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Comparative safety and effectiveness of cognitive enhancers for Alzheimer's dementia: protocol for a systematic review and individual patient data network meta-analysis

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Abstract

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Introduction: Alzheimer's dementia (AD) is the most common cause of dementia, and several organizations, such as the National Institute for health and Care Excellence, suggest that management of patients with AD should be tailored to their needs. To date, little research has been conducted on the treatment effect in different subgroups of AD patients. The aim of this study is to examine the comparative effectiveness and safety of cognitive enhancers for different patient characteristics.

Methods and analysis: We will update our previous literature search from January 2015 forward, using the same terms and electronic databases (e.g., MEDLINE) from our previous review. We will additionally search grey literature and scan the reference lists of the included studies. Randomized clinical trials (RCTs) of any duration conducted at any time comparing cognitive enhancers alone or in any combination against other cognitive enhancers, or placebo in adults with AD will be eligible. The outcomes of interest are cognition according to the Mini-mental State Examination, and overall serious adverse events. For each outcome and treatment comparison, we will perform a Bayesian hierarchical random-effects meta-analysis combining the individual patient data (IPD) from each eligible study. If the identified treatment comparisons form a connected network diagram, we will perform an IPD network meta-analysis (NMA) to estimate subgroup effects for patients with different characteristics, such as AD severity and sex. We will combine aggregated data from studies that we will not be able to obtain IPD, with the IPD provided by the original authors, in a single model. We will use the PRISMA-IPD and PRISMA-NMA statements to report our findings.

Ethics and dissemination: The findings of this study will be of interest to stakeholders, including decision makers, guideline developers, clinicians, methodologists and patients and they will help to improve guidelines for the management of patients with AD.

PROSPERO registry number: CRD42015023507

Strengths and limitations

- This study will be the first network meta-analysis using individual patient data (IPD-NMA) evaluating the comparative effectiveness and safety of cognitive enhancers for different patient characteristics, such as AD severity and sex.
- The outputs of this study will provide clinicians, patients and caregivers with tailored evidence to inform their decision making, improving the quality of life of patients living with Alzheimer's dementia.
- Although our IPD-NMA can be informed by observational studies providing data on adverse drug events, we will restrict to randomized clinical trials as this study design is the gold standard for a clinical trial and there are numerous clinical trials available on this topic.
- A potential difficulty in the conduct of our study is that IPD can only be obtained by contacting the original trial authors. To overcome this difficulty and improve the response rate, we will use validated approaches suggested for electronic surveys and provide a cash incentive to each author.

Keywords: network meta-analysis; multiple treatments meta-analysis; individual participant data; Nootropic Agents; Alzheimer Disease; humans

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Introduction

Alzheimer's dementia (AD) is the most common cause of dementia, and has an insidious onset with progressive deterioration in cognition (e.g., memory, thinking, and perception), function, behavior, and mood. To date, 46.8 million people worldwide live with dementia. This number will almost double every 20 years, and it is estimated to reach 131.5 million by 2050 [1]. As dementia progresses, it impacts quality of life for the individual and causes a substantial burden on the family, caregivers, healthcare system, and society. AD ultimately leads to death with a median survival from diagnosis of only 7 years [2]. Pharmacological treatment consists of cognitive enhancers, including the cholinesterase inhibitors (donepezil, galantamine and rivastigmine), and memantine, a N-Methyl-D-aspartic acid receptor antagonist [3]. It is currently unclear as to whether galantamine, rivastigmine, or donepezil should be used by patients with severe AD, and whether memantine is the most optimal treatment for severe AD, which is the patient population in most need of medication [4].

To determine the relative effectiveness of cognitive enhancers for patients with different patient characteristics (e.g., mild-moderate AD versus severe AD, females versus males), we aim to conduct a systematic review and individual patient data (IPD) network meta-analysis (NMA). NMA allows the simultaneous analysis of randomized clinical trials (RCTs) involving multiple treatments for the same clinical topic and can provide estimated treatment effects even for treatments that have never been directly compared in a head-to-head study. A key assumption in NMA is the transitivity assumption, which requires the balance of the distribution of potential effect modifiers across the treatments comparisons [5-7]. In AD, patients may respond differently to the medication based on severity of AD and sex, and hence severity and sex could be considered treatment effect modifiers. The optimal approach to assess the transitivity assumption is to compare the patient-level characteristics using IPD across treatment comparisons. Under the transitivity assumption, an IPD-NMA may tailor results to the patient characteristics. Tailoring the management of patients with AD is an issue that has been also brought up by several organizations [8], including the Alzheimer's Society of Ontario [9] and the National Institute for health and Care Excellence (NICE) [3]. Also, the Alzheimer's Disease International (ADI) federation in their world Alzheimer report 2015 mention that there has been dramatically little research into the treatment effect across people of different age and sex [1].

The use of aggregated data reported in RCTs does not always allow us to reach a definitive conclusion on which medication is the safest or most effective for patients with different severities of AD and for females/males. This is because the covariates of interest (e.g., sex, severity of disease) are inconsistently reported in RCTs and a relationship at the aggregated study level is not necessarily true at the individual patient level. Indeed, we previously attempted a systematic review and NMA of aggregated data and we were unable to provide definitive conclusions regarding the influence of patient characteristics on the results [10, 11]. The use of IPD will help in the understanding of the relationship between treatment effects at the patient-level, allowing healthcare providers to individualize the management of patients with AD.

The aim of this study is to examine the comparative effectiveness and safety of cognitive enhancers versus placebo or best supportive care by patient characteristics, such as AD severity and sex. We will use IPD-NMA to identify potential treatment effect modifiers, and estimate the most effective and safest treatments for patients with different characteristics. We will combine aggregated data from studies that we are not able to obtain IPD, with the IPD obtained from authors who provide these data. Recent simulations have shown that adding IPD to AD studies in a NMA can significantly improve precision, reduce bias, and increase information compared to NMA relying on aggregated data alone [12].

Methods and analysis

This systematic review and IPD-NMA protocol was prepared according to the preferred reporting items for systematic reviews and meta-analyses protocols (PRISMA-P) guidelines [13], and was registered with the international prospective register of systematic reviews (PROSPERO) (Registration #CRD42015023507).

Eligibility criteria

The research question and protocol are based on our previous systematic review and NMA [11]. Therefore, we will update our previous systematic review [11], and we will use similar population, interventions, comparators, study designs and time period (PICOST) criteria. Eligible studies are RCTs including adults with AD administered a cognitive enhancer compared with each other, best supportive care, or placebo. The specific PICOST criteria are:

Population: Adults (aged ≥18 years) with AD diagnosed using various criteria (e.g., Diagnostic and Statistical Manual of Mental Disorders, Nursing Minimum Data Set criteria) of any duration with either moderate AD, i.e., Mini-mental State Examination (MMSE) of 10-20 or severe AD i.e., MMSE <10 [14]. These criteria have changed over time and we will record how the authors define AD severity for each study.

Interventions: Cognitive enhancers (donepezil, rivastigmine, galantamine, and memantine) alone or in any combination.

Comparators: Cognitive enhancers, best supportive care alone or in any in any combination, and placebo.

Outcomes: The primary outcome of interest is cognition according to the MMSE (efficacy outcome, continuous variable), and the secondary outcome is overall serious adverse events (SAE; safety outcome, dichotomous variable); both outcomes were reported by many of the included trials previously and for which NMA was possible.

Study design: We will restrict to RCTs, as this is the gold standard for examining interventions. We will exclude quasi-RCTs, i.e., quasi-random methods used to allocate patients to groups, such as consecutive allocation.

Time: Studies of any duration conducted at any time.

Other: Unpublished and published studies written in any language will be included.

Search and study selection

We will update our literature search (January 2015 onward) using terms from our previous review [11] in MEDLINE, the Cochrane Central Register of Controlled Trials, Embase. We will search reference lists of included studies and relevant reviews. Grey literature (i.e., difficult to locate and unpublished studies) will be searched via trial registry websites and conference abstracts. We will use the Synthesi.SR tool [15] to screen citations and full-text articles. To ensure reliability, a training exercise will be conducted using our eligibility criteria on a random sample of 50 titles and abstracts from the literature search results. When the team reaches a high agreement (>90%), two team members will screen each title and abstract for inclusion, independently (level 1 screening). After pilot-testing full-text screening criteria, pairs of reviewers will independently review the full-text of potentially relevant articles (level 2 screening). Conflicts will be resolved by discussion. We will provide the number of pilot-tests required at levels 1 and 2 of the screening process, the overall percent agreement, as well reasons for study exclusion at both levels. We will use the PRISMA flow diagram to report the study selection [16].

Data abstraction

The data we plan to abstract include study characteristics (e.g. year of publication), aggregated patient characteristics (e.g. number of patients), outcome results (e.g. MMSE, SAE), and source of funding (categorized as: funded/authored by an employee of a drug manufacturer or other commercial organization, government-sponsored/non-profit organizations, including universities and hospitals, no funding, funding unclearly reported, and funding not reported) [17]. We will also abstract the corresponding authors' mails and email addresses, as well their phone number. Two reviewers will abstract data independently, and all conflicts will be resolved through discussion.

The corresponding authors' contact information will be abstracted from the papers. For missing information, we will search authors' online research profiles (e.g., Google Scholar) or PubMed. We will use recommended approaches for electronic surveys to improve response rates [18]. Specifically, we will 1) send an email to the corresponding authors explaining the study purpose and requesting their data, enclosing a signed letter on letterhead, 2) send reminder emails at 2, 6, 10, and 14 week intervals after the initial email; 3) send a reminder by post in addition to email the 7th week, and 4) contact the corresponding author by phone during the 15th week. A financial incentive will be also offered to the corresponding author in the form of a $100 Amazon gift certificate. We will inform all authors that their article will be appropriately cited and, if they agree, they will be acknowledged in our paper.

We will ask authors to provide IPD on: 1) patients, including age, sex, severity of Alzheimer's disease (e.g. baseline MMSE level), presence of behavioral disturbance, comorbid conditions (e.g., stroke), other medications used for each patient, drop-outs along with reasons for drop-out, and number of participants, 2) medication, including treatment patient was allocated, dosage, 3) outcomes, including event and date of event and time taken to achieve the event for SAEs, and MMSE values and measurement dates, and 4) date and method of randomization. All IPD will be saved on a secure server, adhering to personal health information protection act (PHIPA) [19].

Risk of bias appraisal

As with the original review, we will appraise the risk of bias using the Cochrane Risk of Bias tool [20]. Two reviewers will independently assess the risk of bias in each included study after pilot-testing on a random sample of 5 RCTs. Disagreements will be resolved by discussion. To ensure data consistency, as recommended by the PRISMA-IPD guidelines [21], we will 1) compare IPD provided by the investigator with aggregate data reported in the publication; 2) assess whether the eligibility criteria of each study are in agreement with the IPD, 3) check date consistency, e.g. date patient randomized versus date trial opened. We will also check whether the randomization of patients is adequate (i.e., intervention and comparison groups are balanced for important patient characteristics), by comparing numbers and types of patients in each arm. We will ask the author for clarifications, if inconsistencies are identified. Our IPD analysis will be based on the intention-to-treat principle including all previously excluded patients.

We will draw a comparison-adjusted funnel plot [22] for both the MMSE and SAE. This plot allows the examination of heterogeneity and different types of bias, such as selective reporting, publication, and funding biases. After ordering the treatments included in the network chronologically regarding their year of availability on the market, we will plot the difference between each observed effect and overall treatment effect against the standard error of the observed effect. The comparison-adjusted funnel plot will be used only when RCTs with two treatment arms are included in the analysis, as this method does not account for correlations induced by multi-arm trials and potential asymmetry in the plot can be masked. Whenever an eligible study includes multiple arms we will construct funnel plots for each treatment comparison and outcome separately. Funnel plots for each treatment comparison will be plotted only when at least 10 RCTs are available. Reasons for funnel plot asymmetry will be explored.

Synthesis

The characteristics of the included studies, patients, and treatments, as well as risk of bias of studies will be described irrespective of whether IPD is obtained. We will present summary statistics and potential outlier patient values to describe the outcome data in each study.

We will perform a Bayesian hierarchical random-effects meta-analysis for each treatment comparison, as we anticipate clinical and methodological between-study heterogeneity. All IPD from included studies will be combined into a single model using a multilevel model where each study is a different cluster. We will use the odds ratio for SAE [23] and the mean difference effect size for MMSE [24]. In case we are able to obtain IPD for a subset of trials, then we will use a two-part model with the same between-study variance in both parts and accounting for treatment-by-covariate interactions (including for example co-morbidities such as arrhythmias in the model [25]). The first part will entail a one-stage model using IPD only, whereas the second part will entail applying a pairwise meta-analysis modeling aggregate data [25].

If the treatment comparisons that inform the eligible RCTs form a connected network of trials (see e.g., Figure 1), the random-effects NMA model will be used. If possible, we will

combine information across a network of trials using only IPD. If we are not successful in obtaining IPD for at least one study, we will combine both IPD and aggregated data in a single model; this will allow the inclusion of all trials in the analysis. Information on patient-level covariates (e.g., AD severity, sex, comorbidities, use of non-pharmacologic interventions) received from the authors will be included in the model. We will statistically evaluate whether the transitivity assumption is valid using the design-by-treatment interaction model [26, 27]. If statistical inconsistency is identified, we will perform the loop-specific method [28, 29] using aggregated data to locate the piece of the network responsible for the observed inconsistency. If these approaches suggest network inconsistency, we will check the data for discrepancies and if none are identified, a subgroup or meta-regression analysis will be considered. The subgroup and meta-regression analysis will consider the potential treatment effect modifiers described in the 'Data abstraction' section.

(Figure 1 here)

We will estimate subgroup effects, including patient characteristics received from authors (e.g., age, sex, severity of Alzheimer's disease, previous use of AD medications) using treatment-by-covariate interaction terms within studies and combining these across studies. Other subgroups will include study-level variables, such as intervention characteristics. We will apply 3 model specifications assuming that: a) the regression coefficients are different and unrelated across comparisons, b) the regression coefficients are different but related, sharing the same distribution, and c) the regression coefficients are identical across comparisons [30, 31]. A common-within network between-study variance will be assumed across comparisons [32]. We will compare the results of the models by evaluating the statistical significance of the regression coefficients for interactions, monitoring the reduction in the between-study variance, and using the Deviance Information Criterion (DIC) [33] to compare the overall fit and parsimony of the models. The model with the lowest DIC corresponds to the best-fitting model and a difference of 3 units or more is considered significant [33]. We will use the IPD-NMA model with the best fit for our results and the other model results will be reported in an appendix. The summary treatment effects will be presented using the odds ratios or mean differences along with their corresponding credible intervals (CrIs) and predictive intervals (PrIs) [34]. We will rank the interventions for each of the MMSE and SAE outcomes using the surface under the cumulative ranking curve (SUCRA) [35].

We will conduct multiple sensitivity analyses to examine the robustness of our results. First, we will restrict to studies with IPD only. Second, we will use different priors for the between-study variance [36-38]. Third, we will restrict to RCTs with a low risk of bias for sequence generation, allocation concealment, and blinding components of the Cochrane risk of bias tool. Fourth, we will use imputation techniques for missing outcome data. In particular, for MMSE we will perform the 'informative missingness difference of means' (IMDoM) method [39], and for SAE we will apply the 'informative missingness odds ratio' (IMOR) method accounting for the uncertainty due to missing outcome and basing imputations on observed outcomes [40].

All analyses will be conducted using the Bayesian software OpenBUGS [41] with Markov Chain Monte Carlo (MCMC) samplers. Two chains will be generated and convergence

will be evaluated by their mixing, after discarding the first 10,000 iterations. We will use non-informative priors for all parameters of the models apart from the between-study variance for which we will use the empirical distributions suggested by Turner et al [37] for dichotomous data and Rhodes et al [38] for continuous data. We will present our findings in accordance with the PRISMA extension for NMA [42].

Ethics and dissemination

To the best of our knowledge, this study will be the first IPD-NMA examining the comparative effectiveness and safety of cognitive enhancers versus placebo or best supportive care by AD severity and sex. Such an analysis may be more powerful in comparison with the NMA using aggregated data, and will allow healthcare providers to individualize the management of patients with AD. The findings of our study will fill an important knowledge gap in health care, and will be used to improve the health for patients suffering from this debilitating disease.

The results of this systematic review and IPD-NMA will be of interest to stakeholders, including decision makers, guideline developers, clinicians, methodologists and patients. The dissemination of our findings will be knowledge user-driven and tailored to how and when knowledge users want to receive information. Team members will act as knowledge brokers, using their networks to facilitate dissemination. We will publish our findings in an open access journal, and present them at relevant meetings (Canadian Geriatrics Society; CGS), as well to newsletters of organizations (Alzheimer's Society of Ontario, CGS).

There is a challenge to our study that is worth noting. Our dataset relies on the authors' willingness to share their data [43]. However, we have extensive experience contacting authors, as it is a regular process to ask for additional data on included studies during the systematic review conduct, and we have a good response rate (on average >60%). The additional offer of $100 incentive will help us improve the response rates. If we are unable to obtain IPD for at least one of the included studies, we will include both IPD and aggregated data in the analyses. This is because it has been suggested that combining IPD with aggregate data minimizes the chances of confounding bias in aggregate data NMA [12, 44].

The IPD-NMA does not require ethical approval, as it synthesizes data from clinical trials (and informed consent was already obtained for the original study). We will only request anonymized data from the authors, and we will link each patient to a specific identifier to prevent the patient from being identified.

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Figure captions

Figure 1. Network diagrams for a) Mini-Mental State Exam (MMSE) and b) serious adverse events (SAE) outcomes, as published in our previous systematic review and network meta-analysis [11]

Authors' contributions

AAV, SES and ACT conceived and designed the study, and helped write the draft protocol. HA registered the protocol with the PROSPERO database and edited the draft protocol. JH, BH, JHL, and SM provided input into the design and draft of the protocol. All authors read and approved the final protocol.

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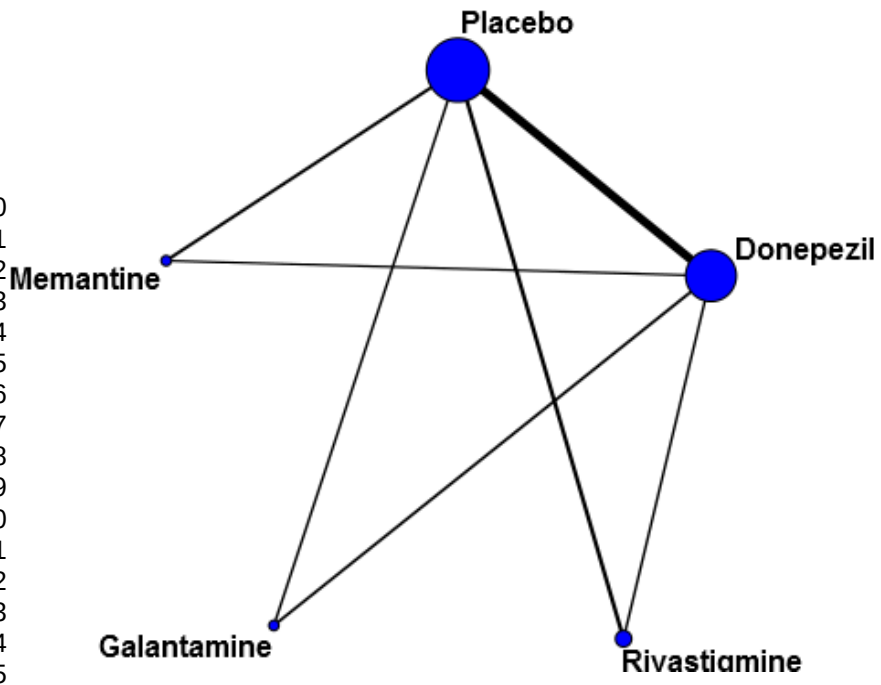
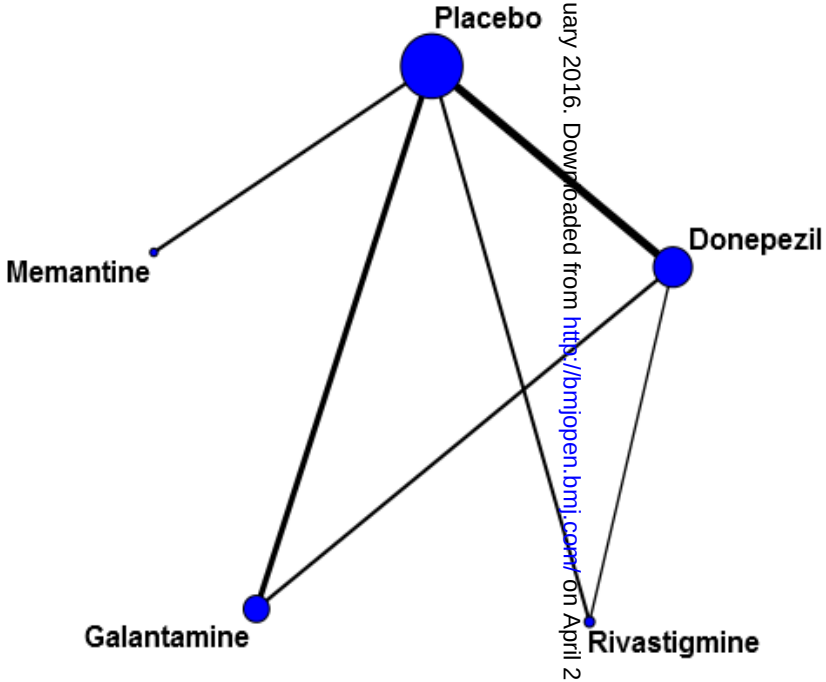
Competing interests

The authors declare that they have no competing interests.



a) Network diagram for Mini-Mental State Exam



b) Network diagram for serious adverse events

Figure 1

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Authors' comments
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Abstract and page 6
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 14
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	N/A
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Page 6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Page 7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits,	This has been already presented in

		such that it could be repeated	our previous publication (see Tricco et al ODPRN report 2015 and Tricco et al Syst Rev 2012) were we used aggregated data
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Page 7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 6
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Page 8 and 9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Page 8 and 9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page 9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	N/A

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

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Comparative safety and effectiveness of cognitive enhancers for Alzheimer's dementia: protocol for a systematic review and individual patient data network meta-analysis

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Keywords:	network meta-analysis, multiple treatments meta-analysis, individual participant data, Nootropic Agents, Alzheimer Disease

Comparative safety and effectiveness of cognitive enhancers for Alzheimer's dementia: protocol for a systematic review and individual patient data network meta-analysis

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ABSTRACT

Words: 299 (Max 300 words)

Introduction: Alzheimer's dementia (AD) is the most common cause of dementia, and several organizations, such as the National Institute for health and Care Excellence, suggest that management of patients with AD should be tailored to their needs. To date, little research has been conducted on the treatment effect in different subgroups of AD patients. The aim of this study is to examine the comparative effectiveness and safety of cognitive enhancers for different patient characteristics.

Methods and analysis: We will update our previous literature search from January 2015 forward, using the same terms and electronic databases (e.g., MEDLINE) from our previous review. We will additionally search grey literature and scan the reference lists of the included studies. Randomized clinical trials (RCTs) of any duration conducted at any time comparing cognitive enhancers alone or in any combination against other cognitive enhancers, or placebo in adults with AD will be eligible. The outcomes of interest are cognition according to the Mini-mental State Examination, and overall serious adverse events. For each outcome and treatment comparison, we will perform a Bayesian hierarchical random-effects meta-analysis combining the individual patient data (IPD) from each eligible study. If the identified treatment comparisons form a connected network diagram, we will perform an IPD network meta-analysis (NMA) to estimate subgroup effects for patients with different characteristics, such as AD severity and sex. We will combine aggregated data from studies that we will not be able to obtain IPD, with the IPD provided by the original authors, in a single model. We will use the PRISMA-IPD and PRISMA-NMA statements to report our findings.

Ethics and dissemination: The findings of this study will be of interest to stakeholders, including decision makers, guideline developers, clinicians, methodologists and patients and they will help to improve guidelines for the management of patients with AD.

Trial registration number: PROSPERO CRD42015023507

STRENGTHS AND LIMITATIONS

- This study will be the first network meta-analysis using individual patient data (IPD-NMA) evaluating the comparative effectiveness and safety of cognitive enhancers for different patient characteristics, such as AD severity and sex.
- The outputs of this study will provide clinicians, patients and caregivers with tailored evidence to inform their decision making.
- Although our IPD-NMA can be informed by observational studies providing data on adverse drug events, we will restrict to randomized clinical trials as this study design is the gold standard for a clinical trial and there are numerous clinical trials available on this topic.
- A potential difficulty in the conduct of our study is that IPD can only be obtained by contacting the original trial authors. To overcome this difficulty and improve the response rate, we will use validated approaches suggested for electronic surveys and provide a cash incentive to each author.

Keywords: network meta-analysis; multiple treatments meta-analysis; individual participant data; Nootropic Agents; Alzheimer Disease

Word count (excluding the abstract, references, tables, boxes, or figures): 3,715

INTRODUCTION

Alzheimer's dementia (AD) is the most common cause of dementia, and has an insidious onset with progressive deterioration in cognition (e.g., memory, thinking, and perception), function, behavior, and mood. To date, 46.8 million people worldwide live with dementia. This number will almost double every 20 years, and it is estimated to reach 131.5 million by 2050.[1] As dementia progresses, it impacts quality of life for the individual and causes a substantial burden on the family, caregivers, healthcare system, and society. AD ultimately leads to death with a median survival from diagnosis of only 7 years.[2] A recent study showed that as age increases, the rates of AD increase overall for both men and women, but it is more prevalent in women (rate/100 years= 2.50 (1.85-3.41)) than men (rate/100 years= 1.89 (1.22-2.94)).[3] Pharmacological treatment consists of cognitive enhancers, including the cholinesterase inhibitors (donepezil, galantamine and rivastigmine), and memantine, a N-Methyl-D-aspartic acid receptor antagonist.[4] It is currently unclear as to whether galantamine, rivastigmine, or donepezil should be used by patients with severe AD, and whether memantine is the most optimal treatment for severe AD, which is the patient population in most need of medication.[5] It has been shown that the use of acetylcholinesterase inhibitors (Ach-Is) and increased doses of donepezil in patients with dementia increase the risk of bradycardia, as well cholinesterase inhibitors doubles the risk of hospitalization for bradycardia in older patients.[6 7] Also, the use of other medications may increase risk of adverse events. For example, cardiac medications like beta-blockers may increase risk of bradycardia, and anti-inflammatories may increase risk for gastrointestinal bleeding.[6 8-10]

To determine the relative effectiveness of cognitive enhancers for patients with different patient characteristics (e.g., mild-moderate AD versus severe AD, females versus males), we aim to conduct a systematic review and individual patient data (IPD) network meta-analysis (NMA). NMA is an extension of pairwise meta-analysis and is the statistical method that combines different sources of evidence from a network of randomized clinical trials (RCTs) comparing different treatments for the same clinical topic within the same model. A NMA model can provide estimated treatment effects even for treatments that have never been directly compared in a head-to-head study. A key assumption in NMA is the transitivity assumption, which requires the balance of the distribution of potential effect modifiers across the treatments comparisons.[11-13] In AD, patients may respond differently to the medication based on severity of AD and sex, and hence severity and sex could be considered treatment effect modifiers. The optimal approach to assess the transitivity assumption is to compare the patient-level characteristics using IPD across treatment comparisons. Under the transitivity assumption, an IPD-NMA may tailor results to the patient characteristics. Tailoring the management of patients with AD is an issue that has been also brought up by several organizations,[14] including the Alzheimer's Society of Ontario[15] and the National Institute for health and Care Excellence (NICE).[4] Also, the Alzheimer's Disease International (ADI) federation in their world Alzheimer report 2015 mention that there has been dramatically little research into the treatment effect across people of different age and sex.[1]

The use of aggregated data reported in RCTs does not always allow us to reach a definitive conclusion on which medication is the safest or most effective for patients with different severities of AD and for females/males. This is because the covariates of interest (e.g., sex, severity of disease) are inconsistently reported in RCTs and a relationship at the aggregated study level is not necessarily true at the individual patient level. Indeed, we previously attempted a systematic review and NMA of aggregated data and we were unable to provide definitive conclusions regarding the influence of patient characteristics on the results.[16 17]

The NMA results of our previous unpublished study were tailored to age, AD severity, comorbidity, and study duration via subgroup analysis. These results were similar to four Cochrane reviews examining cognitive enhancers for AD.[18-21] More specifically, the reviews showed that all cholinesterase inhibitors, donepezil, rivastigmine, and galantamine, significantly improved cognition[18-21] against placebo, yet cholinesterase inhibitors and donepezil improved behavior,[18 19] cholinesterase inhibitors and rivastigmine improved function,[19 20] and rivastigmine improved AD severity.[20] These effects were associated with higher doses of rivastigmine,[20] suggesting that dose may be a treatment effect modifier. However, a (network) meta-analysis using aggregated data may suffer from relatively low statistical power for detecting a treatment-by-covariate interaction and introduces potential aggregation bias (also known as ecological fallacy).[22-24] This bias may occur if one (incorrectly) assumes that relationships observed at the group level hold at the individual level as well.[25-27] The use of IPD will help explain the relationship between treatment effects and patient-level characteristics, allowing healthcare providers to individualize the management of patients with AD (such as for patients with more severe AD or who are using medications such as beta blockers). In addition, in our previous NMA we attempted a subgroup analysis for AD severity, but we were unable to infer on the treatment effectiveness for the severe AD subgroup because there were only few RCTs available that reported on patients with severe AD and a NMA was impossible (disconnected network). The advantage of IPD is that we are not restricted to using the information reported in the publication. For example, for the 15 RCTs that did not report severity of disease in patients, we will be able to include them in the IPD-NMA analysis. Also, we will be able to use the information on severe AD from studies that included patients ranging from mild-to-severe, and moderate-to-severe disease. This will help increase power in our analysis compared to the aggregated data NMA. However, it should be noted that although IPD may increase power for the identification of treatment-by-covariate interactions, it has been shown that the studies usually included in a meta-analysis are underpowered themselves.[28]

The aim of this study is to examine the comparative effectiveness and safety of cognitive enhancers versus placebo or best supportive care by patient characteristics, such as AD severity and sex. We will use IPD-NMA to identify potential treatment effect modifiers, and estimate the most effective and safest treatments for patients with different characteristics. We will combine aggregated data from studies that we are not able to obtain IPD, with the IPD obtained from authors who provide these data. Recent simulations have shown that adding IPD to AD studies in a NMA can significantly improve precision, reduce bias, and increase information compared to NMA relying on aggregated data alone.[29]

METHODS AND ANALYSIS

This systematic review and IPD-NMA protocol was prepared according to the preferred reporting items for systematic reviews and meta-analyses protocols (PRISMA-P) guidelines,[30] and was registered with the international prospective register of systematic reviews (PROSPERO) (Registration #CRD42015023507).

Eligibility criteria

The research question and protocol are based on our previous systematic review and NMA.[17] Therefore, we will update our previous systematic review,[17] and we will use similar population, interventions, comparators, study designs and time period (PICOST) criteria. Eligible studies are RCTs including adults with AD administered a cognitive enhancer compared with each other, best supportive care, or placebo. The specific PICOST criteria are:

Population: Adults (aged ≥18 years) with AD diagnosed using various criteria (e.g., Diagnostic and Statistical Manual of Mental Disorders, Nursing Minimum Data Set criteria) of any duration with either moderate AD, i.e., Mini-mental State Examination (MMSE) of 10-20 or severe AD i.e., MMSE <10.[31] These criteria have changed over time and we will record how the authors define AD severity for each study.

Interventions: Cognitive enhancers (donepezil, rivastigmine, galantamine, and memantine) alone or in any combination.

Comparators: Cognitive enhancers, best supportive care alone or in any combination, and placebo.

Outcomes: The primary outcome of interest is cognition according to the MMSE (efficacy outcome, continuous variable), and the secondary outcome is overall serious adverse events (SAE; safety outcome, dichotomous variable); both outcomes were reported by many of the included trials previously and for which NMA was possible. In particular, in our previous NMA using aggregated data, 60 RCTs with 15,862 patients contributed to a NMA for the MMSE outcome, and 51 RCTs with 19,329 patients contributed to a NMA for serious adverse events.

Study design: We will restrict to RCTs, as this is the gold standard for examining interventions.[32] We will exclude quasi-RCTs, i.e., quasi-random methods used to allocate patients to groups, such as consecutive allocation. Observational studies may provide data on safety, but these typically rely on administrative data and it is challenging to obtain sufficient information on individual patient characteristics.

Time: Studies of any duration conducted at any time.

Other: Unpublished and published studies written in any language will be included.

Search strategy and study selection

We will update our literature search from January 5, 2015 onwards using terms from our previous review[17] in MEDLINE (OVID interface, January 5, 2015 onwards), the Cochrane Central Register of Controlled Trials (CENTRAL; January 5, 2015), Embase (OVID interface, January 5, 2015 onwards). We will use the search strategy and literature search (as created

by an experienced librarian, Dr. Laure Perrier, and peer-reviewed using Peer Review of Electronic Search Strategies (PRESS)[33] by Ms. Becky Skidmore) as described in our previous publication.[16] We present our literature search for MEDLINE in Appendix 1. Briefly, we will search reference lists of included studies and relevant reviews. Grey literature (i.e., difficult to locate and unpublished studies) will be searched via trial registry websites (such as Public Health Agency of Canada, Health Canada, FDA, metaRegister of Controlled Trials) and conference abstracts (such as International Pharmaceutical conference). Non-English articles will be translated to determine their inclusion. In case study publications report data from the same study group (i.e., companion reports), we will include the most complete follow-up data and the other study will be used for supplementary data only.

We will use the Synthesi.SR tool[34] to screen citations and full-text articles. To ensure reliability, our team has previously conducted a pilot test using our eligibility criteria on a random sample of 50 titles and abstracts from the literature search results. When a high agreement (>90%) was reached, two team members screened each title and abstract for inclusion, independently (level 1 screening). After pilot-testing full-text screening criteria, pairs of reviewers independently reviewed the full-text of potentially relevant articles (level 2 screening). Conflicts were resolved by discussion in both levels. In the update of our previous systematic review,[17] we will not conduct a pilot-test, but we will follow the same screening process. We will report the overall percent agreement, as well reasons for study exclusion at both levels. The PRISMA flow diagram will be used to report the study selection.[35]

Data abstraction

The data we plan to abstract include study characteristics (e.g. year of publication), aggregated patient characteristics (e.g. number of patients), outcome results (e.g. MMSE, SAE), and source of funding (categorized as: funded/authored by an employee of a drug manufacturer or other commercial organization, government-sponsored/non-profit organizations, including universities and hospitals, no funding, funding unclearly reported, and funding not reported).[36] We will also abstract the corresponding authors' mails and email addresses, as well their phone number. Two reviewers will abstract data independently, and all conflicts will be resolved through discussion.

The corresponding authors' contact information will be abstracted from the papers. For missing information, we will search authors' online research profiles (e.g., Google Scholar) or PubMed. We will use recommended approaches for electronic surveys to improve response rates.[37] Specifically, we will 1) send an email to the corresponding authors explaining the study purpose and requesting their data, enclosing a signed letter on letterhead, 2) send reminder emails at 2, 6, 10, and 14 week intervals after the initial email; 3) send a reminder by post in addition to email the 7th week, and 4) contact the corresponding author by phone during the 15th week. A financial incentive will be also offered to the corresponding author in the form of a $100 Amazon gift certificate. We will inform all authors that their article will be appropriately cited and, if they agree, they will be acknowledged in our paper. To ensure that we will be able to conduct this study, we will also contact clinical data sharing sites such as Clinical Study Data Request (CSDR) and Yale University Open Data Access (YODA) to obtain IPD on any of the eligible studies.

We will ask authors to provide IPD on: 1) patients, including age, sex, severity of Alzheimer's disease (e.g. baseline MMSE level), presence of behavioral disturbance, comorbid conditions (e.g., stroke, cardiovascular conditions, Parkinson's disease), other medications used for each patient (such as beta-blockers and other antiarrhythmic drugs, as these can increase risk of adverse events, especially gastrointestinal side effects and bradycardia[6 7]), drop-outs along with reasons for drop-out, and number of participants, 2) medication, including treatment patient was allocated, dosage, 3) outcomes, including event and date of event and time taken to achieve the event for SAEs, and MMSE values and measurement dates, and 4) date and method of randomization. All IPD will be saved on a secure server, adhering to personal health information protection act (PHIPA).[38]

Risk of bias and quality appraisal

As with the original review, we will appraise the risk of bias using the Cochrane Risk of Bias tool.[32] Two reviewers will independently assess the risk of bias in each included study after pilot-testing on a random sample of 5 RCTs. Disagreements will be resolved by discussion. To ensure data consistency, as recommended by the PRISMA-IPD guidelines[39], we will 1) compare IPD provided by the investigator with aggregate data reported in the publication; 2) assess whether the eligibility criteria of each study are in agreement with the IPD, 3) check date consistency, e.g. date patient randomized versus date trial opened. We will also check whether the randomization of patients is adequate (i.e., intervention and comparison groups are balanced for important patient characteristics), by comparing numbers and types of patients in each arm. We will ask the author for clarifications, if inconsistencies are identified. Our IPD analysis will be based on the intention-to-treat principle including all previously excluded patients.

We will draw a comparison-adjusted funnel plot[40] for both the MMSE and SAE. This plot allows the examination of heterogeneity and different types of bias, such as selective reporting, publication, and funding biases. After ordering the treatments included in the network chronologically regarding their year of availability on the market, we will plot the difference between each observed effect and overall treatment effect against the standard error of the observed effect. The comparison-adjusted funnel plot will be used only when RCTs with two treatment arms are included in the analysis, as this method does not account for correlations induced by multi-arm trials and potential asymmetry in the plot can be masked. Whenever an eligible study includes multiple arms we will construct funnel plots for each treatment comparison and outcome separately. Funnel plots for each treatment comparison will be plotted only when at least 10 RCTs are available. Reasons for funnel plot asymmetry will be explored. Two review authors will also independently assess the quality of evidence in each NMA using the GRADE approach as extended for network meta-analysis.[41]

Synthesis

The characteristics of the included studies, patients, and treatments, as well as risk of bias of studies will be described irrespective of whether IPD is obtained. We will present summary statistics and potential outlier patient values to describe the outcome data in each study.

We will perform a Bayesian hierarchical random-effects meta-analysis for each treatment comparison, as we anticipate clinical and methodological between-study heterogeneity. All IPD from included studies will be combined into a single model using a multilevel model where each study is a different cluster. We will use the odds ratio for SAE[42] and the mean difference effect size for MMSE.[27] In case we are able to obtain IPD for a subset of trials, then we will use a two-part model with the same between-study variance in both parts and accounting for treatment-by-covariate interactions (including for example co-morbidities such as arrhythmias in the model[43]). The first part will entail a one-stage model using IPD only, whereas the second part will entail applying a pairwise meta-analysis modeling aggregate data.[43]

If the treatment comparisons that inform the eligible RCTs form a connected network of trials (see Figure 1a and Figure 1b), the random-effects NMA model will be used in the primary analysis. If possible, we will combine information across a network of trials using only IPD. If we are not successful in obtaining IPD for at least one study, we will combine both IPD and aggregated data in a single model; this will allow the inclusion of all trials in the analysis. Information on patient-level covariates (e.g., AD severity, sex, comorbidities, use of non-pharmacologic interventions) received from the authors will be included in the model as secondary analyses. We will statistically evaluate whether the transitivity assumption is valid using the design-by-treatment interaction model.[44 45] If statistical inconsistency is identified, we will perform the loop-specific method[46 47] using aggregated data to locate the piece of the network responsible for the observed inconsistency. If these approaches suggest network inconsistency, we will check the data for discrepancies and if none are identified, a subgroup or meta-regression analysis will be considered. The subgroup and meta-regression analyses will consider the potential treatment effect modifiers described in the 'Data abstraction' section.

[Figure 1 here]

We will estimate subgroup effects, including patient characteristics received from authors (e.g., age, sex, severity of Alzheimer's disease, previous use of AD medications) using treatment-by-covariate interaction terms within studies and combining these across studies. Other subgroups will include study-level variables, such as intervention characteristics. We will apply 3 model specifications assuming that: a) the regression coefficients are different and unrelated across comparisons, b) the regression coefficients are different but related, sharing the same distribution, and c) the regression coefficients are identical across comparisons.[48 49] A common-within network between-study variance will be assumed across comparisons.[50] We will compare the results of the models by evaluating the statistical significance of the regression coefficients for interactions, monitoring the reduction in the between-study variance, and using the Deviance Information Criterion (DIC)[51] to compare the overall fit and parsimony of the models. The model with the lowest DIC corresponds to the best-fitting model and a difference of 3 units or more is considered significant.[51] We will use the IPD-NMA model with the best fit for our results and the other model results will be reported in an appendix. The summary treatment effects will be presented using the odds ratios or mean differences along with their corresponding credible intervals (CrIs) and

predictive intervals (PrIs).[52] We will rank the interventions for each of the MMSE and SAE outcomes using the surface under the cumulative ranking curve (SUCRA).[53]

We will conduct multiple sensitivity analyses to examine the robustness of our results. First, we will restrict to studies with IPD only. Second, we will use different priors for the between-study variance[54-56] Third, we will restrict to RCTs with a low risk of bias for sequence generation, allocation concealment, and blinding components of the Cochrane risk of bias tool. Fourth, we will use imputation techniques for missing outcome data. In particular, for MMSE we will perform the 'informative missingness difference of means' (IMDoM) method,[57] and for SAE we will apply the 'informative missingness odds ratio' (IMOR) method accounting for the uncertainty due to missing outcome and basing imputations on observed outcomes.[58]

All analyses will be conducted using the Bayesian software OpenBUGS[59] with Markov Chain Monte Carlo (MCMC) samplers. Two chains will be generated and convergence will be evaluated by their mixing, after discarding the first 10,000 iterations. We will use non-informative priors for all parameters of the models apart from the between-study variance for which we will use the empirical distributions suggested by Turner et al[55] for dichotomous data and Rhodes et al[56] for continuous data. We will present our findings in accordance with the PRISMA extension for NMA.[60]

ETHICS AND DISSEMINATION

To the best of our knowledge, this study will be the first IPD-NMA examining the comparative effectiveness and safety of cognitive enhancers versus placebo or best supportive care by AD severity and sex. Such an analysis may be more powerful in comparison with the NMA using aggregated data, and will allow healthcare providers to individualize the management of patients with AD. The findings of our study will fill an important knowledge gap in health care, and will be used to inform decision making for patients suffering from this debilitating disease.

The results of this systematic review and IPD-NMA will be of interest to stakeholders, including decision makers, guideline developers, clinicians, methodologists and patients. The dissemination of our findings will be knowledge user-driven and tailored to how and when knowledge users want to receive information. Team members will act as knowledge brokers, using their networks to facilitate dissemination, such as The Cochrane Collaboration, PRISMA-IPD, Drug Safety and Effectiveness Network (DSEN). We will also host a knowledge exchange event with our partners to discuss the results and facilitate dissemination. We will publish our findings in an open access journal, and present them at relevant meetings (Canadian Geriatrics Society; CGS), as well to newsletters of organizations (Alzheimer's Society of Ontario, CGS).

There is a challenge to our study that is worth noting. Our dataset relies on the authors' willingness to share their data.[61] However, we have extensive experience contacting authors, as it is a regular process to ask for additional data on included studies during the systematic review conduct, and we have a good response rate (on average >60%). The additional offer of $100 incentive will help us improve the response rates. We will also

contact clinical data sharing sites such as Clinical Study Data Request (CSDR) and Yale University Open Data Access (YODA) for data on any of our included studies. If we are unable to obtain IPD for all studies included in the systematic review, we will combine both IPD and aggregated data (as reported in the study publication) in the analyses. This is because it has been suggested that combining IPD with aggregate data minimizes the chances of confounding bias in aggregate data NMA.[29 62]

The IPD-NMA does not require ethical approval, as it synthesizes data from clinical trials (and informed consent was already obtained for the original study). We will only request anonymized data from the authors, and we will link each patient to a specific identifier to prevent the patient from being identified.

FIGURE CAPTIONS

Figure 1. Network diagrams for a) Mini-Mental State Exam (MMSE) and b) serious adverse events (SAE) outcomes, as published in our previous systematic review and network meta-analysis [17]

AUTHORS' CONTRIBUTIONS

AAV, SES and ACT conceived and designed the study, and helped write the draft protocol. HA registered the protocol with the PROSPERO database and edited the draft protocol. JSH, BRH, JHL, SRM, and GM provided input into the design and draft of the protocol. All authors read and approved the final protocol.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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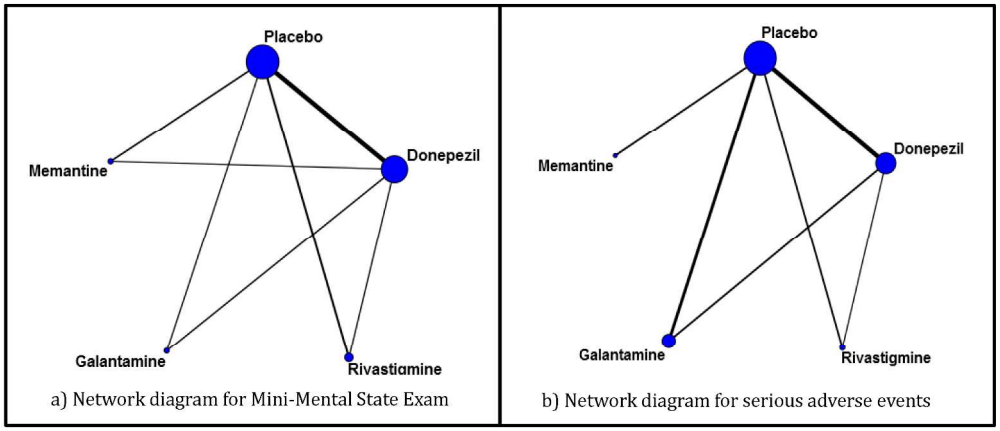

Figure 1. Network diagrams for a) Mini-Mental State Exam (MMSE) and b) serious adverse events (SAE) outcomes, as published in our previous systematic review and network meta-analysis
254x190mm (300 x 300 DPI)

Appendix 1. MEDLINE Search

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, Embase<1980 to 2014 Week 50> Search Strategy:

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1 alzheimer$.mp.
2 "benign senescent forgetfulness".mp.
3 (cognit$ adj2 (impair$ or declin$ or deficit$ or degenerat$ or deteriorat$ or los$ or disorder$ or complain$ or disturb$)).mp.
4 (cerebr$ adj2 (impair$ or declin$ or deficit$ or degenerat$ or deteriorat$ or los$ or disorder$ or complain$ or disturb$)).mp.
5 (mental adj2 (impair$ or declin$ or deficit$ or degenerat$ or deteriorat$ or los$ or disorder$ or complain$ or disturb$)).mp.
6 (ne?rocognit$ adj2 (impair$ or declin$ or deficit$ or degenerat$ or deteriorat$ or los$ or disorder$ or complain$ or disturb$)).mp.)
7 (ne?ro-cognit$ adj2 (impair$ or declin$ or deficit$ or degenerat$ or deteriorat$ or los$ or disorder$ or complain$ or disturb$)).mp.
8 ((cognit$ or memory or cerebral or brain) adj2 (improv$ or enhanc$ or perform$ or process$ or function$ or rehabilitation or aid$ or stimulat$)).mp.
9 cognition.ti.
10 (confusion$ or confused).tw.
11 dement$.mp.
12 ("normal pressure hydrocephalus" and shunt$).mp.
13 "organic brain disease$".mp.
14 "organic brain syndrome".mp.
15 (presenil$ or pre-senil$ or senil$).tw.
16 Alzheimer Disease/
17 Cognition/de
18 Confusion/
19 Dementia/
20 or/1-19
21 abixa.tw.
22 aricept.tw.
23 (acetylcholinesteraseadj inhibitor$).tw.
24 axura.tw.
25 akatinol.tw.
26 (anticholinesterase? or anti-cholinesterase?).tw.
27 (cognitive adjenhanc$).mp.
28 (cholinesterase adj inhibitor$).mp.
29 ChEI.tw.

30 donepezil.mp.
31 ebixa.tw.
32 eranz.tw.
33 exelon.tw.
34 galant?amin$.tw.
35 lycoremine.tw.
36 memantin$.tw.
37 memox.tw.
38 namenda.tw.
39 nimvastid.tw.
40 nivalin$.tw.
41 "N-Methyl-D-aspartic acid receptor antagonist$".tw.
42 prometax.tw.
43 razadyne.tw.
44 reminyl.tw.
45 rivastigmine.mp.
46 exp Cholinesterase Inhibitors/
47 Galantamine/
48 Memantine/
49 Galantamin.rn.
50 Memantine.rn.
51 Donepezil.rn.
52 Donepezil Hydrochloride.rn.
53 Rivastigmine.rn.
54 or/21-53
55 20 and 54
56 exp Animals/ not (exp Animals/ and Humans/)
57 55 and 56
58 (comment or editorial or interview or news).pt.
59 (letter not (letter and randomized controlled trial)).pt.
60 57 not (58 or 59)
61 (201111* or 201112* or 2012* or 2013* or 2014*).ed.
62 60 and 61
63 alzheimer$.mp.
64 "benign senescent forgetfulness".mp.
65 (cognit$ adj2 (impair$ or declin$ or deficit$ or degenerat$ or deteriorat$ or los$ or disorder$ or complain$ or disturb$)).mp.
66 (cerebr$ adj2 (impair$ or declin$ or deficit$ or degenerat$ or deteriorat$ or los$ or disorder$ or complain$ or disturb$)).mp.

67 (mental adj2 (impair$ or declin$ or deficit$ or degenerat$ or deteriorat$ or los$ or disorder$ or complain$ or disturb$)).mp.
68 (ne?rocognit$ adj2 (impair$ or declin$ or deficit$ or degenerat$ or deteriorat$ or los$ or disorder$ or complain$ or disturb$)).mp.
69 (ne?ro-cognit$ adj2 (impair$ or declin$ or deficit$ or degenerat$ or deteriorat$ or los$ or disorder$ or complain$ or disturb$)).mp.
70 ((cognit$ or memory or cerebral or brain) adj2 (improv$ or enhanc$ or perform$ or process$ or function$ or rehabilitation or aid$ or stimulat$)).mp.
71 cognition.ti.
72 (confusion$ or confused).tw.
73 dement$.mp.
74 ("normal pressure hydrocephalus" and shunt$).mp.
75 "organic brain disease$".mp.
76 "organic brain syndrome".mp.
77 (presenil$ or pre-senil$ or senil$).tw
78 Alzheimer disease/
79 cognitive defect/
80 confusion/
81 dementia/
82 organic brain syndrome/
83 or/63-82
84 abixa.tw.
85 aricept.tw.
86 (acetylcholinesteraseadj inhibitor$).tw.
87 axura.tw.
88 akatinol.tw.
89 (anticholinesterase? or anti-cholinesterase?).tw.
90 (cognitive adjenhanc$).mp.
91 (cholinesterase adj inhibitor$).mp.
92 ChEI.tw.
93 donepezil.mp.
94 ebixa.tw.
95 eranz.tw.
96 exelon.tw.
97 galant?amin$.tw.
98 lycoremine.tw.
99 memantin$.tw.
100 memox.tw.
101 namenda.tw.
102 nimvastid.tw.

103 nivalin$.tw.
104 "N-Methyl-D-aspartic acid receptor antagonist$".tw.
105 prometax.tw.
106 razadyne.tw.
107 reminyl.tw.
108 rivastigmine.mp.
109 exp cholinesterase inhibitor/
110 donepezil/ or donepezil plus memantine/
111 galantamine/
112 memantine/
113 rivastigmine/
114 357-70-0.rn.
115 19982-08-2.rn.
116 120011-70-3.rn.
117 120014-06-4.rn.
118 rivastigmine.rn.
119 or/84-118
120 83 and 119
121 randomized controlled trial/ or controlled clinical trial/
122 exp "clinical trial (topic)"/
123 (randomi#ed or randomly or RCT$1 or placebo*).tw.
124 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw.
125 trial.ti.
126 or/121-125
127 120 and 126
128 exp controlled clinical trial/
129 exp "controlled clinical trial (topic)"/
130 (control* adj2 trial*).tw.
131 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw.
132 (nRCT or nRCTs or non-RCT$1).tw.
133 (control* adj3 ("before and after" or "before after")).tw.
134 time series analysis/
135 (time series adj3 interrupt*).tw.
136 pretest posttest control group design/
137 (pre- adj3 post-).tw.
138 (pretest adj3 posttest).tw.
139 controlled study/
140 (control* adj2 stud$3).tw.
141 control group/
142 (control$ adj2 group$1).tw.

143 or/128-142
144 120 and 143
145 cohort analysis/
146 cohort.tw.
147 retrospective study/
148 longitudinal study/
149 prospective study/
150 (longitudinal or prospective or retrospective).tw.
151 follow up/
152 ((followup or follow-up) adj (study or studies)).tw.
153 observational study/
154 (observation$2 adj (study or studies)).tw.
155 population research/
156 ((population or population-based) adj (study or studies or analys#s)).tw.
157 ((multidimensional or multi-dimensional) adj (study or studies)).tw.
158 exp comparative study/
159 ((comparative or comparison) adj (study or studies)).tw.
160 exp case control study/
161 ((case-control* or case-based or case-comparison) adj (study or studies)).tw.
162 or/145-161
163 120 and 162
164 127 or 144 or 163
165 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/
166 exp humans/ or exp human experimentation/ or exp human experiment/
167 165 not 166
168 164 not 167
169 editorial.pt.
170 letter.pt.not (letter.pt. and randomized controlled trial/)
171 168 not (169 or 170)
172 (2011112* or 2011113* or 201112* or 2012* or 2013* or 2014*).dd.
173 171 and 172
174 62 use prmz
175 173 use emez
176 174 or 175
177 remove duplicates from 176
178 177 use prmz [MEDLINE UNIQUE HITS]
179 177 use emez [EMBASE UNIQUE HITS]

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Authors' comments
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Abstract and page 6
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 14
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	N/A
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Page 6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Page 7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits,	This has been already presented in

		such that it could be repeated	our previous publication (see Tricco et al ODPRN report 2015 and Tricco et al Syst Rev 2012) were we used aggregated data
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Page 7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 6
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Page 8 and 9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Page 8 and 9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page 9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	N/A

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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