Guideline: use of cholinesterase inhibitors and memantine in vascular dementia

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BACKGROUND

Vascular dementia (VaD) **represents the second most common type of dementia after Alzheimer's disease (AD), comprising 10–50% of dementia cases. Sometimes the two coexist which is referred as mixed dementia.** VaD may be recognized by the presence of cerebrovascular disease together with a characteristic impairment in executive function, decreased ability to perform activities of daily living (ADL) as well as impairment in memory and other cognitive abilities.

Currently, no established standard treatment for VaD **exists and** patients are usually treated by managing their vascular risk factors for cerebrovascular disease, **with the primary goal of slowing clinical progression. Evidence that disruption of cholinergic pathways contributes to the pathophysiology and clinical expression of vascular dementia has led to clinical trials of cholinesterase inhibitors** (ChEI) **- rivastigmine, galantamine, donepezil, approved for the treatment of AD, in treatment of** VaD. Moreover, it is hypothesized that **glutamatergic neurotoxicity may contribute to the pathophysiology of vascular dementia with memantine (NMDA antagonist) being investigated in clinical trials in patients with VaD.**

RESEARCH QUESTIONS

Our PICO question was whether ChEI or memantine rather than standard of care (no pharmacological treatment) should be used in patients with vascular dementia to improve important clinically meaningful outcomes such as cognitive functioning, global clinical impression, behaviour and performance of ADL.
The guideline developers prioritised this question.
Perspective: Population.
Guideline development followed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group. Several outcomes were identified and judgements were made in relation to its importance. Overall, outcomes for cognitive functioning, ADL and global clinical impression were considered to be of critical importance (rating 7-9) while outcomes for behaviour were classified as important (mean rating of 6). Outcomes related to adverse events were also rated and globally were considered to be important, while number of deaths was classified as a critical outcome.

IDENTIFICATION OF STUDIES

Relevant articles were obtained by searching the PubMed and MEDLINE databases for studies published prior to April 2020. A complementary search of ALOIS (a register of major healthcare databases including pharmaceutical industry trials registers), the specialized register of the Cochrane Dementia and Cognitive Improvement Group, was conducted to ensure important trials were not missed. We also sought to include unpublished data (conference programmes, abstract books, web postings, etc) to achieve a comprehensive review of the evidence.

The following key words were used: "vascular dementia" OR "vascular-alzheimer*" OR "multi-infarct dementia" OR "strategic stroke" OR "post-ischemic dementia" OR "hemorrhage dementia" OR "genetic cerebrovascular disorders" AND "cholinesterase inhibitors" OR "donepezil" OR "rivastigmine" OR "galantamine" OR "Aricept" OR "reminyl" OR "Exelon" OR "memantine" AND "clinical trial" OR "cross-over studies" OR "double-blind methods" OR "placebos" OR "random allocation" OR "single-blind methods" AND "humans". We found 71 publications related to our PICO question.

DATA EXTRACTION AND QUALITY APPRAISAL

The titles and the abstracts of all searched articles were screened including review articles in order to find additional eligible studies. Forty-three studies were suitable for full-text screening. These were reviewed to ensure that included trials met the following criteria: (1) parallel-group, double-blinded, placebo-controlled (RCT), with random assignment to a cholinesterase inhibitor (donepezil, rivastigmine, galantamine) or memantine; (2) human patients with possible or probable VaD diagnosed using validated criteria [eg, the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria of 1993, the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria (NINCDS-ADRDA) or the Diagnostic and Statistical Manual of Mental Disorders third edition revised (DSM-III-R)] and evidence of VD on MRI or CT; (3) assessed at least one of the outcomes defined in our PICO question. non-English language publications were excluded. Additional information had to be available on sample selection criteria, randomisation, double-blinding, trial duration and medication doses and formulations, adverse events and discontinuations during the double-blind trial. Wherever possible, outcomes following an intention-to-treat analysis were used, and if not, then observed case were extracted. Thirty-one articles were excluded because of duplicate data (eg. post hoc analysis) (n=12), insufficient information (n=3), different methodology other than RCT/meta-analysis (n=7) or significant risk of bias (n=9). The remaining twelve studies comprised seven trials included in the meta-analysis and relevant meta-analysis (n=5) for pooled data extraction, when they included the relevant trials identified in our search.
The quality of all included trials was assessed by Cochrane methods, evaluating for random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias (eg. suspicion of publication bias).

We performed a meta-analysis, using fixed-effects models, to estimate the difference between the groups with one of the ChEI or memantine treatment and the groups with placebo. The data of each correspondent clinical outcome (ADL, behaviour, cognitive functioning, GCI) as well as adverse events, were pooled separately. For continuous outcomes, effect sizes were calculated with weighted mean difference (MD) or standardized mean difference (SMD) when using different rating scales within a domain, while for dichotomous outcomes odds-ratio (OR) was calculated. I^2 index was used as a measure of heterogeneity. An evidence profile was created for each of the four drugs individually using the GRADEpro software for each clinical domain and adverse events.

We included two trials accessing the effect of donepezil in 1219 patients with VaD, with only those randomized to 10mg daily dose being included in the current meta-analysis[1,2]. For galantamine, two trials assessed the efficacy and safety of 24 mg daily or flexible-dose 16-24mg daily in 1380 patients[3,4]. For these four trials no concerns about the risk of bias were recognized. Only one trial, with 710 participants, assessing rivastigmine flexibly dosed up to 6mg twice daily was eligible for inclusion in the meta-analysis[5]. For this, the risk of bias was classified as serious due to missing data and the use of a last observation carried forward analysis. Finally, two trials with 900 participants assessed memantine 20mg per day. For these trials, the risk of bias was classified as very serious since in one, as no method of sequence generation or concealment was described and a blinding method was not detailed[6]. For the MMM500 trial, significant missing data and incomplete outcome data (attrition bias) for primary outcomes plus selective reporting (reporting bias) were identified[7]. The duration of the trials ranged from 24 to 28 weeks.

IMPLEMENTATION

After releasing this evidence-based guideline, some implementation strategies might be anticipated to promote evidence-based practice:
- Print educational materials including patient versions and disseminate them among healthcare and social care staff, patients and their carers as well as stakeholders including national societies, patient organizations and collaborative task forces and policy makers.
- Publication of the evidence-based research and presentation in conferences.
- Promote educational meetings and workshops to improve compliance with the clinical guidelines.
- Information dissemination by pharmaceutical companies to promote their products.
- Use local opinion leaders to increase adherence to evidence-based guidelines, as these are recognized as respected and trusted.
- Audition of professional behavioral with feedback of results.

We recommend an update of this guideline in five years.

EVIDENCE PROFILE (GRADEPro)

For **rivastigmine**, there is probably a small cognitive benefit (ADAS-Cog scale) [MD 1.1 lower (2.15 lower to 0.05 lower)] but not for global impression of change [MD 0.1 lower (3.68 lower to 3.48 higher)], behavioural disturbances [MD 0.4 higher (1.36 lower to 2.16 higher)] or ADL [MD 0.6 higher (1.05 lower to 2.25 higher)], assessed with ADCS-CGIC, NPI and ADCS-ADL, respectively. **Level of certainty: low** (downgraded twice due to risk of bias and imprecision). Significantly higher rates of withdrawals due to adverse events (which were mainly vomiting, nausea, diarrhoea and anorexia) were noted in the participants randomized to rivastigmine OR 2.66 (1.53 to 4.62), with a moderate level of certainty (downgraded once due to risk of bias).
For **galantamine**, treatment seems to benefit a cognitive outcome (ADAS-cog) [MD 1.6 lower (2.39 lower to 0.8 lower)] but not functional (CIBIC-Plus dichotomized into improvement or no change versus worsening and ADCS-ADL) [OR 1.07 (0.80 to 1.44); SMD 0.04 SD lower (0.27 lower to 0.2 higher)] or behavioural outcomes (NPI) [MD 0.87 higher (0.43 lower to 2.17 higher)]. **Level of certainty: low** (downgraded twice due to imprecision and indirectness since the two included trials studied different populations of patients, with one including patients diagnosed with probable VaD or AD with cerebrovascular disease, whereas the other included only VaD). Nonetheless, a subgroup analysis of only those patients with mixed dementia, showed similar outcomes to those of the subsample of patients with probable VaD. Significantly higher rates of withdrawals due to adverse events (which were mainly vomiting, nausea, diarrhoea and anorexia) were noted in the participants randomized to galantamine [OR 2.39 (1.65 to 3.48)], with a moderate level of certainty downgraded once due to indirectness.
For **donepezil**, there is a cognitive improvement (ADAS-Cog) among treated patients (10mg dose) [MD 2.17 lower (2.98 lower to 1.35 lower)], as well as an improvement in the overall disease severity (CDR-SB) [MD 0.36 lower (0.6 lower to 0.13 lower)] and performance of ADL (ADFACS) [MD 0.97 lower (1.74 lower to 0.16 lower)], but not in the functional outcome CIBIC-Plus dichotomized into improvement versus no change or worsening [OR 1.13 (0.83 to 1.54)], which was only significant for the 5-mg dose. **Level of certainty: moderate** (downgraded once due to imprecision). Patients randomized to donepezil 10mg were more prone to suffer from at least one side effect (mainly nausea, diarrhoea and anorexia) [OR 1.95 (1.20 to 3.15)]. Level of certainty: high.
For **memantine** there is probably a small clinical benefit for cognitive function (ADAS-cog) [MD 1.86 lower (2.79 lower to 0.94 lower)] – **very low level of certainty** (downgraded due to very serious risk of bias and imprecision) and there may be a small clinical benefit on NOSGER disturbing behaviour outcome [SMD 0.2 SD lower (0.37 lower to 0.03 lower)] – **low level of certainty** (downgraded twice due to very serious risk of bias). No benefit was found for global functioning (CIBIC-plus rating scale dichotomized to improvement versus no change or decline) [OR 1.34 (0.85 to 2.15)] - **low level of certainty** (downgraded twice due to serious risk of bias and imprecision) neither it was for performance on ADL (NOSGER self-care subscale) [SMD 0.04 SD lower (0.2 lower to 0.13 higher)]. There may be no difference between memantine and placebo in the number of people experiencing at least one side effect [OR 1.03 (0.95 to 1.11)] – **low certainty** downgraded for imprecision and risk of bias, and there may be fewer people with agitation as an adverse event for memantine compared with placebo [OR 0.56 (0.33 to 0.96)] – **moderate certainty** (downgraded for risk of bias). Overall, there were no significant differences between ChEI or memantine and placebo in deaths during the trials [OR 1.44 (0.68 to 3.02)] – **very low certainty** (downgraded due to inconsistency, indirectness and imprecision)[8].

ADAS-Cog: Alzheimer's Disease Assessment Scale - Cognitive; ADCS-CGIC: Alzheimer's Disease Cooperative Study – Clinician's Global Impression of Change; CIBIC-Plus: Clinical Global Impression of Change plus Caregiver Input; CDR-SB: The clinical dementia rating sum of the boxes scoring; NPI: Neuropsychiatric Instrument; NOSGER: Nurses observation scale for geriatric patients disturbing behaviour subscale; ADCS-ADL: Alzheimer's Disease Cooperative Study activities of daily living scale; ADFACS: Alzheimer's Disease Functional Assessment and Change Scale

RECOMMENDATIONS

This is the first report on use of ChEI or memantine in patients with VaD in which the GRADE system was used to come up with evidence-based guidelines. Our meta-analysis suggests a **small benefit of all ChEI on cognitive functions** and this is probably significant since differences between drug and placebo on ADAS-cog derived largely from improvement in the cholinesteraseinhibitor groups rather than from a decline in the placebo group, which contrasts with what was verified in the memantine trials, in which the cognitive effects derived largely from worsening in patients in the placebo groups. However, there was **not a corresponding effect in clinical global impression**. For other functional and outcomes, only the 10 mg daily donepezil group differed from placebo regarding disease severity and ADL, with somewhat inconsistent data. Memantine was the only possibly associated with a small benefit in behavioral outcomes but a very serious risk of bias is posed due to a per protocol analysis. ORs for adverse events-related outcomes were significantly greater in patients treated with ChEI, nonetheless most of these adverse effects were mild to moderate and mainly gastrointestinal (nausea, vomiting, diarrhea, anorexia and insomnia). For donepezil, the long-term efficacy and tolerability in patients with VaD was reassured by an extension study where no new safety or tolerability issues were observed and given the long-term safety data it is not unreasonable to assume that donepezil can be tolerated over the long term in patients with VaD. For memantine there seems to be no increase in adverse effects but a decrease in agitation, despite there is some concern for a limited reporting of safety data. We did not find an increased mortality, but conclusions are limited due to a significant heterogeneity among studies and a high placebo mortality rate that was verified in one of the trials[1]. As so, overall data on safety profile of these drugs need to be interpreted with caution.
Yet, **certainty of the evidence of effects is weak mainly due to limitations in the existing trials** (heterogeneous cerebrovascular disease and subgroups of patients regarding lesion location and extent, presentation and disease course; brief duration of the trials; instruments used to assess outcomes in AD trials which may not be clinically meaningful or sensitive enough to the clinical changes in VaD and the exclusion of other important outcomes such as improved patient's quality of life, caregiver burden or delay to nursing home placement). Despite no data from systematic reviews (SR) exist on how patients **value** the main outcomes, there is probably no important uncertainty or variability. Also, there are no SR on **resource requirements** in this population or the impact of these interventions on **health equity**. Regarding **cost-effectiveness** of the intervention, only one study on cost-effectiveness data was conducted in VaD[9]. Donepezil 10 mg was associated with the lowest incremental cost-effectiveness ratio and so we recommend that donepezil might be considered a first choice if a ChEI is to be chosen. Since GRADE also includes costs as a determinant of the strength of recommendation, it reinforces our decision to a conditional recommendation for the intervention.
No SR were conducted about the **acceptability** of the intervention by stakeholders but it is probably well accepted, if we derive information from AD patient populations. In line with this, we consider that the intervention is probably **feasible to implement**.
In conclusion, we suggest that ChEI or memantine may provide small but significant benefits in patients with VaD, despite important uncertainties remain. Clinicians should discuss with patients and families that current evidence suggests that response to ChIs may be quite variable and they should monitor for either treatment-related improvement, worsening or stabilization in all these domains. Patient's values and preferences as well as concerns about costs should also be discussed. The strength of the evidence is weak for the four domains and the overall strength of recommendation is weak.

Type of recommendation: conditional recommendation for the intervention.

RATE OVERALL QUALITY

Determination of direction and strengths of recommendations was based on the best available evidence on the balance between desirable and undesirable effects, the quality of evidence, values and preferences and costs.

PICO question	Recommendation
Do the desirable consequences of treatment with ChEI or memantine in patients with vascular dementia outweigh the undesirable ones?	Probably yes.
Strength of recommendation	Weak
Cognitive functioning	Weak
Global clinical impression of change	Weak
Activities of daily living	Weak
Behaviour	Weak

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