Best Evidence Summaries of Topics in Mental Healthcare

BEST *in* MH *clinical question-answering service*

Question

In older adults diagnosed with pure vascular dementia (not Alzheimer's or mixed dementia) how effective are Acetylcholinesterase inhibitors or memantine, compared to no drug treatment, in improving cognitive, global and functional symptoms of dementia?

Clarification of question using PICO structure (PICTRO for diagnostic questions)

Patients: Older adults diagnosed with vascular dementia
Intervention: Aceylcholinesterase inhibitors or memantine
Comparator: No drug treatment
Outcome: Improving cognitive global and functional symptoms of dementia

Clinical and research implications

No definite clinical implications can be made from the available evidence. There is some evidence that Acetylcholinesterase inhibitors or memantine have statistically significant positive effects on cognitive function, but there appears to be some concern regarding their *clinical* significance and adverse effect burden. The authors of a systematic review suggested that data are insufficient to support their widespread use in patients with vascular dementia. They also suggested that trials of 6-month duration may be too brief to assess overall effectiveness given the relative stability of placebo patient groups, and longer trials would be more likely to show meaningful data on efficacy and safety.

There is also a general consensus that future studies would benefit from outcomes that are specific to patients with vascular dementia, instead of using outcomes that are specific to Alzheimer. The authors of the systematic review stated that an individual patient meta-analysis is needed to provide more specific information on treatment responses across different types and severities of vascular dementia between groups. The authors of a RCT that evaluated reviastigmine suggested that future studies should include neuropathological or biomarker measures to evaluate the presence of concomitant Alzheimer pathology to help better comprehend the effects of treatment.

What does the evidence say?

Number of included studies/reviews (number of participants)
One systematic review (SR) included eight relevant trials with a total of 5,183 participants (Kavirajan et al. 2007, and four randomised controlled trials (RCTs) (n=2,640) met the inclusion criteria for this BEST summary. In addition, a recently published extension study has been briefly considered.

Main Findings
The SR found significant differences in favour of all cholinesterase inhibitors evaluated (donepezil, galantamine, and rivastigmine) and memantine when compared to placebo for cognition, but significant differences were only observed for donepezil (5 mg) for global change outcomes, and donepezil (10 mg) for functional and behavioural outcomes.

Of two trials that evaluated donepezil, one included patients with a specific subtype of vascular cognitive impairment (small-vessel disease) in patients 70 years or younger (Dichgans et al. 2008). In this trial, no significant differences were observed between donepezil 10 mg and placebo groups for various measures of cognitive functions (assessed using V-ADAS-cog, and by ADAS-cog and MMSE) after 18 weeks. This trial did, however, show a significant benefit in favour of donepezil on several measures of executive function and processing speed. The other trial evaluated patients with a mean age of 73 years with probable or possible vascular dementia (Román et al. 2010). In contrast, this trial demonstrated significant differences between donepezil 5 mg and placebo for cognitive function (as assessed using V-ADAS-Cog ($p<0.01$), ADAS-cog ($p=0.04$) and MMSE ($p=0.03$), but not executive function, daily functioning or global assessment. A 30-week open-label extension study of two RCTs (Black et al., 2003; Wilkinson et al., 2003) also reported that the mean ADAS-cog score for all the donepezil-treated patients who elected to go into the open-label study improved over baseline during the double-blind trials and remained above baseline for the entire open-label phase of the study. The authors also stated that this improvement was observed regardless of the initial randomised dosage (5 or 10 mg of donepezil) during the double-blind phase.

One trial compared galantamine versus placebo (Auchus et al. 2007) (an earlier abstract of this study appears to have been included in the SR above). This trial demonstrated a significant difference in favour of galantamine compared with placebo for cognition (ADAS-cog/11) ($p<0.001$) and executive function (EXIT-25) ($p<0.05$), but not for activities of daily living (ADCS-ADL) or global functioning (CIBIC-plus) after 26 weeks.

One trial that evaluated rivastigmine (Ballard et al. 2008) found that treatment demonstrated significant superiority over placebo at week 24 on three measures of cognitive performance: the Vascular Dementia Assessment Scale VaDAS ($p=0.028$), the Alzheimer's Disease Assessment Scale cognitive subscale ($p=0.029$), and the Mini-Mental State Examination (MMSE) ($p=0.007$), but scores of activities of daily living, neuropsychiatric symptoms and global performance were not significantly different.

Authors Conclusions
The authors of the SR concluded that cholinesterase inhibitors and memantine produce small benefits in cognition of uncertain clinical significance in patients with mild to moderate vascular dementia. They also concluded that data are insufficient to support widespread use of these drugs in vascular dementia.

Regarding studies that evaluated donepezil, the authors of one study concluded that there was no significant treatment effect of donepezil on cognition as assessed by V-ADS-cog, and implied that this outcome may be limited. The other trial on donepezil (5mg) concluded that this treatment demonstrated significant improvements in cognitive, but not global function. The authors of the open-label extension study concluded that although the lack of a placebo control group prevents absolute statements regarding the long term efficacy of donepezil in a VaD patient population, the observed trends suggested that it improves cognition and stabilises function in these patients and that improvements are sustained over the long term.

One RCT (Auchus et al. 2007) concluded that no significant difference between galantamine and placebo was reached for the primary end-points of cognition (ADAS-cog/11) and activities of daily living (ADCS-ADL) total score.

The RCT by Ballard et al. (2008) concluded that rivastigmine did not provide consistent efficacy in this overall study population of probable VaD patients. Despite efforts to include patients with only VaD, the apparent efficacy on cognitive measures may have derived from drug effects on concomitant Alzheimer pathology.

Reliability of conclusions/Strength of evidence
The SR was well conducted, and the results are likely reliable. Two of the RCTs were considered to have a low risk of bias (Archus et al. 2007; Ballard et al. 2008) are also likely to be reliable, although the remaining two RCTs had an unclear risk of bias, and hence, the reliability of their results are uncertain.

What do guidelines say?
NICE guidance provides the following recommendation for pharmacological interventions for the cognitive symptoms of non-Alzheimer dementias and mild cognitive impairment:

- For people with vascular dementia, acetylcholinesterase inhibitors and memantine should not be prescribed for the treatment of cognitive decline, except as part of properly constructed clinical studies.

SIGN guidance provides the following recommendations on Cholinesterase inhibitors:

- Evaluation of the efficacy of galantamine in people with moderate to severe dementia needs further research.

- There is currently insufficient evidence to recommend the use of memantine for the treatment of core or associated symptoms in people with dementia.

Definite recommendations for other treatments were not stated.

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Date searches conducted: 31/07/2012
Date answer completed: 06/08/2012

References

SRs

Kavirajan H, Schneider LS. Efficacy and adverse effects of cholinesterase inhibitors and memantine in vascular dementia: a meta-analysis of randomised controlled trials. *Lancet Neurology*, 2007, 6(9), 782-792.

RCTs

Auchus AP, Brashear HR, Salloway S, Korczyn AD, De Deyn PP, Gassmann-Mayer C; GAL-INT-26 Study Group. Galantamine treatment of vascular dementia: A randomized trial. Neurology July 31, 2007 vol. 69 no. 5 448-458.

Ballard C, Sauter M, Scheltens P, He Y, Barkhof F, van Straaten ECW, van der Flier WM, Hsu C, Wu S, Lane R. Efficacy, safety and tolerability of rivastigmine capsules in patients with probable vascular dementia: The VantagE study. *Current Medical Research and Opinion*, September 2008, vol./is. 24/9(2561-2574), 0300-7995 (September 2008).

Dichgans M, Markus HS, Salloway S, Verkkoniemi A, Moline M, Wang Q, Posner H, Chabriat HS. Donepezil in patients with subcortical vascular cognitive impairment: a randomised double-blind trial in CADASIL. *Lancet neurology*, 2008; 7(4): 310–18.

Román GC, Salloway S, Black SE, Royall DR, Decarli C, Weiner MW, Moline M, Kumar D, Schindler R, Posner H. Randomized, placebo-controlled, clinical trial of donepezil in vascular dementia: differential effects by hippocampal size. *Stroke; a journal of cerebral circulation*, 2010, 41(6), 1213-21.

Extension study

Wilkinson D, Román, G, Salloway S, Hecker J, Boundy K, Kumar D, Posner H, Schindler R. The long-term efficacy and tolerability of donepezil in patients with vascular dementia. *International journal of geriatric psychiatry*, 2010, 25(3), 305-13.

Guidelines

National Institute for Health and Clinical Excellence (NICE) / National Collaborating Centre for Mental Health (2007) National Clinical Practice Guideline Number 42: Dementia. The NICE–SCIE Guideline on supporting people with dementia and their carers in health and social care. [Online]. Available from: http://www.nice.org.uk/nicemedia/live/10998/30320/30320.pdf

Scottish Intercollegiate Guidelines Network (SIGN). Management of patients with dementia: A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2006 Feb. (SIGN publication; no. 86). http://www.sign.ac.uk/pdf/sign86.pdf

Results

Systematic Reviews

Author (year)	Search Date	Inclusion criteria	Number of included studies	Summary of results	Risk of bias
Kavirajan (2007)	December 2006	*Study Design:* parallel-group, double blinded, placebo controlled, with random assignment to the experimental or control group. *Participants:* were diagnosed with vascular dementia by prospective criteria *Intervention*: Studies were included if the experimental group included treatment with a marketed cholinesterase inhibitor or memantine. *Comparison*: placebo *Outcomes:* The included studies examined the effects of the intervention upon a variety of outcomes. Broadly these included cognitive effects, clinician impression, and behavioural	8 studies were included in this review (n=5183) (3093 of these were allocated to an experimental group and 2090 to placebo)	Trial durations ranged from 24 weeks to 28 weeks. Three donepezil, two galantamine, one rivastigmine, and two memantine trials were included. Cognitive effects on the Alzheimer's Disease Assessment scale (ADAS-Cog) were significant compared to placebo for all drugs: donepezil 5 mg: WMD -1.15 (95% CI -1.65 to -0.64); donepezil 10 mg: WMD -2.17 (95% CI -2.98 to -1.35); galantamine 24 mg: WMD -1.60 (95% CI -2.39 to -0.80); rivastigmine 12 mg: WMD -1.10 (95% CI -2.15 to -0.05); memantine 20 mg: WMD -1.86 (95% CI -2.79 to -0.94). Only 5 mg daily donepezil had an effect on the Clinicians' Global Impression of Change scale: OR 1.51 (95% CI 1.11–2.7). No behavioural or functional benefits were observed, except for a –0.95 point difference (95% CI –1.74 to –0.16) with 10 mg daily donepezil on the Alzheimer's Disease Functional Assessment and Change Scale.	Low

		and functional benefits.		Compared with placebo, more dropouts and adverse events (anorexia, nausea, vomiting, diarrhoea, and insomnia) occurred with the cholinesterase inhibitors, but not with memantine. No significant differences were observed between drugs and placebo in deaths during the trials, however, the donepezil 319 trial showed a markedly increased risk of death (1.7% vs. 0%): OR 4.57 (95% CI 1.30–16.08).	

RCTs/DTAs

Author (year)	Inclusion criteria	Number of participants	Summary of results	Risk of bias
Archus et al (2007)	*Participants*: Patients were eligible for this trial if the met the criteria for vascular dementia. Entry to the trial required MRI confirmation of the clinical diagnosis of vascular dementia. Participants were also required to have a score of 10-26 on the MMSE, and a score of over 12 on the ADAS-cog scale. Onset of the disease should be between the ages of 40 & 90. *Intervention:* All subject completed a 4 week single blind run in period, in which they received placebo. The intervention group then received increasing doses of galantamine. *Comparison:* The control group received placebo, administered with the same	N=788 randomised (397 experimental group and 391 control group)	After 26 weeks, there was a significant difference in favour of galantamine compared with placebo for cognition (ADAS-cog/11): -1.8 vs. -0.3. $p<0.001$. There was also a significant effect in favour of treatment for EXIT-25 for assessment of executive functioning: -2.4 vs. -1.4, $p<0.05$. There were no significant differences between groups for activities of daily living (ADCS-ADL) or global functioning (CIBIC-plus). Adverse events leading to treatment discontinuation were 13% in the treatment group, and 6% in the placebo group; gastrointestinal events were the most common reason for discontinuing treatment.	Unclear

	escalation patterns as the intervention treatment. *Outcome:* Primary outcomes where assessed as changes between baseline and 26 weeks. The ADAS-cog and the ADCS activities of daily living scales were used. Secondary outcomes were assessed through clinicians' impression of change, caregiver input, and the neuropsychiatric inventory.			
Ballard et al (2008)	*Participants:* were aged 50-85 years and a diagnosis of vascular dementia according to the DSM-IV. The patients were also required to have a MMSE score of 10-24, and contact with a caregiver at least three times per week. *Intervention:* The experimental group received rivastigmine capsules (3-12mg daily). Doses were increase at 4 week interviews, over a 16 week escalation period that reached the maximum tolerated dose. Changes of dosage was allowed to cater for adverse events or other issues. *Comparator:* The control group received placebo, administered with the same escalation patterns as the intervention treatment. *Outcome:* Assessments were made at baseline and weeks 12 and 24. Primary	N=710 (365 experimental group, and 345 control group)	Rivastigmine demonstrated significant superiority over placebo at week 24 on three measures of cognitive performance: the Vascular Dementia Assessment Scale VaDAS (mean 0.7-point improvement on rivastigmine versus 0.6-point decline on placebo; p=0.028), the Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog) (p=0.029), and the Mini-Mental State Examination (MMSE) (p=0.007). There were no significant differences between groups for Alzheimer's Disease Cooperative Study – Clinician's Global Impression of Change (ADCS-CGIC), Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL), global deterioration scale (GDS) or NPI-12 (12-item neuropsychiatric inventory). Nausea and vomiting were the most commonly reported AEs (26.4% versus 3.8% nausea, and 22.0% versus 2.3% vomiting, in the rivastigmine capsules versus placebo groups, respectively). Most AEs were mild or moderate. Serious AEs were reported by 15.2% of rivastigmine-treated patients and 11.0% of patients in the placebo group. AEs contributing	Low

	outcomes were assessed by the vascular dementia assessment scale and the Alzheimer's Disease Assessment Scale cognitive subscale.		to the discontinuation rate in the rivastigmine group included gastrointestinal disorders (causing 5.5% and 0.9% patients to withdraw from the rivastigmine and placebo groups, respectively). There were statistically non-significant increases in mortality, and AEs of cerebrovascular accident and hypertension in the rivastigmine group relative to the placebo group *the authors stated that some of the older patients likely had concomitant Alzheimer pathology	
Dichgans et al (2008)	*Participants:* were men and women aged 25–70 years with a diagnosis of CADASIL. All patients had cognitive impairment as defined by both of two criteria: (1) a description of cognitive problems given by patients or their study partners; and (2) a mini-mental state examination (MMSE) score of 10–27 (inclusive), or a TMT B time score 1.5 SDs below the mean, after adjustment for age and education. *Intervention:* Donepezil (5 mg daily for the first 6 weeks and 10 mg daily thereafter). *Comparator:* Placebo. *Outcome:* The primary outcome was the vascular AD assessment scale cognitive subscale (V-ADAS-cog) at 18 weeks. Secondary outcomes included scores on the ADAS-cog, MMSE, TMT A time and B time, Stroop, executive interview-25 (EXIT25), CLOX, disability assessment for	N=168 (86 experimental group, and 82 placebo group)	Patients treated with donepezil showed significantly greater improvements on TMT A time (p=0.015) TMT B time (p=0.023), and EXIT25 (p=0.022) at 18 weeks. There was no significant difference in the V-ADAS-cog change from baseline, or ADAS-cog and the MMSE at 18 weeks. In addition, no significant differences between groups were observed on the DAD scores for IADL, or CDR-SB. The proportion of patients with treatment-emergent adverse events was higher in the donepezil group than in the placebo group (81% *vs* 71%). Ten donepezil-treated patients discontinued treatment due to adverse events compared to seven patients in the placebo group. Serious adverse events other than death were reported in nine (11%) patients assigned to placebo and in 15 (17%) patients assigned to donepezil. There was only one death in the placebo group.	Low

	dementia, and sum of boxes of the clinical dementia rating scale. Additional secondary efficacy measures included the disability assessment for dementia (DAD) scale, which assesses the patient's ability to do basic ADL and instrumental ADL (IADL), and the sum of boxes of the clinical dementia rating (CDR) scale (CDR-SB), a multidimensional scale for dementia severity.			
Román et al (2010)	*Participants:* were outpatients (age 35 to 94 years) with possible or probable VaD per National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria, had been stroke-free for ≥3 months, had not taken acetylcholinesterase inhibitors or memantine for at least 6 weeks, and did not have unstable medical conditions. *Intervention:* Donepezil 5 mg once daily. *Comparator*: Placebo. *Outcome:* Primary outcome measures were scores on the Vascular AD Assessment Scale-Cognitive Subscale (V-ADAScog) and the Clinician's Interview–Based Impression of Change, plus carer interview (CIBIC-Plus) performed at baseline and at weeks 6, 12, 18, and 24 (or	N=974 (648 experimental group and 326 placebo group).	Compared with placebo, donepezil-treated patients showed significant improvement from baseline to end point on the Vascular-Alzheimer Disease Assessment Scale–Cognitive Subscale ($p<0.01$), but not on the Clinician's Interview–Based Impression of Change, plus carer interview. Of the secondary outcomes evaluated, significant differences between groups were observed for cognitive outcomes: ADAS-Cog ($p=0.04$) and the MMSE ($p=0.03$). With the exception of NCT ($p=0.03$), no significant differences were observed for function (EXIT25; CLOX-1; CLOX-2; Maze), daily functioning (DAD) or global assessment (CDR-SB). Incidence of AEs was similar in the donepezil (80.7%) and placebo (77.6%) groups; commonly occurring AEs included nausea, anorexia, abdominal pain, diarrhea, abnormal dreams, hypertonia, and leg cramps. Most were transient and mild to moderate in severity. AEs were assessed by the investigator as probably/possibly related to the study drug in	Unclear

	at the end of the trial). Secondary efficacy end points included the ADAS-cog, Mini Mental State Examination (MMSE), executive clock-drawing task (CLOX 1/2), Executive Interview (EXIT25), Disability Assessment for Dementia (DAD), and Clinical Dementia Rating-Sum of Boxes (CDR-SB). MMSE and CDR-SB were performed at baseline and at weeks 12 and 24/trial end; EXIT25, CLOX, and DAD were performed at baseline and at week 24/trial end.		29.5% of cases for donepezil and 26.4% of cases for placebo. The most common AEs in this category were diarrhea (donepezil, 8.1%; placebo, 3.1%) and nausea (donepezil, 7.1%; placebo, 2.4%). Eleven deaths occurred in the donepezil group (1.7%), similar to rates previously reported for donepezil trials in VaD, whereas no deaths occurred in the placebo group.	
Wilkinson et al (2010)	*Participants:* In the original trials, participants were men and women aged at least 40 years with a diagnosis of probable or possible VaD of at least 3 months' duration, Mini-Mental State Examination (MMSE) scores between 10 and 26, and with clinical and radiological evidence of cerebrovascular disease were included. Patients with hypertension, diabetes, cardiac disease or stroke were included provided these conditions had been stable for at least 3 months. All patients who completed the double-blind studies were eligible for entry into the open-label study. *Intervention:* Donepezil 5 mg/day and donepezil 10 mg/day. In the open-label extension, all patients received donepezil	N=885 (303 donepezil 5 mg/day, 281 donepezil 10 mg/day, 301 placebo). 30 week open-label extension study	Of the 1219 patients enrolled in the two double-blind studies, 885 (72.6%) continued into the open-label phase. In total, 707 (79.9%) of these 885 patients completed the 30-week open-label extension. Improvements in cognitive function in patients with VaD gained during the 24-week double-blind treatment with donepezil were maintained above baseline during a further 30 weeks of open-label treatment. During the 30-week open-label phase, a total of 108 (12.2%) subjects discontinued prematurely due to AEs: 43 (39.8%) originally randomised to placebo, 36 (33.3%) to 5 mg/day donepezil and 29 (26.9%) to 10 mg/day donepezil.	NA – Open label extension study

	5 mg/day for the first 6 weeks and 10 mg/day thereafter. *Comparator*: Placebo. N/A for open-label study *Outcome:* The primary efficacy measure was the Alzheimer's disease Assessment Scale- cognitive subscale (ADAScog), a measure of cognitive function. Secondary efficacy outcome measures were the Clinical Dementia Rating-Sum of the Boxes (CDR-SB), a measure of overall disease severity; the MMSE, a second measure of cognitive function; and the Alzheimer's Disease Functional Assessment and Change Scale (ADFACS), a functional test assessing the patient's ability to perform instrumental activities of daily living (ADLs) and basic ADLs. Safety results were reported for all patients who received open-label treatment.			

Risk of Bias: SRs

Author (year)	Risk of Bias				
	Inclusion criteria	Searches	Review Process	Quality assessment	Synthesis
Kavirajan (2007)	☺	☺	☺	☺	☺

RCTs

Study	RISK OF BIAS					
	Random allocation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting
Archus (2007)	?	?	?	☺	☺	?
Ballard (2008)	☺	?	☺	☺	☺	?
Dichgans (2008)	☺	☺	?	?	☺	?
Román (2010)	?	?	?	?	☹	?
Wilkinson (2010)	N/A – Open label extension study					

☺Low Risk ☹High Risk ? Unclear Risk

Search Details

Source	Search Strategy	Number of hits	Relevant evidence identified
SRs and Guidelines			
NICE	"vascular dementia" OR VAD OR VD	29	2
DARE	1 MeSH DESCRIPTOR Dementia, Vascular EXPLODE ALL TREES 16 2 (vascular adj5 dementia) IN DARE 59 3 (vd) IN DARE 9 4 (VaD) IN DARE 8 5 (vascular adj (cognitive adj5 impairment)) IN DARE 7 6 #1 OR #2 OR #3 OR #4 OR #5 74	74	1
Primary studies			
CENTRAL	#1 "vascular dementia":ti,ab,kw or "cerebrovascular dementia:ti,ab,kw and "vascular cognitive impairment":ti,ab,kw 423 edit delete #2 (donepezil):ti,ab,kw or (galantamine):ti and (rivastigmine):au and (memantine):ti,ab,kw and "cholinesterase inhibitor":ti,ab,kw 651 edit delete #3 MeSH descriptor Dementia, Vascular, this term only 211 edit delete #4 MeSH descriptor Cholinesterase Inhibitors explode all trees 773 edit delete #5 (#1 OR #3) 473 edit delete #6 (#2 OR #4) 1203 edit delete #7 (#5 AND #6) 52 edit delete	9	5
PsycINFO	1. PsycINFO; VASCULAR DEMENTIA/; 1601 results. 2. PsycINFO; "vascular dementia".ti,ab; 2255 results. 3. PsycINFO; "vascular cognitive impairment".ti,ab; 174 results. 4. PsycINFO; (cerebrovascular adj2 (disease OR	29	

	disorder)).ti,ab; 1290 results. 5. PsycINFO; 1 OR 2 OR 3 OR 4; 3847 results. 6. PsycINFO; CHOLINESTERASE INHIBITORS/; 1375 results. 7. PsycINFO; "acetylcholinesterase inhibitors".ti,ab; 304 results. 8. PsycINFO; Donepezil.ti,ab; 1020 results. 9. PsycINFO; galantamine.ti,ab; 432 results. 10. PsycINFO; galanthamine.ti,ab; 55 results. 11. PsycINFO; rivastigmine.ti,ab; 472 results. 12. PsycINFO; memantine.ti,ab; 754 results. 13. PsycINFO; 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12; 3031 results. 14. PsycINFO; 5 AND 13; 122 results. 15. PsycINFO; CLINICAL TRIALS/; 6188 results. 17. PsycINFO; groups*.ti,ab; 327742 results. 16. PsycINFO; random*.ti,ab; 110794 results. 19. PsycINFO; (singl* adj3 blind*).ti,ab; 1363 results. 20. PsycINFO; EXPERIMENTAL DESIGN/; 8287 results. 21. PsycINFO; controlled.ti,ab; 69144 results. 22. PsycINFO; (clinical adj3 study).ti,ab; 6892 results. 18. PsycINFO; (doubl* adj3 blind*).ti,ab; 16478 results. 23. PsycINFO; trial.ti,ab; 58343 results. 25. PsycINFO; 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24; 503424 results. 24. PsycINFO; "treatment outcome clinical trial".md; 22296 results. 26. PsycINFO; 14 and 25; 72 results. 27. PsycINFO; 26 [Limit to: Publication Year 2007-Current]; 29 results.		
MEDLINE	28. MEDLINE; VASCULAR DEMENTIA/; 3647 results. 30. MEDLINE; "vascular cognitive impairment".ti,ab; 359 results.	75	

	31. MEDLINE; “cerebrovascular dementia”.ti,ab; 6 results. 29. MEDLINE; "vascular dementia".ti,ab; 3900 results. 32. MEDLINE; 28 OR 29 OR 30 OR 31; 15892 results. 33. MEDLINE; CHOLINESTERASE INHIBITORS/; 15662 results. 35. MEDLINE; Donepezil.ti,ab; 1894 results. 34. MEDLINE; "acetylcholinesterase inhibitors".ti,ab; 1092 results. 37. MEDLINE; galanthamine.ti,ab; 405 results. 38. MEDLINE; rivastigmine.ti,ab; 979 results. 36. MEDLINE; galantamine.ti,ab; 866 results. 39. MEDLINE; memantine.ti,ab; 1748 results. 40. MEDLINE; 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39; 18696 results. 41. MEDLINE; 32 AND 40; 355 results. 42. MEDLINE; "randomized controlled trial".pt; 332813 results. 43. MEDLINE; "controlled clinical trial".pt; 84707 results. 45. MEDLINE; placebo.ab; 137953 results. 46. MEDLINE; "drug therapy".fs; 1552470 results. 47. MEDLINE; randomly.ab; 181852 results. 48. MEDLINE; trial.ab; 257338 results. 49. MEDLINE; groups.ab; 1184920 results. 50. MEDLINE; 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49; 2985946 results. 44. MEDLINE; randomi?ed.ab; 297228 results. 51. MEDLINE; 41 and 50 [Limit to: Publication Year 2007-Current]; 86 results.		
EMBASE	1. EMBASE; "vascular dementia".ti,ab; 5452 results. 2. EMBASE; "cerebrovascular dementia".ti,ab; 113 results.	67	

	3. EMBASE; "vascular cognitive impairment".ti,ab; 564 results. 4. EMBASE; 1 OR 2 OR 3; 5922 results. 5. EMBASE; CHOLINESTERASE INHIBITOR/ OR DONEPEZIL/ OR GALANTAMINE/ OR RIVASTIGMINE/; 22329 results. 6. EMBASE; "acetylcholinesterase inhibitors".ti,ab; 1410 results. 7. EMBASE; donepezil.ti,ab; 2706 results. 8. EMBASE; galantamine.ti,ab; 1235 results. 9. EMBASE; galanthamine.ti,ab; 527 results. 10. EMBASE; rivastigmine.ti,ab; 1442 results. 11. EMBASE; memantine.ti,ab; 2499 results. 12. EMBASE; MEMANTINE/; 5622 results. 13. EMBASE; 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12; 26047 results. 14. EMBASE; 4 AND 13; 568 results. 15. EMBASE; random*.tw; 741241 results. 16. EMBASE; factorial*.tw; 19172 results. 17. EMBASE; placebo*.tw; 177117 results. 18. EMBASE; (crossover* OR cross-over*).tw; 61864 results. 19. EMBASE; (doubl* adj3 blind*).tw; 129475 results. 20. EMBASE; (singl* adj3 blind*).tw; 14296 results. 21. EMBASE; assign*.tw; 206249 results. 22. EMBASE; allocat*.tw; 69373 results. 23. EMBASE; volunteer*.tw; 158075 results. 24. EMBASE; CROSSOVER PROCEDURE/; 34521 results. 27. EMBASE; RANDOMIZED CONTROLLED TRIAL/; 326003 results.		

	28. EMBASE; 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27; 1220385 results. 25. EMBASE; DOUBLE-BLIND PROCEDURE/; 109963 results. 26. EMBASE; SINGLE-BLIND PROCEDURE/; 16165 results. 29. EMBASE; 14 AND 28; 161 results. 30. EMBASE; 29 [Limit to: Publication Year 2007-Current]; 67 results.		
Summary	**NA**	**NA**	

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