sample size of 150 participants…..– Unclear sentence, please rephrase

This phrase has been deleted (Page 9; paragraph 1).

6. P. 8, line 53-54: …., so smaller numbers may suffice…. – Unclear sentence, please rephrase

We thank the reviewer for his valuable comments. All of the above errors have been fixed in the revised manuscript.

Reviewer # 2

Reviewer Name: Noll Campbell
Institution and Country: Purdue University, United States
Please state any competing interests or state ‘None declared’: None declared

This study is of high importance given the questions that have yet to be answered regarding the safety and efficacy of de-prescribing interventions. The protocol is well written; however a few comments are offered to improve the clarity of the manuscript.

Abstract:
1. The last sentence of the introduction and first of the methods duplicate each other; suggest removing the first sentence of the methods.

The duplication has been deleted in the revised manuscript (abstract; methods)

2. In the methods section of the abstract, I suggest revising the description of the intervention - it starts with the outcome rather than a description of the intervention, which is a pharmacist consult and clinical service.

We agree with the reviewer and the ‘methods’ section has been re-written accordingly.

Methods:

1. How many pharmacists will serve as interventionists? Will this be one person or multiple people? What level of training is required? Although the intervention is designed to follow an algorithm, this is still a clinical intervention, and the pragmatism of such could result in variable rates of success and

tolerability. Some discussion to the attempts to standardize the approach would be helpful.

There will only be one interventionist, who is the primary investigator and a New Zealand registered pharmacist. The primary investigator has attended the required courses to be trained according to the standards of the Pharmaceutical Society of New Zealand to conduct a medication use review (MUR) or medication therapy assessments (MTAs). This position and training reflects closely the real situation in which such an intervention will be used, if outcomes are positive.

2. The authors could comment on likelihood of success, or difference in expected outcomes based on stage of disease or chronic illness. Are palliative care participants more likely to succeed in de-prescribing? Are less severely ill participants more likely to receive benefit in QOL? This is designed as a pilot study, but this stratification may be of interest for future studies.

We thank the reviewer for raising an interesting point for discussion. This has been addressed in the revised manuscript (Page 5; paragraph 2; lines 17-20).

3. The authors should clarify how the DBI scoring will be executed. Can the DBI accurately account for dose reductions, if discontinuation is not achieved? Similarly, if an as needed medication is used less frequently, will that be accounted for in the outcome measure? Such scenarios would be a success of the intervention, but if not accommodated for in the outcome measure may go unnoticed.

We thank the reviewer for their remark. The DBI can detect dose reductions as well as medicine(s) that have been discontinued, as the equation includes the total daily dose of both anticholinergic and sedative medicines. This has been clarified in the revised manuscript. Primary outcomes have also been changed to include a separate DBI score contributed by PRN medicines, where a PRN medicine has been defined as any medicine that has been used more than once in the past 3 months. A separate DBI PRN score, alongside a total DBI total score is being calculated for each participant at T0, T1 (3 months) and 6 months' post intervention. The necessity of calculating DBI at 3 months was realised to avoid making assumptions of what happened to the participant's DBI at that point of time (Page 8; paragraph 2; lines 1-2).

4. More detail in psychometric properties of the secondary outcomes would be worthwhile. For example, what domains of cognitive function are included? Similarly, how long will it take to complete the assessment? The adverse event scale is reported as 48 questions alone, this introduces the concern that a number of these data points may go missing, and as such appropriate statistical repair may be introduced.

More detail regarding the length of time completing secondary outcomes that require an interview with the participant have been included in the revised manuscript (Page 9, lines 1-3). Appendix 9 has been added to include the assessments used to assess the outcomes that are collected from the InterRAI LTCF national health database. Domains used to assess cognitive function include level of memory impairment, the ability of the resident to understand conversation and to be understood in conversation and level of wandering are used to assess cognitive function.

5. In appendix 6, page 43 of the submitted pdf, advice is given to de-prescribing SSRI's. However, not all SSRI's are considered anticholinergic. It should be clarified if the targets for this trial include all psychotropics, or just those with anticholinergic or sedative properties. The intervention GP's may be confused by this as well, leading them to discontinue a greater number of antidepressants than the intervention may have intended.

We agree with the reviewer that SSRIs have differential anticholinergic potencies for example, paroxetine is highly anticholinergic compared to other SSRIs. Psychotropics will be deprescribed as

per the Drug Burden List [1] and as per defined in the inclusion criteria of the study protocol (Page 4;

6. The limitations section should address the lack of prevention approach after the de-prescribing intervention. For participants who may be using 1 DBI medication, it is plausible that a 2-4-week observation is sufficient, leaving 5 months without intervention until primary outcomes are assessed. It is plausible that other providers, hospitalists or specialists may prescribe a medication in that time. If no preventative component is included in this time period, new medication may complicate the efficacy of the intervention.

We agree with the reviewer that the lack of a preventive component may contaminate the intervention. This has been added as a limitation (Page 9; study limitations; lines 7-9).

7. The clinical observation of ADWE's appears subjective. For example, staff is instructed to call the interventionist and GP if "increased agitation" is noticed. An objective measure would be preferred. Since this study is ongoing, it may be appropriate to list this in the limitations as a subjective assessment open to clinical interpretation rather than apply clinical criteria at this point in the study.

We thank the reviewer for pointing this out. This has been listed as a limitation. (Page 9; study limitations, lines 4-5)

References:

1. Hilmer SN, Mager DE, Simonsick EM, Cao Y, Ling SM, Windham BG, et al. A drug burden index to define the functional burden of medications in older people. Archives of internal medicine. 2007 Apr 23;167(8):781-7. PubMed PMID: 17452540. Epub 2007/04/25. eng.

VERSION 2 – REVIEW

REVIEWER	Sverre Bergh Research centre for old age psychiatry, Innlandet Hospital Trust. Norway.
REVIEW RETURNED	07-Feb-2017

GENERAL COMMENTS	Thank you for the resubmitted manuscript, where comments and suggestions from the reviewers have been addressed. There are still some limitations in the study, but you have explained the reason for these limitations in the letter to the reviewers, and the limitations have also been included in the text in the manuscript. As the inclusion of patients in the study is ongoing, alterations of the design and data collection of the study is not possible. I am looking forward to the presentation of the results in a later paper, and good luck with your study.

REVIEWER	Noll Campbell Purdue University, USA
REVIEW RETURNED	17-Feb-2017

GENERAL COMMENTS	Reviewers have adequately responded to my prior critique. This paper provides sufficient description and justification of the intervention.