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Cholinesterase inhibitors for vascular dementia and other vascular cognitive impairments: a network meta-analysis (Protocol)

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[Intervention Protocol]

Cholinesterase inhibitors for vascular dementia and other vascular cognitive impairments: a network meta-analysis

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

- To assess the benefits and harms of each cholinesterase inhibitor in the treatment of adults with VCI
- To compare cholinesterase inhibitors for efficacy and safety in people with VCI

BACKGROUND

Description of the condition

Vascular cognitive impairment (VCI) is a clinical syndrome that comprises a broad spectrum of cognitive impairments that occur as a result of vascular disease (pathology), ranging from subjective cognitive decline and mild cognitive impairment to dementia (Dichgans 2017; van de Flier 2018). The Vascular Impairment of Cognition Classification Consensus Study (VICCCS) has produced a revised conceptualisation of VCI (Skrobot 2017), in which VCI is divided into mild and major subtypes according to the level of impairment. Mild VCI is not subdivided, but major VCI (vascular dementia) has four subdivisions: post stroke dementia, subcortical ischaemic vascular dementia, multi-infarct (cortical) dementia, and mixed dementias. For the purpose of this review, we will treat VCI as the umbrella term that incorporates vascular dementia and other cognitive syndromes with a presumed vascular basis (as listed in the VICCCS definition, including mild VCI and all subdivisions of major VCI). Two criteria must be met for a diagnosis of VCI: firstly, a demonstration of a cognitive deficit through neuropsychological testing, and secondly, the presence of cerebrovascular disease. VCI is further classified as 'probable' or 'possible', according to the presence of conclusive evidence demon-

strating a causal relationship between the cognitive impairment and the vascular disease (Dichgans 2017).

The clinical presentation of VCI depends on the type, extent and location of the underlying cerebrovascular pathology. Possible symptoms of VCI are numerous and include memory problems, mental slowness and problems with executive function (such as planning, sequencing and problem solving). Patients report difficulties with higher-order cognitive functions, such as planning, organising and monitoring behaviour. Behavioural symptoms and psychological symptoms, including emotional lability, anxiety, depression and apathy are also commonly reported. Other neurological signs and symptoms often occur, including reflex asymmetry, dysarthria (difficulty with speech), gait disorders and problems with balance, parkinsonism, rigidity, or urinary incontinence (O'Brien 2003; van de Flier 2018). VCI due to single infarcts (damage to a part of the brain due to stroke) presents abruptly, while symptoms and signs due to subcortical damage from the resulting lacunae or from white matter disease (a progressive age-related decline in nerves that connect areas of brain to each other) typically develop more insidiously (Erkinjuntti 2004).

As life expectancy increases, VCI has become a growing public health issue. According to recent estimates, approximately 36 million people have dementia worldwide, and this number is expected to reach 66 million by 2030 and 115 million by 2050 (Wortmann 2012). In affluent countries, the prevalence of dementia after 65 years is reported to be between 5% and 10% (Gorelick 2011). Vascular dementia is the second most common form of dementia after Alzheimer's disease and accounts for at least 20% of dementia cases (Wu 2016). The prevalence of VCI is strongly considered to be age-related. In subjects aged between 65 and 84 years, the prevalence of mild forms of VCI that do not reach the criteria required for a diagnosis of dementia is higher than that of vascular dementia. Rates of conversion to dementia, institutionalisation, and mortality are significantly increased in these patients, suggesting that patients with mild VCI are an important target population for prevention of poor outcomes (Dichgans 2017).

Description of the intervention

Accurate assessment and management of vascular risk factors are a key priority in the treatment of VCI, particularly early in the disease when preventive strategies may prove to be more effective (Ritter 2015). Although primary prevention trials have suggested that treatment of hypertension, adherence to a Mediterranean diet, physical activity, and smoking cessation may reduce the risk of cognitive decline, there is limited evidence regarding these interventions for improving cognition in VCI (Ritter 2015). Currently, there are no specific pharmacological treatments recommended for improving either cognition or function in VCI. Management strategies used for patients with VCI are similar to those for other forms of dementia. Key principles include treating psychological and behavioural comorbidities, providing information and support to the patient and caregivers, and maximising the patient's independence (Dichgans 2017).

Cholinesterase inhibitors are medicines recommended as options for managing mild to moderate dementia due to Alzheimer's disease in several clinical guidelines (Hort 2010; NICE 2018). Alzheimer's disease is the most common cause of dementia and is found in approximately 70% of autopsies of people with dementia (Qiu 2009). The three cholinesterase inhibitors currently marketed for the treatment of Alzheimer's disease are donepezil, rivastigmine and galantamine. Cholinesterase inhibitors are taken orally once or twice a day, or, in the case of rivastigmine, can be applied transdermally.

Well-designed, placebo-controlled trials involving large numbers of participants have reported modest cognitive benefit from cholinesterase inhibitors in mild to moderate dementia due to Alzheimer's disease (Hansen 2008). However, a number of harms due to the use of cholinesterase inhibitor treatment have also been reported. A previous Cochrane Review reported that there is evidence of more adverse events overall in people treated with a cholinesterase inhibitor than with placebo. Nausea, vomiting and diarrhoea in particular are reported significantly more frequently in the cholinesterase inhibitor groups than in the placebo groups (Birks 2006).

How the intervention might work

Cholinesterase inhibitors inhibit the activity of the enzyme acetylcholinesterase, and increase acetylcholine levels by decreasing the rate at which the substance is broken down. The aim of prescribing cholinesterase inhibitors for Alzheimer's disease is to compensate for the loss of cholinergic brain cells and to boost cholinergic neurotransmission in forebrain regions (Colović 2013). Reductions in acetylcholine and acetyltransferase activity (markers of cholinergic neurotransmission) are common to both Alzheimer's disease and VCI, raising the possibility that these drugs are beneficial for the former may also be beneficial for the latter (Toghi 1996; Perry 1997). Rivastigmine is a 'pseudo-irreversible' inhibitor of acetylcholinesterase and also of butyryl-cholinesterase, which is a non-specific cholinesterase enzyme. Galantamine is a reversible, competitive inhibitor of acetylcholinesterase with minimal butyryl-cholinesterase inhibitory activity (Lilienfeld 2002). Donepezil is a second-generation cholinesterase inhibitor, which is a non-competitive, reversible antagonist of cholinesterase and is highly selective for acetylcholinesterase compared to butyryl-cholinesterase (Dawbarn 2001).

Why it is important to do this review

To date, the US Food and Drug Administration and the European Medicines Agency have not approved any pharmacological treatments for VCI or Vascular dementia symptoms. As no established

standard treatment for VCI exists, clinicians must extrapolate from large primary and secondary prevention trials in ischaemic heart disease, hypertension and stroke.

Three previous Cochrane Reviews have investigated the efficacy and safety of separate cholinesterase inhibitors for VCI. The review of donepezil for VCI reported some improvements in cognitive function and activities of daily living as well as more global measures of change (Malouf 2004). The review investigating galantamine in VCI concluded that there were some advantages over placebo in the areas of cognition and global clinical state (Craig 2006). Similarly, rivastigmine had some benefit on cognitive response at 24 weeks in people with VCI (Birks 2013). However, these reviews provided no evidence of potential differences in efficacy between these medications, and a review that combines the evidence would be helpful to clinicians.

A number of years have passed since the publication of the original reviews. This new over-arching review will ensure that any new trials are included. It will also allow the use of contemporary approaches to evidence synthesis (e.g. use of GRADE methods to assess evidence quality) that were not in use at the time the previous reviews were written. For the first time, we will include all cholinesterase inhibitors in a network meta-analysis (NMA) in order to address the uncertainty about which cholinesterase inhibitor, if any, is most efficacious and safe in the management of VCI (Salanti 2012).

OBJECTIVES

- To assess the benefits and harms of each cholinesterase inhibitor in the treatment of adults with VCI
- To compare cholinesterase inhibitors for efficacy and safety in people with VCI

METHODS

Criteria for considering studies for this review

Types of studies

We will include all parallel-group, randomised trials in which participants with VCI are assigned to treatment with a cholinesterase inhibitor or placebo, or to alternative cholinesterase inhibitors. We will include any identified trial regardless of publication status.

We will discuss randomised, controlled trials of a cholinesterase inhibitor for VCI which do not meet the inclusion criteria briefly in the 'Excluded studies' section.

Types of participants

We will include patients diagnosed as having VCI on the basis of any validated and internationally recognised diagnostic framework for dementia, including the Diagnostic and Statistical Manual of Mental Disorders (DSM) (APA 2013), and the International Classification of Diseases of the World Health Organization (ICD) (WHO 1992), and any classification systems specific to VCI, such as the National Institute of Neurological Disorders and Stroke and the Association International pour la Recherche et l' Enseignement en Neurosciences (NINDS/AIREN) (Roman 1993). Diagnosis of VCI with no dementia will be based on scores on cognitive impairment scales with a clinical diagnosis to ensure distinction between vascular and non-vascular impairment.

From previous reviews we anticipate that studies of cholinesterase will be limited to a population with defined dementia pathology, for example VCI, Alzheimer's disease. Where the population is composed of a mixed group, we will include if the proportion with VCI is greater than 80%. For studies of undifferentiated dementia or where dementia subtype is not described, we will exclude, as based on general population frequencies, it would be unlikely that the pool of participants would have more than 80% VCI pathology.

Types of interventions

For our new over-arching review investigating the efficacy of individual cholinesterase inhibitors, our primary analysis will focus on trials of cholinesterase inhibitor monotherapy (i.e. rivastigmine, galantamine or donepezil) versus placebo control.

These medications can be administered orally or, in the case of rivastigmine, transdermally. In our primary analysis we will include both routes in a single summary analysis. Reviews in non-vascular dementia suggest that oral and transdermal preparations have different profiles for adverse effect, so we will perform a subgroup analysis to compare the efficacy and tolerability of the two routes in this population.

The licensed cholinesterase inhibitors are available in a range of doses. The drugs usually have a dose-titration period. In our analyses, we will consider the final dose achieved. Reviews in non-vascular dementias suggest doses may differ in efficacy and adverse events. For donepezil, we will include studies where the final dose is a licensed oral dose of 5 mg, 10 mg or 23 mg daily; we will consider each dose separately. For rivastigmine, we will assess the manufacturer's recommended final dose of 6 mg to 12 mg daily for the oral preparation, or 4.6 mg/24 hours or 9.5 mg/24 hours for the transdermal preparation; other doses, if studied, will be considered separately. For galantamine, we will assess the manufacturer's recommended oral dose of 16 mg to 24 mg; other doses, if studied, will be considered separately. For galantamine, we will consider standard and modified-release preparations in the same analysis.

Trials that compare one cholinesterase inhibitor with another will be included in the NMA only.

Types of outcome measures

Primary outcomes

We will estimate the relative effects of the interventions where reported at up to 3 months, from 3 months to 6 months, from 6 to 18 months, and more than 18 months, according to the following primary outcomes :

- Clinical Global Impression (e.g. Clinician's Interview-Based Impression of Change scale, CIBIC-Plus; The Clinical Global Impression of Change, CGIC; Clinical Global Impression, CGI; The Sandoz Clinical Assessment Geriatric Scale, SCAG);
- Cognitive function (e.g. the cognitive part of the Alzheimer's Disease Assessment Scale, ADAS-Cog; Syndrom-Kurz test);
- Functional performance in activities of daily living (e.g. Alzheimer's Disease Cooperative Study-Activities of Daily Living, ADCS-ADL; Behavioural Rating Scale for Geriatric Patients, BGP);
- The number of adverse events. If the number of adverse events is not presented, we will take the number of participants with any adverse events (one or more) in a study. We will accept adverse events as defined in the included studies.

Secondary outcomes

- Serious adverse events (SAEs), including death
- Incidence of development of new dementia: if any studies are concerned exclusively with vascular mild cognitive impairments or related syndromes, then we will describe rates of incident dementia as an outcome. This outcome will be considered separately to the other outcomes of interest to the dementia population.
- Behavioural disturbance (e.g. Neuropsychiatric Inventory, NPI)
- Carer burden
- Institutionalisation
- Quality of life

Search methods for identification of studies

Electronic searches

We will search ALOIS (www.medicine.ox.ac.uk/alois) - the Cochrane Dementia and Cognitive Improvement Group's (CDCIG) specialized register.

ALOIS is maintained by the Information Specialists for the Cochrane Dementia and Cognitive Improvement Group, and contains studies that fall within the areas of dementia prevention, dementia treatment and management, and cognitive enhancement in healthy elderly populations. The studies are identified through:
1 Searching a number of major healthcare databases: MEDLINE, Embase, CINAHL and PsycINFO;
2 Searching a number of trial registers: ClinicalTrials.gov and the World Health Organization's International Clinical Trials Register Platform (ICTRP) which covers ISRCTN; the Chinese Clinical Trials Register; the German Clinical Trials Register; the Iranian Registry of Clinical Trials and the Netherlands National Trials Register, plus others;
3 Searching the Cochrane Library's Central Register of Controlled Trials (CENTRAL);
4 Searching grey literature sources: ISI Web of Science Core Collection;
To view a list of all sources searched for ALOIS on the ALOIS web site (www.medicine.ox.ac.uk/alois).
Details of the search strategies run in healthcare bibliographic databases, used for the retrieval of reports of dementia, cognitive improvement and cognitive enhancement trials, can be viewed on the Cochrane Dementia and Cognitive Improvement Group's website: http://dementia.cochrane.org/searches
We will run additional searches in MEDLINE, Embase, PsycINFO, Cinhal, LILACs, ClinicalTrials.gov and the WHO Portal/ICTRP, from incpetion, to ensure that the searches for this review are as comprehensive and as up-to-date as possible. The search strategy that will be used for the retrieval of reports of trials from MEDLINE (via the Ovid SP platform) can be seen in Appendix 1.

Searching other resources

We will check the reference lists of eligible studies and previous systematic reviews to identify additional studies. We will contact the corresponding authors of the most recent systematic reviews on cholinesterase inhibitors in vascular cognitive impairment to enquire whether they are aware of any additional studies in the area of their review. We will search clinical trial registries (World Health Organization (WHO) International Clinical Trial Registry Platform (ICTRP) search portal; EU clinical trial register; ClinicalTrials.gov) for the protocols and registrations of all included studies. We will contact the pharmaceutical companies (Eisai and Pfizer for donepezil (Aricept); Shire for galantamine (Reminyl); Lunbeck for rivastigmine (Exelon)), and search their press releases pertaining to ChIEs. We will also request all conference posters presented by relevant authors and those sponsored by the pharmaceutical companies. We will seek other grey literature through handsearching of reference lists of the relevant trials and systematic reviews we retrieve. We will also handsearch relevant conference abstracts that are not covered in ALOIS, specifically; International

Stroke Conference 2017-2019 (published in Stroke). European Stroke Organisation Conference 2017-2019 (Published in European Stroke Journal) and Alzheimer's Association International Conference 2017-2019 (Published in Alzheimer's and Dementia journal).

Data collection and analysis

Selection of studies

Independently, two review authors (CB and AHAR) will assess all the potential studies we identify as a result of the search strategy for inclusion. We will resolve any disagreements through discussion or, if required, we will consult a third review author (TJQ). We will create a PRISMA study flow diagram to map out the number of records identified, included and excluded. We will list all studies excluded after full-text assessment and their reasons for exclusion in a 'Characteristics of excluded studies' table.

Data extraction and management

We will extract data on results from the primary outcome measures at the following time points, where reported: up to 3 months, from 3 months to 6 months, from 6 to 18 months, and more than 18 months. We will extract data from more than one time point, if available.

Data on potential effect modifiers

From each included study we will extract the following data that may act as effect modifiers:

- population: diagnostic criteria; baseline mean age; male-to-female ratio; co-morbidities; concurrent medications, ethnicity and socioeconomic status;
- interventions: duration of the intervention, including duration of any washout, run-in or titration period; dosage regimen, including during any titration period; route of administration;
- outcome measures: measure used, time point completed;
- 'risk of bias' domains (see Assessment of risk of bias in included studies);
- funding sources.

Assessment of risk of bias in included studies

The risk of bias in each study will be assessed independently by two review authors (CEB and AHAR), and any disagreement will be resolved by discussion to reach consensus, involving a third reviewer (TJQ), if necessary. We will assess the risk of bias of each included study using the Cochrane criteria (Higgins 2017), which include assessment of the following domains: random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting. We will judge the level of risk of bias within each study explicitly for each domain as being at 'low', 'high', or 'unclear' risk of bias. We will describe all judgements fully and present the conclusions in the 'risk of bias' tables.

We will judge studies as being at low risk of bias in the incomplete outcome data domain when numbers and causes of dropouts are balanced between arms. For continuous outcomes, we will consider the following factors: the level of missing data, the difference between groups, and the reasons for missingness. We will also take into account whether the approach to missing data (e.g. observed case (OC) or last observation carried forward (LOCF)) gave different effect estimates. For dichotomous outcomes, we will compare the proportions missing in each group with each other and with the adverse event risk. If there is a substantial difference in missing data between groups, or the proportion of missing data is comparable with the adverse events risk, we will rate the risk of attrition bias as high. We will assess selective outcome reporting by comparing outcomes the trialists intended to analyse against the published study results. Where no trial protocol is available, we will assign a judgement of high risk of bias when study results do not include the primary outcome measures of the review.

Measures of treatment effect

For binary outcomes, we will use odds ratios (ORs) with 95% confidence intervals (CIs) as the measure of treatment effect. For continuous outcomes, we will use mean differences (MDs) with 95% CI. If different instruments are used to measure the same continuous outcome, we will use the standardised mean difference (SMD) with 95% CIs. If participant-related outcomes are reported both as binary and continuous outcomes, we will analyse binary outcomes in one analysis and continuous outcomes in another analysis. For time-to-event outcomes, we will use hazard ratios (HRs) and their 95% CIs.

We will present results from network meta-analysis (NMA) as summary relative effect sizes for each possible pair of treatments.

Relative treatment ranking

For each study intervention, we will also estimate the ranking probabilities for all treatments of being at each possible rank. We will then obtain a treatment hierarchy using the surface under the cumulative ranking curve (SUCRA) and mean ranks (Salanti 2011).

Unit of analysis issues

We do not anticipate any cluster randomised or cross-over trials. If any such trials are retrieved, we will follow guidance from the

Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2017).

For multi-arm trials, we will include all intervention groups that would meet the criteria for inclusion in pairwise comparisons, if they were investigated alone.

Dealing with missing data

In order to assess the effect of missing outcome data, we plan to use OC analyses wherever possible, but in some analyses, we may have to pool trials reporting OC and LOCF data. This will be made explicit in the accompanying text. We will assess the impact of this OC approach in a sensitivity analysis, by comparing the results of analyses based on the two main approaches (OC and LOCF). We will report the degree of missing data explicitly in the Characteristics of included studies section. Where mixed methods or area-under-the curve methods are reported by study authors, we will extract the results from these analyses only if OC results are unavailable.

Assessment of heterogeneity

Assessment of clinical and methodological heterogeneity within treatment comparisons

To evaluate the presence of heterogeneity deriving from different trial designs or different clinical characteristics of study participants, we will generate descriptive statistics for trial and study population characteristics across all eligible trials that compare each pair of interventions. Two authors will assess the presence of clinical heterogeneity within each pairwise comparison by comparing these characteristics. Statistical heterogeneity will be assessed using the I^2 statistic and its 95% CI that measures variability that cannot be attributed to random error. We will take an I^2 measurement of more than 50% as indicative of substantial heterogeneity (Higgins 2017).

Assessment of transitivity across treatment comparisons

We expect that the transitivity assumption will hold, with the assumption that all pairwise comparisons will not differ with respect to the distribution of effect modifiers (for example, rivastigmine, galantamine and donepezil will have been administered in a similar way across all included trials).

We will evaluate the assumption of transitivity by comparing the clinical and methodological characteristics (potential effect modifiers presented in Data extraction and management) across the different pairwise comparisons.

Assessment of reporting biases

In view of the difficulty of detecting and correcting for publication bias and other reporting biases, we will aim to minimise the potential impact of these biases by ensuring a comprehensive search for eligible studies and by being alert to duplication of data. If there are 10 or more studies in the NMA, we will use a funnel plot to explore the possibility of small study effects (a tendency for estimates of the intervention effect to be more beneficial in smaller studies) and account for the fact that studies estimate effects for different comparisons. The funnel plots will be aggregate combining all relevant studies.

Data synthesis

Methods for direct treatment comparisons

We will perform standard pairwise meta-analyses using a fixed-effect model in the review-writing software Review Manager 5.3 for every treatment comparison at our prespecified time points, where the summary analysis will include at least two studies (Review Manager 2014). If substantial heterogeneity is found (i.e. an I^2 value > 50%), we will analyse the data using a random-effects model.

Methods for indirect and mixed comparisons

NMA is a method used to synthesise information from a network of trials that address the same question, but involve different interventions. NMA combines direct and indirect evidence across a network of randomised trials into a single effect size, and, under certain assumptions, it can increase the precision of the estimates while respecting randomisation. The models will enable us to estimate the probability that each intervention is the best for each outcome, given the relative effect sizes as estimated in NMA.

Each cholinesterase inhibitor and dose will be considered as a separate intervention (node) in the analysis. The NMA will compare the cholinesterase inhibitor medications and doses to one another. We will report the findings for these interventions in the results and the conclusions of the review.

We assume that the three cholinesterase inhibitors (donepezil, rivastigmine and galantamine), are directly comparable treatments. In other words, we assume that the distribution of important characteristics (effect modifiers) is the same across all treatment comparisons (Salanti 2012). The placebo node is defined as any drug intervention that does not contain an active ingredient, or any trial arm that contains no investigator-intended treatment.

We will perform NMA for each primary outcome measure, using MetaInsight, (bespoke NMA software developed by the University of Leicester). We will receive support in the design, analyses and interpretation of the NMA from the National Institute for Health Research (NIHR) Complex Reviews Support Unit.

Subgroup analysis and investigation of heterogeneity

Assessment of statistical heterogeneity

Assumptions when estimating the heterogeneity

As we expect to have few studies (around two to four) in each direct comparison, in standard pairwise meta-analysis we will assume a common heterogeneity variance for all direct comparisons. In NMA we will assume a common estimate for the heterogeneity variance across the different comparisons.

Measures and tests for heterogeneity

The assessment of statistical heterogeneity in the entire network will be based on the magnitude of the heterogeneity variance parameter (T^2) estimated from the NMA models. For dichotomous outcomes the magnitude of the heterogeneity variance will be compared with the empirical distribution as derived by Turner (Turner 2012). We will also estimate a total I^2 value for heterogeneity in the network as described elsewhere (Jackson 2014).

Assessment of statistical inconsistency

Consistency in a network of interventions refers to the agreement between direct and indirect evidence on the same comparisons. If the network is substantially inconsistent, joint analysis can be misleading. Differences in trial protocols, inclusion or exclusion criteria, and effect modifiers within the network will lead to inconsistency.

Local approaches for evaluating inconsistency

To evaluate the presence of inconsistency locally we will use the loop-specific approach. This method evaluates the consistency assumption in each closed loop of the network separately as the difference between direct and indirect estimates for a specific comparison in the loop (inconsistency factor) (Veroniki 2013). The magnitude of the inconsistency factors and their 95% CIs can then be used to infer information about the presence of inconsistency in each loop. We will assume a common heterogeneity estimate within each loop. We will present the results of this approach graphically in a forest plot using MetaInsight (University of Leicester).

Global approaches for evaluating inconsistency

To check the assumption of consistency in the entire network we will use the 'design-by-treatment' model as described by Higgins 2017. This method accounts for different sources of inconsistency that can occur when studies with different designs (two-arm trials versus three-arm trials) give different results as well as disagreements between direct and indirect evidence. Using this approach, we will draw inferences about the presence of inconsistency from any source in the entire network based on a Chi^2 test. Inconsistency and heterogeneity are interwoven; to distinguish between these two sources of variability we will employ the I^2 for inconsistency, as it measures variability that cannot be attributed to random error or heterogeneity (within comparison variability). We will also seek guidance from the NIHR Complex Reviews Support Unit, to address any inconsistencies.

Investigation of heterogeneity and inconsistency

If sufficient studies are available, we will perform network meta-regression or subgroup analyses, or both, by using the following effect modifiers as possible sources of inconsistency or heterogeneity, or both: baseline severity, diagnostic criteria, duration of intervention.

Sensitivity analysis

If sufficient studies are identified for each comparison, we will undertake sensitivity analyses that include only trials that we have rated as being at low risk of bias across all domains.
We will conduct sensitivity analyses including only participants with vascular dementia, that is, excluding trials in which some or all participants have mild VCI.

'Summary of findings' table

The main results of the review will be presented in 'Summary of findings' (SoF) tables as recommended by Cochrane (Schünemann 2011). We will include overall grading of the evidence for the primary outcomes and SAEs for each comparison, based on the methodology developed by the GRADE Working Group (Puhan 2014). We will assess the quality of evidence using the GRADE criteria: study limitations, indirectness, inconsistency, imprecision of events estimates, and risk of publication bias. We will assign four levels of evidence quality to our results; high, moderate, low and very low, using GRADEpro GDT software (GRADEpro GDT). We will provide estimates of the direct and indirect evidence and of the network meta-analysis.

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REFERENCES

Additional references

APA 2013

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th Edition. Washington (DC): American Psychiatric Society, 2013.

Birks 2006

Birks J. Cholinesterase inhibitors for Alzheimer's disease. *Cochrane Database of Systematic Reviews* 2006, Issue 1. DOI: 10.1002/14651858.CD005593

Birks 2013

Birks J, McGuinness B, Craig D. Rivastigmine for vascular cognitive impairment. *Cochrane Database of Systematic Reviews* 2013, Issue 5. DOI: 10.1002/14651858.CD004744.pub3

Colović 2013

Colović MB, Krstić DZ, Lazarević -Pašti TD, Bond žić AM, Vasić VM. Acetylcholinesterase Inhibitors: pharmacology and toxicology. *Current Neuropharmacy* 2013;**11**(3):315–35.

Craig 2006

Craig D, Birks J. Galantamine for vascular cognitive impairment. *Cochrane Database of Systematic Reviews* 2006, Issue 1. DOI: 10.1002/14651858.CD004746.pub2

Dawbarn 2001

Dawbarn D, Shelly JA. *Neurobiology of Alzheimer's Disease*. 2nd Edition. Oxford (UK): Oxford University Press, 2001.

Dichgans 2017

Dichgans M, Leys D. Vascular cognitive impairment. *Circulation Research* 2017;**120**:573–91. DOI: https://doi.org/10.1161/CIRCRESAHA.116.308426

Erkinjuntti 2004

Erkinjuntti T, Román G, Gauthier S, Feldman H, Rockwood K. Emerging therapies for vascular dementia and vascular cognitive impairment. *Stroke* 2004;**35**:1010–7.

Gorelick 2011

Gorelick PB, Scuteri A, Black SE, DeCarli C, Greenberg SM, Iadecola C, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2011;**42**:2672–713. DOI: 10.1161/STR.0b013e3182299496

GRADEpro GDT [Computer program]

McMaster University (developed by Evidence Prime). GRADEpro GDT. Hamilton (ON): McMaster University (developed by Evidence Prime), 2015.

Hansen 2008

Hansen RA, Gartlehner G, Webb AP, Morgan LC, Moore CG, Jonas DE. Efficacy and safety of donepezil, galantamine, and rivastigmine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. *Clinical Interventions in Aging* 2008;**3**:211–25.

Higgins 2017

Higgins JP, Altman DG, Sterne JA. Chapter 8: Assessing risk of bias in included studies. In: Higgins JP, Churchill R, Chandler J, Cumpston MS, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.2.0 (updated June 2017). The Cochrane Collaboration, 2017. Available from training.cochrane.org/handbook.

Hort 2010

Hort J, O'Brien JT, Gainotti G, Pirttila T, Popescu BO, Rektorova I, et al. EFNS guidelines for the diagnosis and management of Alzheimer's disease. *European Journal of Neurology* 2010;**17**:1236–48.

Jackson 2014

Jackson D, Barrett JK, Rice S, White IR, Higgins JP. A design-by-treatment interaction model for network meta-analysis with random inconsistency effects. *Statistics in Medicine* 2014;**33**:3639–54.

Lilienfeld 2002

Lilienfeld S. Galantamine: a novel cholinergic drug with a unique dual mode of action for the treatment of patients with Alzheimer's disease. *CNS Drug Reviews* 2002;**8**:159–76.

Malouf 2004

Malouf R, Birks J. Donepezil for vascular cognitive impairment. *Cochrane Database of Systematic Reviews* 2004, Issue 1. DOI: 10.1002/14651858.CD004395.pub2

MetaInsight

Owen RK, Bradbury N, Xin Y, Cooper NJ, Sutton AJ. MetaInsight: An interactive web-based tool for analysing, interrogating and visualizing network meta-analyses using R-shiny and netmeta. *Research Synthesis Methods* (Submitted).

NICE 2018

National Institute of Clinical Excellence. NICE guidelines: donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease. Technology appraisal guidance [TA217]. www.nice.org.uk (accessed 6 January 2019).

O'Brien 2003

O'Brien JT, Erkinjuntti T, Reisberg B, Roman G, Sawada T, Pantoni L, et al. Vascular cognitive impairment. *Lancet Neurology* 2003;**2**:89–98.

Perry 1997

Perry E, Kay DW. Some developments in brain ageing and dementia. *British Journal of Biomedical Science* 1997;**54**:201–15.

Puhan 2014

Puhan MA, Schünemann HJ, Murad MH, Li T, Brignardello-Petersen R, Singh JA, et al. GRADE Working Group. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ* 2014;**349**(g5630).

Qiu 2009
Qiu C, Kivipelto M, von Strauss E. Epidemiology of Alzheimer's disease: occurrence, determinants, and strategies toward intervention. *Dialogues in Clinical Neuroscience* 2009;**11**:111–28.

Review Manager 2014 [Computer program]
Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Ritter 2015
Ritter A, Pillai JA. Treatment of vascular cognitive impairment. *Current Treatment Options in Neurology* 2015; **17**:367. DOI: 10.1007/s11940-015-0367-0

Roman 1993
Roman G, Tatemichi T, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology* 1993;**43**:250–60.

Salanti 2011
Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *Journal of Clinical Epidemiology* 2011;**64**:163–71.

Salanti 2012
Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Research Synthesis Methods* 2012;**3**:80–97.

Schünemann 2011
Schünemann HJ, Oxman AD, Higgins JP, Vist GE, Glasziou P, Guyatt GH. Chapter 11: Presenting results and 'Summary of findings' tables. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Skrobot 2017
Skrobot OA, O'Brien J, Black S, Chen C, DeCarli C, Erkinjuntti T, et al. The vascular impairment of cognition classification consensus study. *Alzheimer's & Dementia* 2017;**13**:624–33.

Toghi 1996
Toghi H, Abe T, Kimura M, Saheki M, Takahashi S. Cerebrospinal fluid acetylcholine and choline in vascular dementia of Binswanger and multiple small infarcts types as compared with Alzheimer-type dementia. *Journal of Neural Transmission* 1996;**103**:1211–20.

Turner 2012
Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. *Internal Journal Epidemiology* 2012;**41**: 818–27.

van de Flier 2018
van der Flier WM, Skoog I, Schneider JA, Pantoni L, Mok V, Chen CL, et al. Vascular cognitive impairment. *Nature Reviews Disease Primers* 2018;**15**:18003.

Veroniki 2013
Veroniki AA, Vasiliadis HS, Higgins JP, Salanti G. Evaluation of inconsistency in networks of interventions. *Internal Journal Epidemiology* 2013;**42**:332–45.

WHO 1992
World Health Organization. *The ICD-11 Classification of Mental and Behavioural Disorders: Clinical Description and Diagnostic Guidelines*. 10th Edition. Geneva: World Health Organization, 1992.

Wortmann 2012
Wortmann M. Dementia: a global health priority - highlights from an ADI and World Health Organization report. *Alzheimers Research and Therapy* 2012;**4**:40. DOI: 10.1186/alzrt143

Wu 2016
Wu YT, Fratiglioni L, Matthews FE, Lobo A, Breteler MM, Skoog I, et al. Dementia in western Europe: epidemiological evidence and implications for policy making. *Lancet Neurology* 2016;**15**:116–24. DOI: 10.1016/S1474-4422 (15)00092-7

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE search strategy

1 exp CADASIL/
2 exp Cerebrovascular Disorders/
3 exp Dementia, Multi-Infarct/
4 exp Dementia, Vascular/
5 exp Neurocognitive Disorders/
6 "subcortical ischemic vascular disease*".ti,ab.
7 "vascular cognitive impairment*".ti,ab.
8 "vascular dement*".ti,ab.
9 dement*.ti,ab.
10 VaD.ti,ab.
11 VCI.ti,ab.
12 or/1-11
13 exp Cholinesterase Inhibitors/
14 exp TACRINE/
15 exp GALANTAMINE/
16 exp Donepezil/
17 "acetylcholinesterase inhibitor*".ti,ab.
18 "anti-alzheimer* ADJ2 drug*".ti,ab.
19 "anti-cholinesteras*".ti,ab.
20 "anti-dementia drug*".ti,ab.
21 "cholinesterase inhibitor*".ti,ab.
22 "memory drug".ti,ab.
23 "SDZ ENA 713".ti,ab.
24 Anticholinesterase*.ti,ab.
25 anti-cholinesterase.ti,ab.
26 aricept.ti,ab.
27 cognex.ti,ab.
28 donezepil.ti,ab.
29 E2020.ti,ab.
30 exelon.ti,ab.
31 galantamine.ti,ab.
32 galanthamine.ti,ab.
33 Nivalin.ti,ab.
34 Razadyne.ti,ab.
35 reminyl.ti,ab.
36 rivastigmine.ti,ab.
37 tacrine.ti,ab.
38 or/13-37
39 12 and 38

CONTRIBUTIONS OF AUTHORS

All authors have made a substantial contribution to the conception and design of the protocol; have drafted the work or revised it critically for intellectual content; have approved final version to be published; and agree to be accountable for all aspects of the work.

DECLARATIONS OF INTEREST

Ceri E Battle - none known

Azmil H Abdul-Rahim - none known

Susan D Shenkin - none known

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Terry J Quinn - none known

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