ARTICLE DETAILS

TITLE (PROVISIONAL) | Decreasing the load? Is a multidisciplinary multistep medication review in older people an effective intervention to reduce a patient’s drug burden index? Protocol of a randomised controlled trial.

AUTHORS | Van der Meer, Helene; Wouters, Hans; Van Hulten, Rolf; Pras, Niesko; Taxis, Katja

VERSION 1 - REVIEW

REVIEWER | Lisa Kouladjian
1) Sydney Medical School - Northern, University of Sydney, NSW, Australia
2) Kolling Institute of Medical Research, Northern Sydney Local Health District, NSW Australia

REVIEW RETURNED | 10-Aug-2015

GENERAL COMMENTS | Summary of the paper
The paper entitled "Decreasing the load? – A tool for medication reviews in older community dwelling people (the DBI TMO study): protocol of a randomised controlled trial" outlines the protocol for a randomised controlled trial using a multidisciplinary multistep medication review intervention, together with the Drug Burden Index to reduce the exposure to anticholinergic and sedative medications in older community dwelling adults. The described study is timely and important with the expanding older population and an increasing need to overcome inappropriate prescribing.

General Comments
In general, the manuscript is well written with good grammar and flow. However, some aspects of the methodology need further clarification. Please find some specific comments below:
• It is hard to determine the primary objective of the study. In the abstract and the introduction, the authors have stated "evaluate whether a multidisciplinary multistep medication review is an effective intervention to reduce a patient's DBI". The title of the paper implies that the DBI will be the tool to "decrease the load" on older adults. Furthermore, the "Intervention" is described as the 3MR. It seems that the DBI is currently being used as a screening tool rather than the intervention itself. A suggestion would be to clearly state the objective of the study, and to update the title of the study. Is it the DBI, or the 3MR (or both together?) the intervention for this study?
• Further to this, the sample size calculation (Page 6 line 24) is also based on the “primary outcome”. If the primary outcome is to reduce exposure to anticholinergic and sedative medications measured by the DBI, after patients have had 3MR, was there a previous study the power calculation was based on? What is a “medium effect size”? It is noted (page 7 line 53) that “the primary outcome is the difference of patients having a decrease of DBI≥0.5 from baseline to
follow-up”. How was this determined? Is this clinically significant based on previous studies? A suggestion is to calculate sample sizes based on estimates from previous studies or pilot data, and also take into account participants who may decline to be involved with the study.

- Page 5, line 18-20. A question about ethics regarding a “postponed intervention” and delaying a service to high risk patients is raised. How long will the delay be? It is suggested to state the delay and whether patients in the control setting will be informed on the delay to the service. A suggestion is to confirm the process for patients in the control arm.

- Page 5, “Participants” section: The data which is presented here can be better summarised in a table. The numbers of participants (160) and pharmacies (15) have been stated, however how many pharmacists from the pharmacies be involved? Will there be one general practitioner to a pharmacist? Or one pharmacist and one GP to a patient? Please state how many participants are planned to be involved in their respective categories? Will you be planning to over-recruit to account for participant withdrawal? A suggestion would be to account for withdrawal considering the study will match patients (page 8, line 54).

- Page 5, line 56: How will the DBI be calculated? There is no mention in the methodology on how the DBI will be calculated, to allow for screening of patients. Will the DBI be reported as part of the 3MR? Will participants (GPs, Pharmacists and patients) be educated about the meaning of the DBI and its clinical importance? The DBI takes into account anticholinergic and sedative medications which some practitioners may overlook – e.g. inhalers, eye drops etc. It is suggested to specify how the DBI is calculated, and which medications will be incorporated into the DBI calculation.

- Page 9, line 22: “assuming that within these 3 months the maximum effect of possible medication changes made during the 3MR are reached” – What if the maximum effect is not reached, can the researchers explain the procedure if maximum effect isn’t reached, as sometimes clinical practice may not reflect ideal study scenarios.

- Page 8, line 9: Secondary parameters – Some of the tools used to measure the secondary parameters are dated e.g. UKU side effect rating scale (1987), Trailmaking test (1955) etc. and use of these scales may underestimate the secondary parameters measured, e.g. may not take into account newer medications which have anticholinergic effects used by patients. A suggestion would be to use newer published/validated measures.

Additional Specific Issues to address


- Page 4, Line 34 – Reference 18 is a meta-analysis of anticholinergic medications only. Considering the DBI also accounts for sedative medications, perhaps additional referencing to a review of the DBI and its association to clinical outcomes may strengthen the authors’ argument – Kouladjian L et al 2014 Clin Interv Aging 9:1503-1515

- Page 4, Line 46 – It could not be determined from the reference (due to language barriers) if the process of a medication review is conducted by a regular community pharmacist, or a pharmacist which has undergone additional training (similar to accredited pharmacists in Australia). A suggestion would be to specify the experiences of a pharmacist involved in the medication review process. Further to this (page 5 line 42), what does “experience with
medication reviews” entail? How will the investigators determine the experience of a pharmacist?

- Page 5, line 54: Suggest defining “Chronic Polypharmacy” or the definition of polypharmacy used in this study in the introduction.

REVIEWER
Catherine Floroff
Medical University of South Carolina
USA

REVIEW RETURNED 10-Aug-2015

GENERAL COMMENTS

Overall, this was a well-referenced protocol that will evaluate a novel Multidisciplinary Multistep Medication Review. Only a few scales or pharmacological indicator tools to apply to older adults in relation to medication management have been used in randomized controlled trials. This protocol will be a welcomed addition to published literature utilizing multidisciplinary intervention with different combinations (eg, educational material, computerized support systems, and medication reviews by other pharmacists).

There are some particular areas that could be revisited. As with other published drug burden scales, the DBI has several limitations which must be considered when developing this protocol. Therefore, it would be helpful to be as detailed as possible when explaining how the DBI tool is utilized throughout this protocol. Here are some additional considerations:

- Abstract: The first sentence in the methods section is incomplete.
- Methods and analysis:
  - Pharmacist inclusion criteria – experience with medication reviews: this seems rather broad. How much experience does each pharmacist need? Does each pharmacist have to have had specialty training to conduct medication reviews for the purposes of this protocol?
  - Intervention – step 2: how will the pharmacist prioritize problems and/or recommendations? Will there be a uniform process for prioritization with each medication profile review?
  - Study parameter – main study parameter: it would be helpful to explain the rationale for defining a decrease in DBI as ≥0.5 as the cutoff.
  - Quality of data: how will actual use of medication be verified with the patient? What will happen if the patient cannot provide a complete and accurate medication history?
- The DBI calculation should be included in the protocol as have been modified versions published in the literature.
- It would be useful to include references that the multidisciplinary team will refer to when identifying clinically significant medications with anticholinergic and sedative effects (eg, observational studies, Lexi-Comp, Physicians’ Desk Reference) since it is difficult to determine exactly what constitutes an anticholinergic or sedative medication.
A minimum daily dose of medications may be different in other countries. Would you be using the package insert for reference to minimum daily dosing or some other tertiary reference?

Will you only be including chronic medications or medications used on a PRN basis? Traditionally, the DBI calculation has only included chronic medications. However, sedatives and hypnotics are often used on a PRN basis by community dwelling older adults for chronic conditions (e.g., insomnia, anxiety).

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<th>REVIEWER</th>
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<td>University of Otago, New Zealand</td>
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| REVIEW RETURNED | 19-Aug-2015 |

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A drug burden index to define the functional burden of medications in older people.

3. under key words- change cholinergic antagonists to muscarinic antagonists
4. How will discontinuation syndromes or withdrawal effects associated with antidepressant and/or sedatives be reported and monitored?

**REVIEWER**
Prof Sarah Hilmer
Royal North Shore Hospital and University of Sydney
Australia
I conduct similar research.

**REVIEW RETURNED**
20-Aug-2015

**GENERAL COMMENTS**
While I think that the application of DBI to the pharmacy medication review setting is an important area to study, the lack of clarity about the aim, recruitment, randomisation, intervention and sample size, make it difficult to assess this trial protocol.

**Introduction:**
Please clarify aim. Is it to use DBI to identify high risk patients for 3MR or is it to use 3MR to reduce DBI or is it both? Please clarify the appropriateness of the comparison group with respect to the clarified aim.

**Methods:**
Please provide more detail on:
- recruitment and randomisation - how will patients be recruited on the basis of DBI without an accurate medication list that presumably needs to be acquired through the medication review (Step 1 of 3MR)? At what stage in the review process will patients be recruited and randomised?
- randomisation - please clarify in terms of sample size how many participants will be recruited per pharmacy (presumably 10-11)? Will matching into intervention/control pairs be performed after all participants recruited from each pharmacy involved? How much delay is this likely to result in? Only a small proportion of patients is likely to have DBI>1 (Castelino et al., Drugs and Aging, 27(2), 135-148 describes DBI in Australian Home Medicines Review, a comparable service).
- intervention - how will intervention focus on lowering anticholinergic and sedative medicines? Will DBI be calculated? How? Manually or using software? Have minimum registered doses and a list of anticholinergic and sedative medicines been generated from the Dutch national formulary? Will DBI be part of recommendations or discussed at the multidisciplinary meeting?
- sample size - is there any pilot feasibility or observational data to inform this? What is the 'medium effect size'? How has the effect of clustering been accounted for? Is randomisation at the level of the pharmacist? Has cross over of patients in intervention and control groups with the same GP been considered? Are additional participants recruited to allow for drop-outs?
Covariates:
- consider the importance of a measure of comorbidity as a predictor of both outcomes and medication use

Outcome data:
- Please clarify where this will be obtained and when baseline data will be obtained relative to the stages of the medication review process.

Novelty: this is very similar to the study protocol described in reference 34 (DIM-NHR Study).

Consort checklist: while full checklist is not applicable at the protocol stage, it would be helpful to provide more explicit detail on those elements that can be described.

Minor points:

Introduction - Increasing DBI has been consistently shown to be associated with impaired physical function but is not consistently associated with impaired cognitive function. Instead of reference 18, which reviews only anticholinergics, please consider Kouladjian et al Clin Interv Aging. 2014, a review of DBI.

Need specific references for DBI calculation.

**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1
Reviewer Name Lisa Kouladjian, 1,2.
Institution and Country 1) Sydney Medical School - Northern, University of Sydney, NSW, Australia
2) Kolling Institute of Medical Research, Northern Sydney Local Health District, NSW Australia
Please state any competing interests or state 'None declared': None Declared

Summary of the paper
The paper entitled “Decreasing the load? – A tool for medication reviews in older community dwelling people (the DBI TMO study): protocol of a randomised controlled trial” outlines the protocol for a randomised controlled trial using a multidisciplinary multistep medication review intervention, together with the Drug Burden Index to reduce the exposure to anticholinergic and sedative medications in older community dwelling adults. The described study is timely and important with the expanding older population and an increasing need to overcome inappropriate prescribing.

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In general, the manuscript is well written with good grammar and flow. However, some aspects of the methodology need further clarification. Please find some specific comments below:

- It is hard to determine the primary objective of the study. In the abstract and the introduction, the authors have stated “evaluate whether a multidisciplinary multistep medication review is an effective intervention to reduce a patient’s DBI”. The title of the paper implies that the DBI will be the tool to “decrease the load” on older adults. Furthermore, the “Intervention” is described as the 3MR. It seems that the DBI is currently being used as a screening tool rather than the intervention itself. A suggestion would be to clearly state the objective of the study, and to update the title of the study. Is it the DBI, or the 3MR (or both together?) the intervention for this study?

Authors: thanks for this suggestion, we have now changed the title to: “Decreasing the load? Is a multidisciplinary multistep medication review an effective intervention to reduce a patient’s drug...
burden index?" We have also amended the objective as: “The aim of our study is to evaluate whether a Multidisciplinary Multistep Medication Review (3MR) is an effective intervention to reduce a patient’s DBI.” So now the title and the objective of our study are in line.

• Further to this, the sample size calculation (Page 6 line 24) is also based on the “primary outcome”. If the primary outcome is to reduce exposure to anticholinergic and sedative medications measured by the DBI, after patients have had 3MR, was there a previous study the power calculation was based on? What is a “medium effect size”? It is noted (page 7 line 53) that “the primary outcome is the difference of patients having a decrease of DBI≥0.5 from baseline to follow-up”. How was this determined? Is this clinically significant based on previous studies? A suggestion is to calculate sample sizes based on estimates from previous studies or pilot data, and also take into account participants who may decline to be involved with the study.

Authors: Thanks for these suggestions. Our sample size calculation is based on standard procedures following a published formula (see reference by Cohen J. A power primer. Psychol Bull 1992; Jul;112(1):155-9.) We have added the following explanation under the heading “sample size calculation”: “To our knowledge, only one pilot randomized study has been done that was aimed at decreasing the DBI. We therefore cannot estimate an effect size ‘a priori’ as this should be based on multiple independent studies. Since a small effect size will probably be clinically irrelevant and a large effect size may be unrealistic, we chose a medium effect size. With the aim to include 160 patients and the expectation of a non-response rate of 60%, we will invite a total of 400 participants.” Under the heading “Main study parameter”, we have also added the following explanation about the clinical significance of the outcome measure: “The cessation of one anticholinergic or sedative medication would lower the DBI with about 0.5. We consider the cessation of one drug to be clinically relevant, and therefore defined the primary outcome as the difference in proportion of patients having a decrease of DBI ≥ 0.5 from baseline to follow-up between the intervention and control group.”

• Page 5, line 18-20. A question about ethics regarding a “postponed intervention” and delaying a service to high risk patients is raised. How long will the delay be? It is suggested to state the delay and whether patients in the control setting will be informed on the delay to the service. A suggestion is to confirm the process for patients in the control arm.

Authors: We have added information on the delay for control patients in the protocol under heading “intervention” as follows: “Participants in the control arm will receive their medication review after the follow-up measurement. All participants will be informed about the possible delay of their medication review as part of the informed consent procedure.”

• Page 5, “Participants” section: The data which is presented here can be better summarised in a table.

Authors: We have considered this suggestion, but we think that the information is clearly presented in the text using bullet points. Using a table which may not be placed directly under the heading participants may not improve readability and clarity of the paper. The numbers of participants (160) and pharmacies (15) have been stated, however how many pharmacists from the pharmacies be involved? Will there be one general practitioner to a pharmacist? Or one pharmacist and one GP to a patient? Please state how many participants are planned to be involved in their respective categories?

Authors: Thanks for this suggestion, we have now amended the section to include more information about the study setting including some explanations of the Dutch primary care practice and cooperations between general practitioners and community pharmacists as follows: We changed the heading participants to “participants and setting” and added: “We will approach a total of 400 patients to recruit about 160 participants. One pharmacist will conduct the medication
reviews in each pharmacy. As one community pharmacy is mostly associated with several medical practices the pharmacist will collaborate with different general practitioners (GP), but only one GP for each patient.”

Will you be planning to over-recruit to account for participant withdrawal? A suggestion would be to account for withdrawal considering the study will match patients (page 8, line 54).

Authors: We have amended the power calculation to include information about over recruiting to account for patient attrition: “With the aim to include 160 patients and the expectation of a non-response rate of 60%, we will invite a total of 400 patients.”

• Page 5, line 56: How will the DBI be calculated? There is no mention in the methodology on how the DBI will be calculated, to allow for screening of patients. Will the DBI be reported as part of the 3MR? Will participants (GPs, Pharmacists and patients) be educated about the meaning of the DBI and its clinical importance? The DBI takes into account anticholinergic and sedative medications which some practitioners may overlook – e.g. inhalers, eye drops etc. It is suggested to specify how the DBI is calculated, and which medications will be incorporated into the DBI calculation.

Authors: We have now included the formula we will use to calculate the DBI in the methods section under the heading “main study parameter”. We also added information about the calculation and medication inclusion: “All chronically used (≥ 3 months) medications (excluding dermatological- (ATC D) and sensory medication (ATC S)) having anticholinergic properties (including dry mouth, constipation and urine retention) or sedative properties based on standard Dutch reference sources will be included in the calculation. For each drug the value of the DBI will range from 0 to 1 depending on the δ. The cessation of one anticholinergic or sedative medication would lower the DBI with 0.5. We consider the cessation of one drug to be clinically relevant, and therefore defined the primary outcome as the difference in proportion of patients having a decrease of DBI ≥ 0.5 from baseline to follow-up between the intervention and control group.” Pharmacists and general practitioners will be informed about the DBI and its calculation as it will be used as a selection criterion for participants. There will be no additional training for the pharmacists/GPs, but see below for experience to carry out medication reviews.

• Page 9, line 22: “assuming that within these 3 months the maximum effect of possible medication changes made during the 3MR are reached” – What if the maximum effect is not reached, can the researchers explain the procedure if maximum effect isn’t reached, as sometimes clinical practice may not reflect ideal study scenarios.

Authors: Thanks for this suggestion. Our decision to determine the outcome of the intervention three months after the intervention has been based on the assumption that any considerable change in medication should have been initiated within this time period hence we can see this in a decrease of the DBI (primary outcome). If we take a much longer time, other changes including health status of the patient, hospital admissions will occur, hence making it more difficult to see a change in outcome measure related to the intervention. It may be a limitation of the study that some effects measures as secondary outcome measures may take longer than thee months.

• Page 8, line 9: Secondary parameters – Some of the tools used to measure the secondary parameters are dated e.g. UKU side effect rating scale (1987), Trailmaking test (1955) etc. and use of these scales may underestimate the secondary parameters measured, e.g. may not take into account newer medications which have anticholinergic effects used by patients. A suggestion would be to use newer published/validated measures.

Authors: The instruments we have selected to determine cognitive effects as secondary outcome measures are established, widely used and validated measures: Seven Minute Screen; the
Trailmaking Test A & B and the Digit Symbol Coding Test of the Wechsler Adult Intelligence Scale III. We have selected the UKU side effect rating scale in absence of a better, validated, feasible, easy-to-use measure to determine the burden with anticholinergic side effects of patients. None of these instruments include a list of anticholinergic medication, so these instruments are independent of the medication available at the time.

Additional Specific Issues to address

Authors: thanks we have updated the reference list.

• Page 4, Line 34 – Reference 18 is a meta-analysis of anticholinergic medications only. Considering the DBI also accounts for sedative medications, perhaps additional referencing to a review of the DBI and its association to clinical outcomes may strengthen the authors’ argument – Kouladjian L et al 2014 Clin Interv Aging 9:1503-1515

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• Page 4, Line 46 – It could not be determined from the reference (due to language barriers) if the process of a medication review is conducted by a regular community pharmacist, or a pharmacist which has undergone additional training (similar to accredited pharmacists in Australia). A suggestion would be to specify the experiences of a pharmacist involved in the medication review process. Further to this (page 5 line 42), what does “experience with medication reviews” entail? How will the investigators determine the experience of a pharmacist?

Author: The medication reviews will be carried out by accredited community pharmacists or community pharmacists in training to become accredited. To become an accredited community pharmacist in the Netherlands a 2-year training has to be undergone, a theoretical and practical training in performing medication reviews is part of it. We added this in the protocol under “participants and setting”. The pharmacists will not receive any additional training as part of the present study.

• Page 5, line 54: Suggest defining “Chronic Polypharmacy” or the definition of polypharmacy used in this study in the introduction.

Authors: We added “chronic” to the introduction. We use the definition of chronic polypharmacy as stated in the Dutch guideline for medication reviews. We have added this reference to the inclusion criteria.

Reviewer: 2
Overall, this was a well-referenced protocol that will evaluate a novel Multidisciplinary Multistep Medication Review. Only a few scales or pharmacological indicator tools to apply to older adults in relation to medication management have been used in randomized controlled trials. This protocol will be a welcomed addition to published literature utilizing multidisciplinary intervention with different combinations (eg, educational material, computerized support systems, and medication reviews by other pharmacists).

There are some particular areas that could be revisited. As with other published drug burden scales, the DBI has several limitations which must be considered when developing this protocol. Therefore, it would be helpful to be a detailed as possible when explaining how the DBI tool is utilized throughout
this protocol. Here are some additional considerations:

- **Abstract:** The first sentence in the methods section is incomplete.

**Author:** Thanks, we finished it.

- **Methods and analysis:**
  - **Pharmacist inclusion criteria** – experience with medication reviews: this seems rather broad. How much experience does each pharmacist need? Does each pharmacist have to have had specialty training to conduct medication reviews for the purposes of this protocol?

**Author:** The medication reviews will be carried out by accredited community pharmacists or community pharmacists in training to become accredited. To become an accredited community pharmacist in the Netherlands a 2-year training has to be undergone, a theoretical and practical training in performing medication reviews is part of it. We added this in the protocol under “participants and setting”. The pharmacists will not receive any additional training as part of the present study.

  - **Intervention** – step 2: how will the pharmacist prioritize problems and/or recommendations? Will there be a uniform process for prioritization with each medication profile review?

**Author:** The medication reviews will be performed following the Dutch guideline on medication reviews as outlined in the protocol (5 steps). This includes for example the Start&Stopp criteria to prioritize interventions. The prioritization for individual patients is up to the clinical decision making process between patient, pharmacist and GP. We will not give additional guidelines for this.

  - **Study parameter** – main study parameter: it would be helpful to explain the rationale for defining a decrease in DBI as ≥0.5 as the cutoff.

**Author:** We added the following explanation under “Main study parameter”: “For each drug the value of the DBI will range from 0 to 1 depending on the $\delta$. The cessation of one anticholinergic or sedative medication would lower the DBI with about 0.5. We consider the cessation of one drug to be clinically relevant, and therefore defined the primary outcome as the difference in proportion of patients having a decrease of DBI ≥ 0.5 from baseline to follow-up between the intervention and control group.”

  - **Quality of data:** how will actual use of medication be verified with the patient? What will happen if the patient cannot provide a complete and accurate medication history?

**Author:** We will use electronic pharmacy dispensing records to establish patient's medication use and double check these data by asking patient’s about actual medication use. We added this to the protocol under the heading “main study parameter”: “The DBI will be measured for all participants at baseline and follow-up using electronic pharmacy dispensing records corrected for actual medication intake based on a double check with the patient by telephone.”

  - **The DBI calculation should be included in the protocol as have been modified versions published in the literature.**

**Author:** thanks, we added the formula under the heading main study parameter .

  - It would be useful to include references that the multidisciplinary team will refer to when identifying clinically significant medications with anticholinergic and sedative effects (eg, observational studies, Lexi-Comp, Physicians’ Desk Reference) since it is difficult to determine exactly what constitutes an anticholinergic or sedative medication.
Author: We use a Dutch database in which anticholinergic and sedative medications are identified. We added the definition of anticholinergic and sedative medications to the protocol: “All chronically used (≥ 3 months) medications (excluding dermatological- (ATC D) and sensory medication (ATC S)) having anticholinergic properties (including dry mouth, constipation and urine retention) or sedative properties based on standard Dutch reference sources will be included in the calculation.”

- A minimum daily dose of medications may be different in other countries. Would you be using the package insert for reference to minimum daily dosing or some other tertiary reference?

Author: We have now specified this as follows under “main study parameter”: “δ: minimum recommended daily dose as stated in Dutch standard reference sources.”

- Will you only be including chronic medications or medications used on a PRN basis? Traditionally, the DBI calculation has only included chronic medications. However, sedatives and hypnotics are often used on a PRN basis by community dwelling older adults for chronic conditions (eg, insomnia, anxiety).

Author: Only medications used for 3 months or longer will be included in the DBI calculation. We added this to the protocol: “All chronically used (≥ 3 months) medications (excluding dermatological- (ATC D) and sensory medication (ATC S)) having anticholinergic properties (including dry mouth, constipation and urine retention) or sedative properties based on standard Dutch reference sources will be included in the calculation.”

Reviewer: 3
Reviewer Name Dr Prasad Nishtala
Institution and Country University of Otago, New Zealand
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
Page 2, line 21. Is a decrease of DBI by 0.5 units clinically significant?

Author: We added the formula and the following explanation: “For each drug the value of the DBI will range from 0 to 1 depending on the δ. The cessation of one anticholinergic or sedative medication would on average lower the DBI with 0.5. We consider the cessation of one drug to be clinically relevant, and therefore defined the primary outcome as the difference in proportion of patients having a decrease of DBI ≥ 0.5 from baseline to follow-up between the intervention and control group.”

Page 4, line 8- change dynamic to pharmacodynamic

Author: We have adapted it to pharmacodynamic.

Page 4, line 31, please ref the landmark study by Hilmer et al, DBI and cognitive and functional decline in older people.


Page 5, line 55, under inclusion criteria, combine polypharmacy & DBI≥1
Page 5, line 21, is there any data that the instruments listed to detect change in DBI are validated for detecting drug-induced cognitive impairment?

Authors: Thanks, the reviewer raises a very important point. The tests we have chosen are (as highlighted above), validated and established instruments to measure cognition. Other researchers have used those tests as well and found correlations between anticholinergic/sedative load and cognitive decline. See for example a recent review by Fox et al, Age Ageing. 2014;43(5):604-15. Effect of medications with anti-cholinergic properties on cognitive function, delirium, physical function and mortality: a systematic review. More work is needed in this area.

Page 5, line 22, is three month follow up enough to measure some of the secondary outcomes example, cognitive decline or improvement.

Authors: Thanks for this suggestion. Our decision to determine the outcome of the intervention three months after the intervention has been based on the assumption that any considerable change in medication should have been initiated within this time period hence we can see this in a decrease of the DBI (primary outcome). If we take a much longer time, other changes including health status of the patient, hospital admissions will occur, hence making it more difficult to see a change in outcome measure related to the intervention. It may be a limitation of the study that some effects measures as secondary outcome measures may take longer than three months.

Page 6, line 27, detect a medium effect size –please clarify and quantify

Authors: We have added the following explanation under the heading “sample size calculation”: “To our knowledge, only one pilot randomized study has been done that was aimed at decreasing the DBI. We therefore cannot estimate an effect size ’a priori’ as this should be based on multiple independent studies. Since a small effect size will probably be clinically irrelevant and a large effect size may be unrealistic, we chose a medium effect size. With the aim to include 160 patients and the expectation of a non-response rate of 60%, we will invite a total of 400 participants.”

Will prn and OTC anticholinergics/sedatives incorporated into computing DBI?

Authors: The following definition of inclusion is added to the protocol: “All chronically used (≥ 3 months) medications (excluding dermatological- (ATC D) and sensory medication (ATC S)) having anticholinergic properties (including dry mouth, constipation and urine retention) or sedative properties based on standard Dutch reference sources will be included in the calculation.” Using this definition, we will exclude prn medication, we will include OTC medication if prescribed by the doctor or if use is confirmed by the patient during telephone call.

Page 7, line 6, unsure what the START & STOPP criteria has to do with the intervention to reduce DBI. This is a bit confusing to me, though I understand a comprehensive medication review will involve optimisation of overall medicines. The aim of the intervention is to reduce DBI? Why digress from the main am?

Author: As stated in our protocol, the medication reviews will be based on current Dutch guidelines on medication reviews (which include the START/STOPP criteria) but with a focus on lowering the load with anticholinergic/sedative medication. For ethical reasons we could not ask the pharmacist to only focus on DBI medication and disregard other necessary optimisations of therapy.

Page 9, line 50, a multi-level modelling at pharmacy level and patient-level may be desired. I would
like the authors to reflect on this.

Author: As outlined in our protocol we will use generalized linear mixed models which allow a multi-level analysis so we will include clustering on patient and on pharmacy level. We will take into account cluster patients per pharmacy as there could be differences between pharmacies for example population group (living in the city or small town). We will also analyze cluster per patient as each patient might react different on the medication review, due to different comorbidities, number of medications, DBI value or attitude towards medication change. For example a patient with many medications, a high DBI and positive about changing his/her medication might have a greater decrease in DBI than a patient with a lower DBI who is not willing to stop any medications.

Other comments:
1. The authors should show how the DBI will be calculated. This is important as any modification to the original index will limit interpretation to clinical outcomes. Please see ref:
   Modifications to the drug burden index calculation may limit interpretation of its association with clinical outcomes in older adults.

   Please change ref 17 to this seminal study.


2. The authors should refer to the seminal study published in JAMA in their protocol. A drug burden index to define the functional burden of medications in older people.


   Author: Thanks, we adapted our references.

3. under key words- change cholinergic antagonists to muscarinic antagonists

   Authors: Thanks we have changed this.

4. How will discontinuation syndromes or withdrawal effects associated with antidepressant and/or sedatives be reported and monitored?

   Authors: Such effects should be detected using our secondary outcome measures on cognition, physical functions, side effects and quality of life.

Reviewer: 4
Reviewer Name Prof Sarah Hilmer
Institution and Country Royal North Shore Hospital and University of Sydney
Australia
Please state any competing interests or state 'None declared': I conduct similar research.
No competing interests.
Introduction:
Please clarify aim. Is it to use DBI to identify high risk patients for 3MR or is it to use 3MR to reduce DBI or is it both?

Authors: thanks for this suggestion, we have now changed the title to: “Decreasing the load? Is a multidisciplinary multistep medication review an effective intervention to reduce a patient’s drug burden index?” We have also amended the objective as: “The aim of our study is to evaluate whether a Multidisciplinary Multistep Medication Review (3MR) is an effective intervention to reduce a patient’s DBI.” So now the title and the objective of our study are in line.

Please clarify the appropriateness of the comparison group with respect to the clarified aim.

Authors: Thanks, the reviewer raises an important point. Control patients will also be patients with a high DBI who will receive a medication review directly after completion of the study, with a delay of 3 months. We could have chosen a comparison group which receive a medication review “usual care” without focus on DBI, however this would have required a much larger sample size due to the variation in usual care practice in carrying out medication reviews among pharmacists/GP practices. We believe it is ethically appropriate to have a delay in medication reviews for the control patients. This approach should give us a clear answer on our research questions. We have amended the protocol as outlined above and below, so we hope that aim and procedures are clear regarding this point.

Methods:
Please provide more detail on:
- recruitment and randomisation - how will patients be recruited on the basis of DBI without an accurate medication list that presumably needs to be acquired through the medication review (Step 1 of 3MR)? At what stage in the review process will patients be recruited and randomised?

Author: Thanks for this important suggestion, we have amended the section “Selection process, randomisation, intervention allocation and blinding” which reads now as follows:
“A preliminary list of potentially eligible patients will be obtained by electronic search in the electronic pharmacy dispensing records based on a limited set of inclusion criteria (age, chronic polypharmacy, use of psychotropic medication (ATC NO5/NO6)). Note by, patients in the Netherlands are registered with one pharmacy, so the pharmacies keep relatively accurate dispensing records of all prescribed medication. Inclusion/exclusion criteria will be checked by the researchers, pharmacists and GPs to obtain a list of eligible patients who will be approached for informed consent as outlined below. Within each pharmacy, all included patients will then be matched in pairs by gender, age, DBI and number of medications. Subsequently, within each pair, one participant will be randomly assigned to the intervention condition. Random allocation will be done by the principal investigator who is not involved in the data collection. The principal investigator will inform the pharmacists about the patients’ allocation. Pharmacists and patients cannot be kept blind. All researchers involved in data collection will be kept blind to the allocation. Therefore this is a single blinded study.”

- randomisation - please clarify in terms of sample size how many participants will be recruited per pharmacy (presumably 10-11)? Will matching into intervention/control pairs be performed after all participants recruited from each pharmacy involved? How much delay is this likely to result in? Only a small proportion of patients is likely to have DBI>=1 (Castelino et al., Drugs and Aging, 27(2), 135-148...
describes DBI in Australian Home Medicines Review, a comparable service).

Authors: We expect to recruit on average 10-11 per pharmacy, varying with the size/location of the pharmacy (e.g., we expect larger numbers in areas with a higher proportion of seniors or higher number of registered patients). As outlined above, we will complete the selection procedure for one pharmacy to obtain one complete list of eligible patients who have given consent to participate, so we can do the randomization procedure at the same time for all included patients. We assume that recruitment will take about 2 weeks per pharmacy. Patients will be informed about the study per letter and have the chance to reply if they like to participate. A week after the letters are sent all patients who did not answer will be contacted by phone, therefore we directly know who is willing to participate and who is not.

Pilot data suggest that per pharmacy at least about 30-40 patients have a DBI ≥ 1 within the age group of ≥65 years old and at least one psychotropic medication. We assume that this will fit our sample size calculation.

- intervention - how will intervention focus on lowering anticholinergic and sedative medicines? Will DBI be calculated? How? Manually or using software? Have minimum registered doses and a list of anticholinergic and sedative medicines been generated from the Dutch national formulary? Will DBI be part of recommendations or discussed at the multidisciplinary meeting?

Author: The DBI will be calculated for each patient as part of the preparation of the medication review. This will be done manually by pharmacy students who assist the pharmacists during some steps in the process (we have added this information under “intervention”). The pharmacist and general practitioners will be informed about the DBI and which medications contribute to the DBI value so they can use this information to optimize a patients medication. We have now established a database with medication commonly used chronically in the Dutch health care setting including information on minimum dose, and anticholinergic/sedative properties based on Dutch standard reference sources as outlined in the section “main study parameter”.

- sample size - is there any pilot feasibility or observational data to inform this? What is the ‘medium effect size’? How has the effect of clustering been accounted for? Is randomisation at the level of the pharmacist? Has cross over of patients in intervention and control groups with the same GP been considered? Are additional participants recruited to allow for drop-outs?

Authors: Thanks, our sample size calculation is based on standard procedures following a published formula (see reference by Cohen J. A power primer. Psychol Bull 1992; Jul;112(1):155-9. We have added the following explanation under the heading “sample size calculation”: “To our knowledge, only one pilot randomized study has been done that was aimed at decreasing the DBI. We therefore cannot estimate an effect size ‘a priori’ as this should be based on multiple independent studies. Since a small effect size will probably be clinically irrelevant and a large effect size may be unrealistic, we chose a medium effect size. With the aim to include 160 patients and the expectation of a non-response rate of 60%, we will invite a total of 400 participants.”

We will explore effects of clustering in our generalized linear mixed models. Randomization will be at the level of the patient. Therefore theoretically, there could be “cross contamination” as we have intervention as well as control patients in the same pharmacy/GP practice. However, we believe that the chances for cross-contamination are minimal. Pharmacists/GPs are not blinded and will agree to delay medication reviews in control patients. Any cross-contamination would have to take place during routine consultations of patients. We do not expect that within the short time frame of the study, that pharmacists/GP will change their practice in changing prescribing/counselling of the control patients based on the experience of undertaking the medication reviews with intervention patients.
Covariates:
- consider the importance of a measure of comorbidity as a predictor of both outcomes and medication use

Author: Thanks. Unfortunately it is outside the scope of our present study to collect additional data on all co-morbidities e.g., from GP records. However, we believe that our randomization procedure should ensure that we have comparable groups and hence co-morbidities should not matter. This would be much different in a cohort study.

Outcome data:
- Please clarify where this will be obtained and when baseline data will be obtained relative to the stages of the medication review process.

Author: As shown in the flow chart, baseline data will be obtained before the medication review as described above. Our aim is to collect baseline data as close as possible before the medication review.

Novelty: this is very similar to the study protocol described in reference 34 (DIM-NHR Study).

Authors: Some aspects of the present study are indeed similar to another study we are currently carrying out. The main similarity is the intervention which is also based on a 3MR. However, the patient groups/setting is different: nursing home patients vs community dwelling older patients as well as the selection criteria of focusing on patients with a high DBI vs all nursing home patients.

Consort checklist: while full checklist is not applicable at the protocol stage, it would be helpful to provide more explicit detail on those elements that can be described.

Author: We now provide the spirit checklist.

Minor points:

Introduction - Increasing DBI has been consistently shown to be associated with impaired physical function but is not consistently associated with impaired cognitive function. Instead of reference 18, which reviews only anticholinergics, please consider Kouladjian et al Clin Interv Aging. 2014, a review of DBI.

Author: We added this reference.

Need specific references for DBI calculation.


### VERSION 2 – REVIEW

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Lisa Kouladjian</th>
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<tbody>
<tr>
<td></td>
<td>University of Sydney, Australia</td>
</tr>
<tr>
<td>REVIEW RETURNED</td>
<td>22-Oct-2015</td>
</tr>
</tbody>
</table>

**GENERAL COMMENTS**

The authors have addressed the major issues after the first review. Below are minor points of clarification.
• Title: As the authors have stated this is a single-blinded study (page 9), can this be reflected in the title?
• Page 3, lines 41-49: This sentence does not read well. Please rephrase to read “...of medication related problems. [24] Annual Multidisciplinary Multistep Medication Reviews (3MR) are recommended...”
• Page 4, line 11: Add “single-blinded” to “randomized controlled trial”.
• Page 4, line 52 and page 6, line 5 & 6: The authors have altered the manuscript to describe the inclusion of pharmacists in “training” and/or “pharmacy students”. This needs further clarification: does a pharmacist in training mean a registered pharmacist who is training to be an accredited pharmacist who conducts 3MR, or is it a graduate pharmacist? Can you explain the reasoning to involve pharmacy students? Or, can you please clarify/keep consistent the terminology of “training” vs “pharmacy student”?
• Page 4, line 16: please add “(refer to ‘Selection process, randomisation, intervention allocation and blinding’)” after the sentence “Patients will be recruited from... intervention group”
• Page 6, line 3-11: This paragraph needs clarification. The authors have stated that the medication reviews will focus on lowering the load of anticholinergic/sedative medications. Will the control group receive a medication review without a focus on lowering the DBI load? Or will the control group receive a medication review following routine clinical practice (as described in the introduction)? “after the follow-up measurement” is also unclear. Please clarify the differences of what the control and intervention groups are receiving; in its current state, the manuscript reads as though both groups are receiving the same service (3MR with a focus on lowering the Ach/Sed load).
• Page 6, line 34: Is the use of the STOPP/START criteria part of the normal 3MR process or have the investigators added this? If so, are the research team aiming to collect this data to analyse? A suggestion in this paragraph may also be for the authors to detail how each pharmacist will focus on lowering the load of anticholinergic/sedative medications (as mentioned at the top of the page). Will it involve identification, recommendations to deprescribe or cease? Consider the algorithm used in “Reducing Inappropriate Polypharmacy: The Process of Deprescribing JAMA Intern Med. 2015;175(5):827-834”
• Page 8, Secondary parameters: The authors have not addressed a previous comment relating to the tools used to measure the secondary parameters. The scales currently stated to be used (UKU side effect rating scale etc.) were designed to measure specific medication classes. If the measures cannot be changed, consider justifying use of these methods. Recent studies clearly outline anticholinergic side effects which can be incorporated into the secondary parameters. “Drugs with anticholinergic effects and cognitive impairment, falls and all-cause mortality in older adults: A systematic review and meta-analysis British Journal of Clinical Pharmacology Volume 80, Issue 2, pages 209–220, August 2015”
• Page 8, line 56: How will the randomisation occur by the principle investigator to avoid bias?

REVIEWER
Catherine Floroff, PharmD, BCPS
Sentara Healthcare
600 Gresham Drive
Norfolk, VA 23510

REVIEW RETURNED
22-Oct-2015
**GENERAL COMMENTS**
Overall, the protocol was much more clear and able to repeated if needed.

**REVIEWER**
Prasad Nishtala
University of Otago, New Zealand

**REVIEW RETURNED**
19-Oct-2015

**GENERAL COMMENTS**
The reviewer completed the checklist but made no further comments.

**VERSION 2 – AUTHOR RESPONSE**

Reviewer: General Comments:
The authors have addressed the major issues after the first review. Below are minor points of clarification.

- **Title:** As the authors have stated this is a single-blinded study (page 9), can this be reflected in the title?
  
  **Author:** Thanks for this idea, we are willing to change the title, but if the editor agrees, we would like to keep it for two reasons. First, the current title is already very long. Second, we think that it is not very important to stress that this is a single blinded study in the title, as this type of study cannot be done double blind as far as we know.

- **Page 3, lines 41-49:** This sentence does not read well. Please rephrase to read “…of medication related problems. [24] Annual Multidisciplinary Multistep Medication Reviews (3MR) are recommended…”
  
  **Author:** Thank you, we have rephrased this sentence.

- **Page 4, line 11:** Add “single-blinded” to “randomized controlled trial”.
  
  **Author:** We added “single-blinded”.

- **Page 4, line 52 and page 6, line 5 & 6:** The authors have altered the manuscript to describe the inclusion of pharmacists in “training” and/or “pharmacy students”. This needs further clarification: does a pharmacist in training mean a registered pharmacist who is training to be an accredited pharmacist who conducts 3MR, or is it a graduate pharmacist? Can you explain the reasoning to involve pharmacy students? Or, can you please clarify/keep consistent the terminology of “training” vs “pharmacy student”?
  
  **Author:** Pharmacist in training means registered pharmacists in training to be accredited for the performance of medication reviews. We have clarified the meaning of “pharmacist in training” on page 4 (“accredited community pharmacist or registered pharmacist in training to be accredited”). To become an accredited community pharmacist in the Netherlands a 2-year training has to be undergone, a theoretical and practical training in performing medication reviews is part of it. So these pharmacists are allowed to perform the medication review.

  Pharmacy students will be involved to assist the pharmacist with the medication reviews as these reviews will cost much time. These students have completed their bachelor degree in pharmacy plus a 2 year master study of pharmacy and are in their final year of pharmacy study. They are allowed to assist in a medication review under supervision of a qualified pharmacist. The responsibility will remain with the pharmacist. We believe the role of the students are sufficiently described in the manuscript on page 5 as follows: “Pharmacy students will be assisting the community pharmacists during some steps of the reviews.”
• Page 4, line 16: please add “(refer to ‘Selection process, randomisation, intervention allocation and blinding’)” after the sentence “Patients will be recruited from… intervention group”
Author: We have added this.

• Page 6, line 3-11: This paragraph needs clarification. The authors have stated that the medication reviews will focus on lowering the load of anticholinergic/sedative medications. Will the control group receive a medication review without a focus on lowering the DBI load? Or will the control group receive a medication review following routine clinical practice (as described in the introduction)? “after the follow-up measurement” is also unclear. Please clarify the differences of what the control and intervention groups are receiving; in its current state, the manuscript reads as though both groups are receiving the same service (3MR with a focus on lowering the Ach/Sed load).
Author: The control group does not receive a medication review in the study period. We have explained this on page 4 under ‘methods and analysis’: ‘Participants in the control group will receive the 3MR after the study period (postponed intervention).’ We have changed the sentence on page 6 under ‘Intervention’ to read as follows: ‘Participants in the control arm will receive no medication review during the trial, they will receive a medication review after the follow-up measurement (postponed intervention).’
After completion of the trial, the control groups will receive the same medication review as the intervention group. The medication review will be based on current Dutch guidelines with a focus on lowering the anticholinergic/ sedative medication (page 6).

• Page 6, line 34: Is the use of the STOPP/START criteria part of the normal 3MR process or have the investigators added this? If so, are the research team aiming to collect this data to analyse?
Author: The STOPP/START criteria are part of the normal 3MR (based on the Dutch guideline on medication reviews). We will not collect additional data on the use of the criteria.

A suggestion in this paragraph may also be for the authors to detail how each pharmacist will focus on lowering the load of anticholinergic/sedative medications (as mentioned at the top of the page). Will it involve identification, recommendations to deprescribe or cease? Consider the algorithm used in “Reducing Inappropriate Polypharmacy: The Process of Deprescribing JAMA Intern Med. 2015;175(5):827-834”
Author: We will not use any additional tools/algorithms as part of the medication reviews as we have decided to do them according to the current Dutch guideline. The choice on how to decrease the load is left to the pharmacist and general practitioner in agreement with the patient.

• Page 8, Secondary parameters: The authors have not addressed a previous comment relating to the tools used to measure the secondary parameters. The scales currently stated to be used (UKU side effect rating scale etc.) were designed to measure specific medication classes. If the measures cannot be changed, consider justifying use of these methods. Recent studies clearly outline anticholinergic side effects which can be incorporated into the secondary parameters.
“Drugs with anticholinergic effects and cognitive impairment, falls and all-cause mortality in older adults: A systematic review and meta-analysis British Journal of Clinical Pharmacology Volume 80, Issue 2, pages 209–220, August 2015”
Author: We agree with the reviewer that the UKU side effect rating scale has been designed to measure anticholinergic side effects of antipsychotics. However, to our knowledge there is no other suitable instrument available to detect specific anticholinergic side effects which is superior to the UKU side effect rating scale. We have carefully read the review mentioned by the reviewer, but could not find any recommendation of more suitable instruments to detect anticholinergic side effects. The review focuses on measuring cognitive impairment, falls and all cause mortality. In our study next to
the UKU side effect rating scale, we will use two validated and widely used measures for cognitive impairment (the 7 minute and the trail making test) as well as widely used, accepted, validated measures on quality of life and physical mobility. All measures we used (with the exception of the UKU side effect rating scale) do not measure effects of a specific medication class. They are all well suited to detect negative effects of sedative/anticholinergics on cognition and physical mobility as well as quality of life if these occur. We believe we have therefore made a well suited choice of secondary outcome measures.

• Page 8, line 56: How will the randomisation occur by the principle investigator to avoid bias? 
Author: The randomization will be carried out by the principle investigator according to standard procedures as described in the protocol. We are not sure how we should describe/carry this out otherwise.
Decreasing the load? Is a Multidisciplinary Multistep Medication Review in older people an effective intervention to reduce a patient's Drug Burden Index? Protocol of a randomised controlled trial

Helene G van der Meer, Hans Wouters, Rolf van Hulten, Niesko Pras and Katja Taxis

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