

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Systematic review of systematic reviews of non-pharmacological interventions to treat behavioural disturbances in older patients with dementia. The SENATOR-OnTop series
AUTHORS	Abraha, Iosief; Rimland, Joseph; Trotta, Fabiana; Dell'Aquila, Giuseppina; Cruz-Jentoft, Alfonso; Petrovic, Mirko; Gudmundsson, Adalsteinn; Soiza, Roy; O'Mahony, Denis; Guaita, Antonio; Cherubini, Antonio

VERSION 1 - REVIEW

REVIEWER	Kate Laver Flinders University, Australia I am an author on a protocol registered with prospero to conduct a systematic review of systematic reviews for both pharmacological and non pharmacological interventions for the management of behavioural and psychological symptoms of dementia.
REVIEW RETURNED	21-Jun-2016

GENERAL COMMENTS	<p>This systematic review of systematic reviews summarises non-pharmacological interventions for the management of behavioural and psychological symptoms of dementia and draws together a vast amount of literature. The results are presented narratively and in tables. The authors should be commended for the amount of work involved and for addressing an important issue which is not well synthesised in the literature. Some comments for the authors:</p> <p>The first major concern is the brief explanation of how the authors managed systematic reviews. It appears that they have identified all systematic reviews for each intervention, classified these somehow (although this process is not well described) and then appraised and described each review. The authors then refer to primary studies. Presumably these are sourced from the systematic reviews but the process of identifying these studies is not clear. Including reviews that include the same studies gives them more weighting and prominence.</p> <p>The second major concern is that the paper is very long and while it draws together relevant literature it does not succinctly synthesise the information that it gathers. As the authors state, it is also more of a compendium than a published systematic review. It would be useful to use GRADE to rate the quality of evidence for each intervention approach.</p> <p>More minor points include:</p> <p>Including the 'SENATOR-OnTop series' in the title is unusual and would be better omitted</p> <p>Consistent terminology to describe the methodology should be used: ie a systematic review of systematic reviews</p> <p>There are a number of typos and grammatical errors throughout. For</p>
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	<p>example, in the abstract: CINAHL and PsycInfo are spelt incorrectly and cognitive stimulation is presented twice.</p> <p>There are sentences in the introduction that require references to support (eg after the first sentence and after stating that AD is responsible for 60% of dementia cases).</p> <p>The results section is further lengthened due to the explanation of the various intervention approaches within the text.</p> <p>The tables require proofreading as there are errors within them.</p>
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REVIEWER	Nicola Vanacore National Centre of Epidemiology, Surveillance and Promotion to health. National Institute of Health. Italy.
REVIEW RETURNED	24-Jul-2016

GENERAL COMMENTS	<p>This is an impressive systematic overview of non-pharmacological interventions to treat behavioral disturbances in older patients with dementia. The authors identify forty-one systematic reviews (SR) and 142 primary studies. AMSTAR (A Measurement Tool to Assess Reviews) instrument was used to assess the methodological quality of each SR. Moreover for many interventions a pooled analysis of results of each was calculated also if in the method section the statistical approach has not be reported (i.e. music therapy I2=58%, P=0.009].</p> <p>I have two suggestions for the authors.</p> <ol style="list-style-type: none"> 1. The paper include SR and primary studies. The methodological quality has been considered only for the SR. I believe that the authors should propose an umbrella review with aim to summarize the SR (see the reference reported below) and a systematic review to summarize the primary studies. The last studies should be assessed also for the methodological quality in according to different design of study (i.e. RCT or observational study). I think that only the methodological quality of evidence may be help to guide the social-health operators in the current clinical practice. The authors should verify that the SR identified in the paper not were included the primary studies. I suggest to report the quantitative data only for the studies with moderate-high methodological quality. 2. The term non-pharmacological intervention should be modified. I think that a lot of qualified and complex interventions may be not described simplicity as non-pharmacological. I think that can't describe this set of professionalism in negative compared to the drug. The authors report four group of interventions (Sensory Stimulation Interventions; Cognitive/Emotion-oriented Interventions, Behavior Management Techniques and other therapies). I suggest to use the term of "sensory-cognitive and behavior interventions" in substitution of non- pharmacological treatment. <p>In conclusion I hope that this relevant process to summarize the evidence should then to focus in the production of specific guidelines. At last, the authors should help readers orient themselves critically in this multitude of articles identified.</p> <p>Aromataris E1, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P. Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. <i>Int J Evid Based Healthc.</i> 2015 Sep;13(3):132-40.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Kate Laver

Institution and Country: Flinders University, Australia

Competing Interests: I am an author on a protocol registered with prospero to conduct a systematic review of systematic reviews for both pharmacological and non pharmacological interventions for the management of behavioural and psychological symptoms of dementia.

This systematic review of systematic reviews summarises non-pharmacological interventions for the management of behavioural and psychological symptoms of dementia and draws together a vast amount of literature. The results are presented narratively and in tables. The authors should be commended for the amount of work involved and for addressing an important issue which is not well synthesised in the literature. Some comments for the authors:

The first major concern is the brief explanation of how the authors managed systematic reviews. It appears that they have identified all systematic reviews for each intervention, classified these somehow (although this process is not well described) and then appraised and described each review. The authors then refer to primary studies. Presumably these are sourced from the systematic reviews but the process of identifying these studies is not clear. Including reviews that include the same studies gives them more weighting and prominence.

*We thank the reviewer for pointing out this important detail. We have now provided greater details regarding the process to identify the primary studies. The following additions have been made to the manuscript:

Methods: *Briefly, to obtain the evidence regarding the non-pharmacological interventions, we first identified published SRs using a systematic search across several databases. After processing eligible SRs, we identified and obtained primary studies from these SRs to generate the compendium of non-pharmacological interventions, to assess the body of evidence and finally to provide recommendations according to the GRADE approach.³⁸

Inclusion Criteria for Primary Studies

From the included SRs, we obtained any experimental comparative study, either randomised or nonrandomised, that investigated any non-pharmacological intervention to treat BPSD in older patients. Observational studies or before-after studies with historical controls, were excluded.

Results: **From these SRs, we obtained 142 primary studies from which we abstracted details of the non-pharmacological interventions.

Discussion: ***With the present study, using the primary studies included in the SRs, we have created a compendium of the types of non-pharmacological interventions, including the component of each single intervention, the dosage (when available), and the duration of the treatment.

The second major concern is that the paper is very long and while it draws together relevant literature it does not succinctly synthesise the information that it gathers. As the authors state, it is also more of a compendium than a published systematic review. It would be useful to use GRADE to rate the quality of evidence for each intervention approach.

*We thank the reviewer for this consideration. We tried to synthesise the content of the reviews, but the aim of this systematic review of systematic reviews is to provide a comprehensive perspective of findings to clinicians and other healthcare workers. Synthesizing too concisely would have led to a loss of information we feel is important to our target audience.

As for the GRADE approach, it is part of our initial intention to use this approach to rate the evidence and provide recommendations as stated in the protocol. This issue has already been addressed and we are preparing a manuscript.

In the present paper we have added the following paragraph:

Risk of bias assessment and grading the quality of evidence

We used the Cochrane Collaboration method to evaluate the risk of bias. The domain considered were random sequence generation, allocation concealment⁴⁰, blinding of participants, personnel, or outcome assessor⁴⁰, incomplete outcome data⁴¹, selective reporting⁴² and other potential biases (e.g., balance in baseline characteristics). The overall quality of evidence was assessed using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) methodology that takes into account the risk of bias, consistency of results across the studies, precision of the results, directness, and likelihood of publication bias⁴³. Results regarding the risk of bias assessment and grading the quality of evidence will be provided in a companion paper.

More minor points include:

Including the 'SENATOR-OnTop series' in the title is unusual and would be better omitted

Consistent terminology to describe the methodology should be used: ie a systematic review of systematic reviews

*We agree to include in the title, the specification, "systematic review of systematic reviews". We have decided, however, to retain the 'SENATOR-OnTop series' as it identifies all our publications.

There are a number of typos and grammatical errors throughout. For example, in the abstract: CINAHL and PsycInfo are spelt incorrectly and cognitive stimulation is presented twice.

There are sentences in the introduction that require references to support (eg after the first sentence and after stating that AD is responsible for 60% of dementia cases).

The results section is further lengthened due to the explanation of the various intervention approaches within the text.

The tables require proofreading as there are errors within them.

*Thank you for drawing your attention to these issues. A native English speaker has now proofread and edited the manuscript in order to eliminate the typographical errors.

Reviewer: 2

Reviewer Name: Nicola Vanacore

Institution and Country: National Centre of Epidemiology, Surveillance and Promotion to health.

National Institute of Health. Italy.

Competing Interests: None declared

This is an impressive systematic overview of non-pharmacological interventions to treat behavioral disturbances in older patients with dementia. The authors identify forty-one systematic reviews (SR) and 142 primary studies. AMSTAR (A Measurement Tool to Assess Reviews) instrument was used to assess the methodological quality of each SR. Moreover for many interventions a pooled analysis of results of each was calculated also if in the method section the statistical approach has not been reported (i.e. music therapy I²=58%, P=0.009).

* We thank Dr. Nicola Vanacore for his positive comments. As for the statistical approach, we have described it in the protocol. However, we added the following sentence, for clarity, in the methods section: "As outlined in our protocol, we extracted data from primary studies to perform meta-analyses and heterogeneity was addressed using the Cochrane Collaboration approach".

I have two suggestions for the authors.

1. The paper include SR and primary studies. The methodological quality has been considered only for the SR. I believe that the authors should propose an umbrella review with aim to summarize the SR (see the reference reported below) and a systematic review to summarize the primary studies. The last studies should be assessed also for the methodological quality in according to different design of study (i.e. RCT or observational study). I think that only the methodological quality of

evidence may be help to guide the social-health operators in the current clinical practice. The authors should verify that the SR identified in the paper not were included the primary studies. I suggest to report the quantitative data only for the studies with moderate-high methodological quality.

*We thank Dr. Nicola Vanacore for his proposal. Dr. Vanacore is proposing to perform two types of approaches: one, an umbrella review, for the SRs and a second, a traditional systematic review, to summarise the results of the primary studies. We think that the basic approach of the proposed method described in the paper by Aromataris has been adopted in the method employed in our paper. However, as outlined in our protocol (Abraha BMJ Open 5:e007488) our aim was complex for different reasons: (a) there is no clear taxonomy for non-pharmacological interventions, therefore we were obliged to perform a broad search of SRs; (b) despite using the AMSTAR to assess the quality of the reviews, we were much more focused on the evidence, which was necessarily based on the quality of the primary studies; (c) our final objective was to provide recommendations based on the best available method (we used GRADE ,which is now adopted worldwide) to evaluate the evidence. Since this research covers a very extensive topic, we thought of dividing the evidence into two manuscripts, the second of which will consider the quality of the evidence and recommendations according to the GRADE methodology.

2. The term non-pharmacological intervention should be modified. I think that a lot of qualified and complex interventions may be not described simplicity as non-pharmacological. I think that can't describe this set of professionalism in negative compared to the drug. The authors report four group of interventions (Sensory Stimulation Interventions; Cognitive/Emotion-oriented Interventions, Behavior Management Techniques and other therapies). I suggest to use the term of “sensory-cognitive and behavior interventions” in substitution of non- pharmacological treatment.

* Although we understand the concern of the reviewer, we respectfully disagree that the term non-pharmacological is not appropriate to describe the interventions. First of all, the term non-pharmacological intervention is the core of the WP2 (ONTOP) of the SENATOR project which is funded by the European Union. Then, we wanted to underline that drugs are not the only choice for BPSD in patients with dementia, but many other interventions, which are difficult to describe without quite a long sentence, have been used. We therefore propose to keep the term.

In conclusion I hope that this relevant process to summarize the evidence should then to focus in the production of specific guidelines. At last, the authors should help readers orient themselves critically in this multitude of articles identified.

* We agree with Dr. Vanacore's statement. The upcoming manuscript will deal with the summary of the evidence, as well as the recommendations regarding the non-pharmacological interventions.

VERSION 2 – REVIEW

REVIEWER	Nicola Vanacore National Institute of Health, Italy
REVIEW RETURNED	18-Sep-2016

GENERAL COMMENTS	I thank the authors for the clarifications which have provided
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Corrections: Systematic review of systematic reviews of non-pharmacological interventions to treat behavioural disturbances in older patients with dementia. The SENATOR-OnTop series

Abraha I, Rimland JM, Trotta FM, *et al.* Systematic review of systematic reviews of non-pharmacological interventions to treat behavioural disturbances in older patients with dementia. The SENATOR-OnTop series. *BMJ Open* 2017;**7**:e012759. doi: 10.1136/bmjopen-2016-012759

The authors would like to thank dr. Reisberg and colleagues for their appreciation and for their valuable comments our manuscript. Reisberg and colleagues correctly noticed the discrepancy in presentation of the categorization of the non-pharmacological intervention between the main text and the abstract. The authors would like to underline that the categorization of the interventions in the main text is the correct one and therefore the results in the abstract should be modified as follows:

38 SRs and 129 primary studies were identified, comprising the following categories of non-pharmacological interventions: (1) sensory stimulation interventions (25 SRs, 66 primary studies) that encompassed: shiatsu and acupuncture, aromatherapy, massage/touch therapy, light therapy, sensory garden and horticultural activities, music/dance therapy, dance therapy, snoezelen multisensory stimulation therapy, transcutaneous electrical nerve stimulation; (2) cognitive/emotion-oriented interventions (13 SRs; 26 primary studies) that included cognitive stimulation, reminiscence therapy, validation therapy, simulated presence therapy; (3) behaviour management techniques (6 SRs; 22 primary studies); (4) Multicomponent interventions (3 SR; four primary studies); (5) other therapies (5 SRs, 15 primary studies) comprising exercise therapy, animal-assisted therapy, special care unit and dining room environment-based interventions.

Please note that the numbers provided are absolute numbers and the following reviews can fall in different categories as they considered different types of non-pharmacological interventions and thus explain any discrepancy in numbers: Seitz 2012¹ that considered aromatherapy, light therapy, music/dance therapy, snoezelen therapy, and reminiscence therapy; O'Neil 2011² that considered snoezelen, behavioural management techniques; Chaudhury 2013³ that considered light therapy and the role of physical environment in supporting person-centred dining in LTC; and Whear 2014⁴ that examined the effect of improved lighting and table-setting contrast in a dining room environment. In addition, two primary studies fell in two different categories: Proctor 1999⁵ was in reviews that dealt with behavioural management techniques (BMT) and one review that, within the multicomponent interventions, examined the combined effect of BMT with educational intervention; and Teri 2003⁶ was considered in the BMT reviews and the exercise-based reviews.

In addition, the authors want to point out the following minor corrections in the main text: page 17 under the paragraph on Behavioural management techniques it should read 'One review of reviews and five SRs' instead of 'One overview of reviews and four SRs'.

page 21, the authors missed describing the seventh study with repeated measures design: "In the a small repeated measures study Mossello *et al.* evaluated the effect of animal assisted therapy in ten patients attending an Alzheimer Day Care Centre. The design consisted in 2 weeks' pre-intervention, 3 weeks' control activity with plush dogs, and 3 weeks' animal assisted therapy. NPI was used to assess BPSD and CMAI to assess mood; both outcomes remained unchanged across the study. Anxiety measured with NPI decreased during animal assisted therapy ($p=0.04$)⁷."

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