CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

MOOD, COGNITION AND FATIGUE FOLLOWING STROKE

EVIDENCE TABLES

Vascular Cognitive Impairment: Pharmacological Therapy

Update 2019

Lanctôt KL, Swartz RH (Writing Group Chairs) on Behalf of the Canadian Stroke Best Practice Recommendations Mood, Cognition and Fatigue following Stroke Writing Group and the Canadian Stroke Best Practice and Quality Advisory Committee, in collaboration with the Canadian Stroke Consortium

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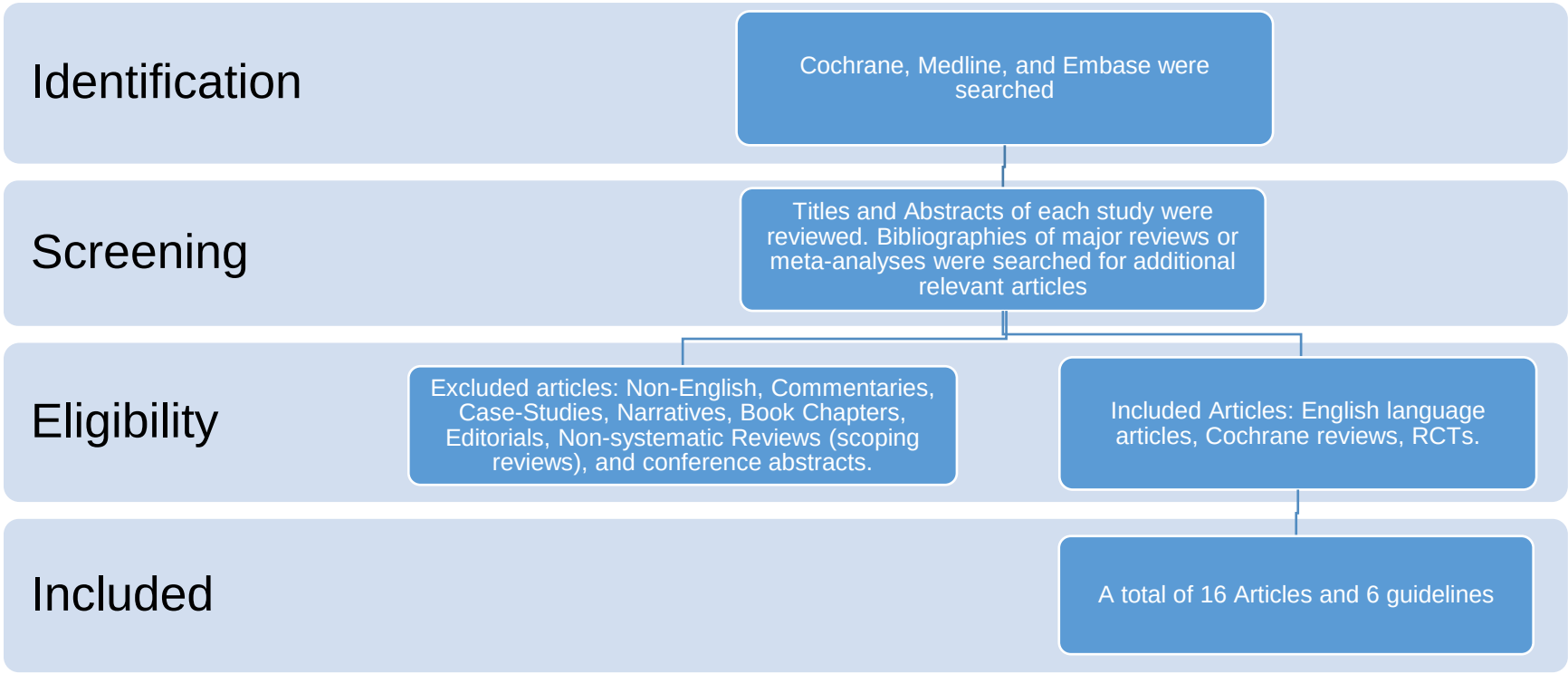
Search Strategy



The Medline, Embase, PsycInfo, and Cochrane databases were searched using the terms [stroke OR cerebrovascular disorders] and [cognition OR neuropsychology OR mild cognitive impairment OR cognitive training OR cognitive rehabilitation]. The title and abstract of each article was reviewed for relevance. Bibliographies were reviewed to find additional relevant articles. Articles were excluded if they were: non-English, commentaries, case-studies, narrative, book chapters, editorials, non-systematic review, or conference abstracts. Additional searches for relevant best practice guidelines were completed and included in a separate section of the review. A total of 16 articles and 6 guidelines were included and were separated into categories designed to answer specific questions.

Published Guidelines

Guideline	Recommendations
Stroke Foundation. Clinical Guidelines for Stroke Management 2017. Melbourne Australia. (Part 5)	None
Winstein CJ, Stein J, Arena R, Bates B, Cherney LR, Cramer SC, Deruyter F, Eng JJ, Fisher B, Harvey RL, Lang CE, MacKay-Lyons M, Ottenbacher KJ, Pugh S, Reeves MJ, Richards LG, Stiers W, Zorowitz RD; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Quality of Care and Outcomes Research. **Guidelines for adult stroke rehabilitation and recovery: a guideline for healthcare professionals from the American Heart Association/American Stroke Association.** ***Stroke* 2016;47:e98–e169.**	The usefulness of donepezil in the treatment of poststroke cognitive deficits is not well established. Class IIb; LOE B The usefulness of rivastigmine in the treatment of poststroke cognitive deficits is not well established. Class IIb: LOE B The usefulness of antidepressants in the treatment of poststroke cognitive deficits is not well established. Class IIb; LOE B The usefulness of dextroamphetamine, methylphenidate, modafinil, and atomoxetine in the treatment of poststroke cognitive deficits is unclear. Class IIb; LOE C
Intercollegiate Stroke Working Party. National clinical guideline for stroke, *5th* Edition. London: Royal College of Physicians, 2016.	None
Gorelick PB, Scuteri A, Black SE, DeCarli C, Greenberg SM, Iadecola C, Launer LJ, Laurent S, Lopez OL, Nyenhuis D, Petersen RC, Schneider JA, Tzourio C, Arnett DK, Bennett DA, Chui HC, Higashida RT, Lindquist R, Nilsson PM, Roman GC, Sellke FW, Seshadri S; on behalf of the American Heart Association Stroke Council, Council on Epidemiology and Prevention, Council on Cardiovascular Nursing, Council on Cardiovascular Radiology and Intervention, and Council on Cardiovascular Surgery and Anesthesia. **Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association.** ***Stroke* 2011;42:2672–2713.**	1. Donepezil can be useful for cognitive enhancement in patients with VaD *(Class IIa; Level of Evidence A).* 2. Administration of galantamine can be beneficial for patients with mixed Alzheimer disease/VaD *(Class IIa; Level of Evidence A).* *3.* The benefits of rivastigmine and memantine are not well established in VaD *(Class IIb; Level of Evidence A).*
National Stroke Foundation. Clinical Guidelines for Stroke Management 2010 Recommendations. Melbourne Australia.	None
Scottish Intercollegiate Guidelines Network (SIGN). Management of patients with stroke: Rehabilitation, prevention and management of complications, and	None

Guideline	Recommendations
discharge planning: A national clinical guideline, 2010. Edinburgh, Scotland.	
VA/DoD clinical practice guideline for the management of stroke rehabilitation 2010.	**Use of drugs to improve cognitive impairment** 1. Consider using acetylcholinesterase inhibitors (AChEIs), specifically galantamine, donepezil, and rivastigmine, in patients with vascular dementia or vascular cognitive impairment in the doses and frequency used for Alzheimer's disease. 2. Consider using the NMDA receptor inhibitor memantine (Namenda) for patients with vascular dementia (VaD) or vascular cognitive impairment (VCI). [B] 3. The use of conventional or atypical antipsychotics for dementia-related psychosis or behavioral disturbance should be used with caution for short term, acute changes. 4. Recommend against centrally acting a2-adrenergic receptor agonists (such as clonidine and others) and a1-receptor antagonists (such as prazosin and others) as antihypertensive medications for stroke patients because of their potential to impair recovery. [D] 5. Recommend against the use of amphetamines to enhance motor recovery following stroke. [D]

Evidence Tables

Cholinesterase Inhibitors

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Donepezil					
Chang et al. 2011 **Korea** **RCT**	CA: ☑ Blinding: Patient ☑ Assessor☑ ITT: ☒	14 patients, aged 18-75 years, recovering from first-ever stroke, (right hemisphere lesion), with stroke onset of >3 months and signs of cognitive impairment, based on Mini-Mental Status Examination (MMSE) scores 10-26, and a Clinical Dementia Rating (CDR) of 0.5 to 2.0. Mean age was 55 years, 64% were male. Time from stroke onset ranged from 4-40 months.	Patients were randomized to receive 5 mg donepezil daily, or matching placebo for 4 weeks. Assessment of cognitive function was performed before, immediately after and one month after treatment using the MMSE, Rey-Osterreith Complex Figure Test (ROCFT), and the Verbal Learning Test (VLT). Functional MRI was performed before and after treatment.	**Primary Outcome:** Improvement in measures of cognitive function	Mean baseline MMSE scores were 24.2 and 24.8 for patients in the donepezil and placebo groups, respectively. Patients in the donepezil group demonstrated significantly greater improvements in mean MMSE scores over the study period, compared with patients in the placebo group ($p<0.01$). There were no significant differences between groups over time in mean ROCFT or VLT change scores. Patients in the donepezil group showed significantly greater increased activation in both prefrontal areas, both inferior frontal lobes, and in the left inferior parietal lobe on fMRI, following treatment, compared with patients in the placebo group.
Roman et al. 2010 **USA** **RCT**	CA: ☒ Blinding: Patient ☑ Assessor☑ ITT: ☑	974 patients, 35-94 years with possible or probable vascular dementia with previous stroke, but who had been stroke-free for ≥3 months, had not taken acetylcholinesterase inhibitors or memantine for at least 6 weeks. Mean age was 73 years, 57% were male. 74% of those screened for eligibility were included in the study.	Participants were randomized to receive donepezil (5mg/day; n=648) or placebo (n=326), for 24 weeks.	**Primary outcomes**: Changes in the Vascular Alzheimer's Disease Assessment Scale cognitive subscale (V-ADAS-cog) and the Clinician's Interview-Based Impression of Severity Plus version (CIBIS-Plus). **Secondary outcomes**: Mental State Examination (MMSE), clock drawing task, Executive Interview (EXIT25), Disability Assessment for Dementia (DAD), and the Clinical Dementia Rating – Sum of Boxes (CDR-SB).	At the end of treatment, participants in the donepezil group demonstrated significantly greater improvement on the V-ADAS-cog ($p<0.01$). The two groups did not differ significantly in terms of improvement in global function rated on the CIBIS-Plus ($p>0.05$). At the end of treatment, participants in the donepezil group demonstrated significantly greater improvement on MMSE ($p=0.03$). There were no significant differences between groups for any of the secondary outcomes. The number of adverse events were similar for those receiving donepezil (80.7%) and placebo (77.6%) and were generally mild-moderate in severity. Whereas no deaths occurred in the placebo group, 11 participants in the donepezil group died during the study period, with 3 deaths determined to be possibly related to the use of donepezil. Lost to follow-up: donepezil =17.4%; placebo=13.2%.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Black et al. 2003 **Canada** **RCT**	CA: ☒ Blinding: Patient ☑ Assessor☑ ITT: ☑	603 stroke patients, aged ≥40 years with possible (29.5%) or probable (70.5%) vascular dementia of >3 months duration. mean age, 73.9 years; 55.2% men. Patients with neurodegenerative disorders other than vascular dementia, MMSE>26 or <10, and diagnosis with a major depression or other psychiatric disorder, were excluded. 63% of those screened for eligibility were included in the study.	Participants were randomized to receive 5 mg donepezil (n=198), 10 mg (n=206) donepezil daily or placebo (n=199) for 24 weeks.	**Primary outcomes**: Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog) and the Clinician's Interview-Based Impression of Severity Plus version (CIBIS-Plus). **Secondary outcomes**: Mental State Examination (MMSE), Sum of the Boxes of the Clinical Dementia Rating (CDR-SB), Alzheimer's Disease Functional Assessment and Change Scale (ADFACS).	Over the 24- week study period, participants in both the 5 and 10 mg donepezil groups demonstrated significantly greater improvement on the ADAS-cog, compared with the placebo group (p<0.01 and p<0.001, respectively). Those in the 5-mg group, but not the 10 mg group, were also rated as having made significantly greater improvement in global function (CIBIS-Plus) than those in the placebo group (p=0.01). Significantly greater improvements in mean MMSE scores was demonstrated in patients in both 5 and 10 mg groups, compared with control (p<0.05 and p<0.001, respectively) The proportion of patients with treatment-emergent events was significantly higher in the 10/mg treatment group than in the placebo group (94.7% vs. 88.4%, p=0.03). The 5mg and placebo groups did not differ significantly in the rate of treatment-emergent events (88.9% vs. 88.4%, p>0.05). In General, adverse events were mild-moderate and affected the digestive system, musculoskeletal system or nervous system. Lost to follow-up: donepezil 5m/day=18.7%, donepezil 10m/day=28.2%, placebo=15.1%.
Donepezil 308 Study Group Wilkinson et al. 2003 **USA** **RCT**	CA: ☒ Blinding: Patient ☑ Assessor☑ ITT: ☑	616 stroke patients with probable (76%) or possible (24%) vascular dementia of >3 months duration. Mean age 75.0 years, 40% women. Patients with neurodegenerative disorders other than vascular dementia age<40, MMSE>26 or <10, uncontrolled hypertension, diabetes or cardiac disease, recurrent stroke within the past 3 months, or diagnosis with a psychiatric disorder, were excluded. 69% of those screened for eligibility were included in the study.	Participants were randomized to receive 5 mg donepezil (n=198), 10 mg (n=206) donepezil daily or placebo (n=199) for 24 weeks.	**Primary outcomes**: Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog) and the Clinician's Interview-Based Impression of Severity Plus version (CIBIS-Plus). **Secondary outcomes**: Mental State Examination (MMSE), Sum of the Boxes of the Clinical Dementia Rating (CDR-SB), Alzheimer's Disease Functional Assessment and Change Scale (ADFACS).	At the end of the study period, participants in both the 5ml and 10ml donepezil groups demonstrated significantly greater improvement on the ADAS-cog than did those in the placebo group (least squares mean change= -0.75 [±0.33] and -2.65 [±0.48] vs. -0.10 [±0.39], respectively, both at p<0.01). Compared to placebo, donepezil was also associated with a significantly better rating on the CIBIC-Plus at the end of the treatment period (p=0.004 for 5ml/day and p=0.047 for 10ml/day). The rate of treatment-emergent adverse events was 86.5% in the placebo group, 90.4% in the 5ml/day donepezil group, and 91.6% in the 10ml/day donepezil group. Diarrhea, Nausea, abnormal dreams, leg cramps, and rhinitis were each significantly more frequent in the active treatment groups. Lost to follow-up: donepezil 5m/day=19.2%, donepezil 10m/day=24.7%, placebo=16.6%.
Rivastigmine					

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Birks et al. 2013 **UK** **Cochrane Review**	N/A	3 RCTs (n=800) examining the use of rivastigmine for the treatment of vascular cognitive impairment, vascular dementia, or mixed dementia. The percentage of participants recovering from stroke within these trials was 100% (Narasimhalu et al. 2010), 70% (Mok et al 2007) and 66% (Ballard et al. 2008)	In the 3 trials, participants were randomized to receive 1) 3-12 mg rivastigmine or placebo for 24 weeks; 2) maximum dose of 6 mg or placebo for 26 weeks and 3) 6-9 mg or placebo for 24 weeks	**Primary outcomes:** Measures of global impression, functional performance, behavioural disturbance, and cognitive function	No pooling of results was possible for any outcomes A single study (n=710) demonstrated a significant treatment effect in favour of rivastigmine in cognitive response (change in Mini Mental State Exam score: MD= 0.06, 95% CI 0.11 to 1.09, p=0.02, and change in Vascular Dementia Assessment Scale from baseline MD= -1.3, 95% CI-2.62 to 0.02, p=0.05. No significant effects of treatment were reported for either of the other two trials (n=40 and 50) with respect to cognition, neuropsychiatric symptoms, function, or global performance.
Narasimhalu et al. 2010 **Singapore** **RCT**	CA: ☑ Blinding: Patient ☑ Assessor☑ ITT: ☑	50 patients, aged 55– 85 years, with cognitive impairment, without dementia, recruited 3 months following ischemic stroke. Mean age was 69 years, 66% were women. Mean MMSE baseline score was 23.8 32.5% of those screened for eligibility were included in the study.	Participants were randomized 1:1 to receive rivastigmine (6-9 mg daily, as tolerated) or placebo for 24 weeks.	**Primary outcomes**: Changes in The Ten-Point Clock Test and the Color Trails Test 1 and 2. **Secondary outcomes**: Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog), the AD Cooperative Study Assessment of Daily Living (ADCS-ADL), and the Geriatric Depression Scale (GDS).	At 24 weeks, there were no significant between group differences for either primary outcome. Mean change from baseline (rivastigmine vs. placebo): Clock drawing test 0.1 vs. 0.5, p=0.39; Color Trails 1 -12.7 vs. -21.4, p=0.53; Color Trails Test 2 -16.1 vs.-0.6, p=0.09. There were no significant differences between groups for any of the secondary outcomes, with the exception of the verbal fluency subscale of the ADAS-cog, for which participants in the treatment group demonstrated significantly more improvement (mean change from baseline was 1.7 vs. 0.03, p=0.02). Losses to follow-up were 28% in both groups.
Moretti et al. 2003 **Italy** **RCT**	CA: ☒ Blinding: Patient ☒ Assessor☒ ITT: ☒	208 patients, aged 65-80 years, with probable vascular dementia (assessed using DSM-IV criteria) and evidence of moderate-to-severe ischemic white matter changes and at least 1 lacunar infarct, with MMSE scores ≥14. Mean age was 75.7 years.	Participants were randomized 1:1 to receive 3-6mg rivastigmine or 100 mg aspirin daily for one year.	**Primary outcomes:** The Clinical Dementia Rating (CDR), the Mini Mental State Exam (MMSE), the Ten-Point Clock (TPC) Test, word fluency phonological tests, the Behavioral Pathology in AD Rating Scale (BEHAVE-AD), the Geriatric Depression Scale (GDS), and the Cumulative Illness Rating Scale (CIRS).	At the end of the study, significant deterioration was observed for participants in both groups in terms of scores on the MMSE, phonological fluency, and the Ten-point Clock Test. Participants randomized to receive rivastigmine demonstrated significantly less deterioration on both the MMSE and the Ten-point Clock Test (p<0.05). Participants in the rivastigmine group also demonstrated significantly more improvement on the GDS and on the BEHAVE-AD total score and each of the subscales except delusions (all at p<0.001). Transitory nausea was reported by 21% and 27% of patients in the rivastigmine and aspirin groups, respectively. Muscle contraction were reported by 14% of those in the rivastigmine group whereas 25% of those in the aspirin group reported heartburn.
Galantamine					

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Auchus et al. 2007 (GAL-INT-26 Study Group) **USA** **RCT**	CA: ☒ Blinding: Patient ☑ Assessor☑ ITT: ☑	788 patients, 40-90 years with probable vascular dementia, confirmed by MRI. MMSE score 10-26, and a score of ≥ 12 on the Alzheimer's Disease Assessment Scale–Cognitive subscale (ADAS-cog/11). Mean age was 72.3 years, 64% were men. Mean MMSE score was 20.3. 45.3% of those screened for eligibility were included in the study.	Patients were randomized to receive 8 or 12 mg galantamine (n=396) b.i.d. or placebo (n=390) for 26 weeks.	**Primary outcomes:** Alzheimer's Disease Assessment Scale–Cognitive subscale (ADAS-cog/11) and the Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory (ADCS-ADL) total score.	91% of participants had cardiovascular risk factors, including stroke. The mean Hachinski score was 11.7. At the end of 26 weeks, patients treated with galantamine had experienced significantly greater improvement in ADAS-cog/11(mean change =-1.8 vs. -0.3, p<0.001). At 26 weeks, there was no difference between groups in ADCS-ADL score (mean change =0.7 vs. 1.3, p=0.783). 77% of patients in the galantamine group completed the trial vs. 85% in the placebo group. More adverse events were reported in the galantamine group (14% vs. 7%). More adverse events in the galantamine group led to treatment discontinuations (13% vs. 6%). receiving
Erkinjuntti, et al. 2002 **Finland** **RCT**	CA: ☒ Blinding: Patient ☑ Assessor☑ ITT: ☑	592 patients with probable vascular dementia or possible Alzheimer's disease and evidence of stroke within the previous 12 months, MMSE score 10–25, and ≥ 12 on the Alzheimer's disease assessment scale cognitive subscale (ADAS-cog). Mean age was 75 years, 47% were male. 79% of those screened for eligibility were included in the study.	Participants were randomized to receive 24 mg galantamine (n=396) or placebo (n=196) for 6 months.	**Primary outcomes**: Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog) and the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus). **Secondary outcomes**: An extended version of the ADAS-cog and the Neuropsychiatric Inventory.	Participants in the galantamine group demonstrated significantly more improvement on the ADAS-cog (mean change = -1.7±0.4 vs. 1.0±0.5, p<0.001). Significantly more patients in the galantamine group improved or reported no change on the CIBIC-plus (213±74% vs. 95%±59%, p=0.001) at the end of the study period. The galantamine group also demonstrated significantly more improvement on the extended version of the ADAS-cog (p<0.0001) and the Neuropsychiatric Inventory (p=0.016). The rate of adverse events was 20% in the galantamine group and 8% in the placebo group. Most of the adverse events were reported to be mild to moderate in severity and of short duration. The most frequently reported adverse events were nausea and vomiting. Lost to follow-up: galantamine=25.8%; control=16.8%

Note: CA: Concealed Allocation; ITT: Intention-to-treat

MNDA Receptor Antagonists (Memantine)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
et al. 2002 **UK** **RCT**	CA: ☒ Blinding: Patient ☑ Assessor☑ ITT: ☑	579 individuals with probable vascular dementia, with onset at least one-year prior, with baseline MMSE scores of 10-22 Mild to moderate disease). Mean age was 75 years, 52% male. Mean MMSE score was 17.6. 69% of those screened for eligibility were included in the study.	Participants were randomized to receive 20 mg memantine (n=295) or placebo (n=284) daily for 28 weeks.	**Primary outcome**: Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) and the Clinical Global Impression of Change (CGI-C) **Secondary outcomes**: The Mini Mental State Exam (MMSE), the Gottfries-Brane-Steen Scale (GBS), and the Nurse's Observation Scale for Geriatric Patients (NOSGER).	Memantine was associated with significantly greater improvement on the ADAS-cog at the end of the 28-week study period (mean change =-1.75, 95% CI -3.02 to -0.49; p<0.01). There were no significant between group differences reported with respect to the CGI-C. Treatment-emergent adverse events occurred in 77% of those in the treatment group and 75% of those in the control group. The most common adverse events for patients in the memantine group were dizziness and constipation. Lost to follow-up: memantine=19%; placebo=20%
Orgogozo et al. 2002 **France** **RCT**	CA: ☒ Blinding: Patient ☑ Assessor☑ ITT: ☑	321 patients ≥60 years, with mild-moderate symptomatic vascular cognitive impairment of 6 months duration, a Modified Ischemic Score ≥5 and MMSE score 12-20. Mean age was 76.5 years, 49% were women. Mean MMSE score was 16.9. 79.7% of those screened for eligibility were included in the study.	Participants were randomized to receive a maximum dose of 20 mg memantine daily (n=165) or placebo (n=156) for 28 weeks.	**Primary outcome**: Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) and the Clinician's Interview Based Impression of Change (CIBIC-plus) **Secondary outcomes**: Mini Mental State Exam (MMSE), Gottfries-Brane-Steen Scale (GBS), and Nurse's Observation Scale for Geriatric Patients (NOSGER).	At the end of the study period, participants who received memantine gained an average of 0.4 points on the ADAS-cog, whereas the placebo group mean score had declined by 1.6 points, (a difference of 2.0 points, 95% CI 0.49 to 3.60). Although a greater number of participants in the memantine group were rated as improved or stable on the CIBIC-Plus (60% vs. 52%), this difference was not significant (p=0.227). The Mean change in MMSE scores over the study period was significantly greater for participants in the memantine group (1.75 vs. 0.52, p=0.003) Adverse events were reported by 76% of those in the memantine group and 74% of those in the placebo group. Serious adverse events were reported by 23% and 26% for the memantine and placebo groups, respectively. The most common adverse events were agitation, confusion, and dizziness. Lost to follow-up: memantine=43.6%; placebo=39.1%

Note: CA: Concealed Allocation; ITT: Intention-to-treat

Other Pharmacological Agents

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Actovegin					
Guekht et al. 2017 **Russia** **RCT** ***A Randomized Trial of Efficacy, 12 Months International Double-Blind Actovegin (ARTEMIDA)***	CA: ☑ Blinding: Patient ☑ Assessor☑ ITT: ☑	503 patients, ≥60 years, with acute onset of ischemic stroke, with a NIHSS score of 3–18, MoCA score ≤25, and without dementia. Mean age was 70 years, 48% were male. Mean baseline NIHSS score was 5.4.	Patients were randomized to receive either intravenous Actovegin (2,000 mg/250 mL daily for ≤20 infusions, followed by 1,200 mg/d orally or placebo for 6 months. Actovegin and placebo were then discontinued, and patients were followed up for an additional 6 months	**Primary outcome:** Change in Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog+) from baseline to 6 months **Secondary outcomes:** Change in ADAS-cog+ from baseline to 3 and 12 months, MoCA, incidence of dementia	At baseline, the mean (SD) ADAS-cog+ score was similar between Actovegin and placebo groups (29.4 vs.29.9, respectively). The mean decrease from baseline in ADAS-cog+ at month 6 was significantly greater for Actovegin (−6.8 vs.-4.6; MD= −2.3; 95% CI, −3.9, −0.7; *p*=0.005). The mean decrease from baseline in ADAS-cog+ at month 3 was not significantly greater for Actovegin (−5.4 vs.-4.3, p>0.05), but was significant at 12 months (-8.2 vs. -4.5; MD=−3.7 95% CI, −5.5, −1.9, p<0.001). At 3, 6 and 12 months significantly more patients in the Actovegin group met the definition of responder (≥4-point improvement in ADAS-cog+ score from baseline). By 12 months, non-significantly fewer patients in the Actovegin group were diagnosed with dementia (8.7% vs. 12.7%). At 3, 6 and 12 months, the mean increase in MoCA scores was significantly greater patients in the Actovegin group. The incidence of treatment associated adverse events was similar between groups (37.9% for placebo vs. 35.6% for Actovegin.
Citicoline					
Alvarez-Sabin et al. 2013 **Spain** **RCT**	CA: ☒ Blinding: Patient ☒ Assessor☑ ITT: ☒	347 patients, ≥18 years with first-ever ischemic stroke and persistent neurological deficit. Mean age was 67.2 years, 57% were male. Median baseline NIHSS score was 14.	Participants were randomized to receive citicoline (1 g/day; n=172) or usual care (n=175) for 12 months.	**Primary outcome:** A neuropsychological battery was used to assess 6 domains of cognitive functioning: attention / executive function, language, memory, Spatial perception, motor speed, and temporal orientation.	At one year, the odds of having no cognitive impairment were higher for participants who received citicoline, after controlling for risk factors and stroke severity: Attention/executive function (OR=2.38, 95% CI 1.27 to 4.46, p=0.007) and temporal orientation (OR= 2.16, 95% CI 1.02 to 4.57, p<0.045). No significant between group differences were reported with respect to the other cognitive domains. Lost to follow-up: citicoline=38%; control=47%
Nimodipine					
Pantoni et al. 2005 **Italy**	CA: ☒ Blinding: Patient	230 patients, aged 55-87 years, with subcortical vascular dementia, of 6 months to 2	Participants were randomized to receive nimodipine (90 mg/day;	**Primary outcome**: Sandoz Clinical Assessment Geriatric scale (SCAG) score	There was no significant difference in the proportion of patients with a SCAG change of >5 over the study period (p=0.29). 36.2% of patients in the nimodipine group

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
RCT	☑ Assessor☑ ITT: ☑	years duration with MMSE scores 12-24, a Global Deterioration Score of 3-5 and Hachinski ischemic score ≥4. Mean age was 75.3 years, 60% were male. 87% of those screened for eligibility were included in the study.	n=124) or placebo (n=118) for 12 months.	change of >5 from baseline at one year. **Secondary outcomes**: Global Deterioration Score (GDS), Set Test, Digit Span, Mini Mental State Exam (MMSE), Zahlen-Verbindungs Test (ZVT-G), Hamilton Depression Rating Scale (HDRS).	demonstrated an improvement compared with 29.1% in the placebo group. The proportion of patients with MMSE scores that worsened by ≥ 3 points at the end of treatment was significantly lower in the nimodipine group (28.1%vs. 50.5%, pp<0.01). Fewer patients in the nimodipine group were classified as severe by GDS (18.2% vs. 33.9%, p<0.05). The risk of adverse events was higher in the placebo group (180 vs. 135; RR= 1.29, 95% CI 1.03 to 1.61). Lost to follow-up: nimodipine=13.7%; placebo=34.7%
Antidepressants (SSRIs)					
Jorge et al. 2010 **USA** **RCT**	CA: ☒ Blinding: Patient ☑ Assessor☑ ITT: ☑	129 stroke patients aged 50-90 years, within 3 months following stroke who were not depressed (Hamilton Scale for Depression <12), who were participants of a study of post-stroke depression. 71.5% of those assessed for eligibility were included in the study.	Participants were randomized within 3 months of stroke to receive escitalopram (n=43), placebo (n=45), or non-blinded problem-solving therapy (n=41) for one year. Escitalopram was prescribed at a dose of 10mg or 5 mg per day for participants greater than or less than 65 years of age, respectively.	**Primary outcome:** The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Trail-Making Test Parts A and B, Controlled Oral Word Association, the Wechsler Adult Intelligence Scale-III, the Stroop test, and the Structured Clinical Interview for DSM-IV.	At the end of the study period, participants who received escitalopram demonstrated significantly greater improvement on the RBANS total score than those who received placebo (mean change=9.9 vs. 4.0, p=0.02) or problem-solving therapy (mean change=9.9 vs. 1.9, p<0.01), controlling for stroke mechanism and change in depression symptomology. There were no significant differences between groups in change scores for other outcomes over the study period. No significant between group differences were reported with respect to the frequency of aggregate or specific adverse events.
Narushima et al. 2007 **USA** **RCT**	CA: ☒ Blinding: Patient ☑ Assessor☑ ITT: ☑	47 patients admitted consecutively to a rehabilitation hospital within 6 months of stroke, who were participants of an antidepressant trial (Robinson et al. 2000). Mean MMSE score was 27.	Participants were randomized to receive either fluoxetine (10mg/d gradually increased to 40 mg/day, n=19) or nortriptyline (dose of 25 mg/day gradually increased to 100 mg/day, n=11) or placebo (n=17) for 12 weeks. Participants then crossed-over to 12 weeks of placebo treatment. Measures of executive function were assessed 2 year after treatment	**Primary outcomes:** Controlled Oral Word Association (COWA), Wisconsin Card Sorting Test Perseverative Errors (WCST–PE), Wechsler Adult Intelligence Scale–Revised	At the end of treatment there were no significant differences between groups in scores of executive function. Patients given active treatment (fluoxetine or nortriptyline) showed an improvement in executive performance after 21 months (p=0.03), whereas patients given placebo showed a significant decline (p=0.02). Mean change scores for COWA and WCST-PE between groups were significantly different (p<0.05). There was improvement in the antidepressant therapy group and decline in the placebo group. All but one patient who received placebo showed deterioration of executive function at 2 years.

Note: CA: Concealed Allocation; ITT: Intention-to-treat

Reference List

Alvarez-Sabin J, Ortega G, Jacas C, Santamarina E, Maisterra O, RIbo M, Molina C, Quintana M, Roman GC. Long-term treatment with citicoline may improve poststroke vascular cognitive impairment. *Cerebrovasc Dis* 2013;35:146-54.

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* 2007;69:448–58.

Birks J, McGuinness B, Craig D. Rivastigmine for vascular cognitive impairment. *Cochrane Database of Systematic Reviews* 2013; Issue 5. Art. No.: CD004744. DOI: 10.1002/14651858.CD004744.pub3

Black S, Roman GC, Geldmacher DS, et al. Efficacy and tolerability of donepezil in vascular dementia: positive results of a 24-week, multicenter, international, randomized, placebo-controlled clinical trial. *Stroke* 2003;34:2323-32.

Chang WH, Park YH, Ohn SH, Park CH, Lee PK and Kim YH. Neural correlates of donepezil-induced cognitive improvement in patients with right hemisphere stroke: a pilot study. *Neuropsychol Rehabil* 2011; 21: 502-14.

Erkinjuntti T, Kurz A, Gauthier S, Bullock R, Lilienfeld S, Damaraju V. Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: a randomised trial. *Lancet* 2002;359:1283-90.

Guekht A, Skoog I, Edmundson S, Zakharov V, Korczyn AD. ARTEMIDA Trial (A Randomized Trial of Efficacy, 12 Months International Double-Blind Actovegin): A Randomized Controlled Trial to Assess the Efficacy of Actovegin in Poststroke Cognitive Impairment. *Stroke* 2017; 48:1262-1270

Jorge RE, Acion L, Moser D, Adams HP Jr, Robinson RG. Escitalopram and enhancement of cognitive recovery following stroke. *Arch Gen Psychiatry* 2010;67:187-96.

Moretti R, Torre P, Antonello RM, Cazzato G, Brava A. Rivastigmine in subcortical vascular dementia: a randomized, controlled, open 12-month study in 208 patients. *Am J Alzheimers Dis Other Demen* 2003;18:265-72.

Narasimhalu K, Effendy S, Sim CH, et al. A randomized controlled trial of rivastigmine in patients with cognitive impairment no dementia because of cerebrovascular disease. *Acta Neurol Scand* 2010;121:217-24.

Narushima K, Paradiso S, Moser DJ, Jorge R, Robinson RG. Effect of antidepressant therapy on executive function after stroke. *Br J Psychiatry* 2007;190:260–265.

Orgogozo JM, Rigaud AS, Stoffler A, Mobius HJ, Forette F. Efficacy and safety of memantine in patients with mild to moderate vascular dementia: a randomized, placebo-controlled trial (MMM 300). *Stroke* 2002;33:1834-39.

Pantoni L, del Ser T, Soglian AG, et al. Efficacy and safety of nimodipine in subcortical vascular dementia: a randomized placebo-controlled trial. *Stroke* 2005;36:619-24.

Roman GC, Salloway S, Black SE, et al. Randomized, placebo-controlled, clinical trial of donepezil in vascular dementia: differential effects by hippocampal size. *Stroke* 2010;41:1213-21.

Wilcock G, Mobius HJ, Stoffler A. A double-blind, placebo-controlled multicentre study of memantine in mild to moderate vascular dementia (MMM500). *Int Clin Psychopharmacol* 2002;17:297-305.

Wilkinson D, Doody R, Helme R, et al. Donepezil in vascular dementia: a randomized, placebo-controlled study. *Neurol* 2003;61:479-86.