HEART & STROKE FOUNDATION | CANADIAN Stroke BEST PRACTICE RECOMMENDATIONS

CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Mood, Cognition and Fatigue Following Stroke

Evidence Tables

Vascular Cognitive Impairment: Pharmacological Therapy

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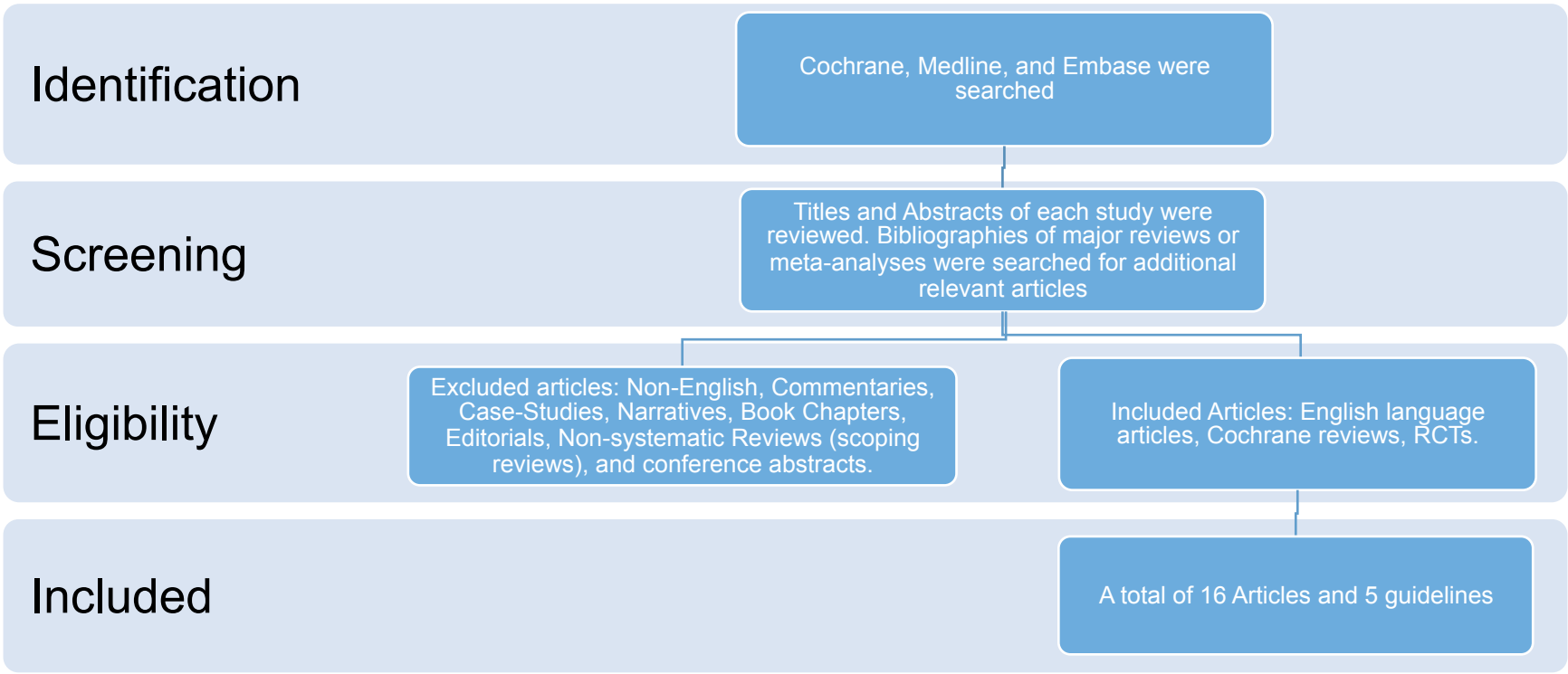
Search Strategy



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 5 guidelines were included and were separated into categories designed to answer specific questions.

Published Guidelines

Guideline	Recommendations
National Stroke Foundation. Clinical Guidelines for Stroke Management 2010 Recommendations. Melbourne Australia.	**Assessment of Cognition** 1. All patients should be screened for cognitive and perceptual deficits using validated and reliable screening tools (GPP). 2. Patients identified during screening as having cognitive deficits should be referred for comprehensive clinical neuropsychological investigations (GPP). **Attention and Concentration** 1. Cognitive rehabilitation can be used in stroke survivors with attention and concentration deficits (C). **Memory** 1. Any patient found to have memory impairment causing difficulties in rehabilitation or adaptive functioning should: • Be referred for a more comprehensive assessment of their memory abilities (GPP) • Have their nursing and therapy sessions tailored to use techniques which capitalize on preserved memory abilities (GPP) • Be assessed to see if compensatory techniques to reduce their disabilities, such as notebooks, diaries, audiotapes, electronic organizers and audio alarms, are useful (D) • Be taught approaches aimed at directly improving their memory (GPP) • Have therapy delivered in an environment as like the patient's usual environment as possible to encourage generalization (GPP) **Executive functions** 1. Patients considered to have problems associated with executive functioning deficits should be formally assessed using reliable and valid tools that include measures of behavioural symptoms (GPP). 2. External cues, such as a pager, can be used to initiate everyday activities in stroke survivors (C). In stroke survivors with impaired executive functioning, the way in which information is provided should be considered (C).
Intercollegiate Stroke Working Party. National clinical guideline for stroke, 4th edition. London: Royal College of Physicians, 2012.	**Cognitive impairments** 1. Interventions or patient management should be organised so that people with cognitive difficulties can participate in the treatments and are regularly reviewed and evaluated. 2. Every patient seen after a stroke should be considered to have at least some cognitive losses in the early phase. Routine screening should be undertaken to identify the patient's broad level of functioning, using simple standardised measures (eg Montreal Cognitive Assessment (MOCA)). 3. Any patient not progressing as expected in rehabilitation should have a more detailed cognitive assessment to determine whether cognitive losses are causing specific problems or hindering progress. 4. Care should be taken when assessing patients who have a communication impairment. The advice from a speech and language therapist should be sought where there is any uncertainty about these individuals' cognitive test results (see section 6.20). 5. The patient's cognitive status should be taken into account by all members of the multidisciplinary team when planning and delivering treatment. 6. Planning for discharge from hospital should include an assessment of any safety risks from persisting cognitive

Guideline	Recommendations
	impairments. 7. Patients returning to cognitively demanding activities (eg some work, driving) should have their cognition assessed formally beforehand. **Attention and concentration** 1. Any person after stroke who appears easily distracted or unable to concentrate should have their attentional abilities (eg focused, sustained and divided) formally assessed. 2. Any person with impaired attention should have cognitive demands reduced through: • having shorter treatment sessions • taking planned rests • reducing background distractions • avoiding work when tired. 3. Any person with impaired attention should: • be offered an attentional intervention (eg Time Pressure Management, Attention Process Training, environmental manipulation), ideally in the context of a clinical trial • receive repeated practice of activities they are learning. **Memory** 1. Patients who complain of memory problems and those clinically considered to have difficulty in learning and remembering should have their memory assessed using a standardised measure such as the Rivermead Behavioural Memory Test (RBMT). 2. Any patient found to have memory impairment causing difficulties in rehabilitation or undertaking activities should: • be assessed medically to check that there is not another treatable cause or contributing factor (eg delirium, hypothyroidism) • have their profile of impaired and preserved memory abilities determined (as well as the impact of any other cognitive deficits on memory performance, for example attentional impairment) • have nursing and therapy sessions altered to capitalise on preserved abilities • be taught approaches that help them to encode, store and retrieve new information, for example, spaced retrieval (increasing time intervals between review of information) or deep encoding of material (emphasising semantic features) • be taught compensatory techniques to reduce their prospective memory problems, such as using notebooks, diaries, electronic organisers, pager systems and audio alarms • have therapy delivered in an environment that is as similar to the usual environment for that patient as possible. **Executive Functioning** 1. Any person who appears to have adequate skills to perform complex activities but who fails to organise the tasks needed should be formally assessed for the dysexecutive syndrome, for example using the Behavioural Assessment of the Dysexecutive Syndrome (BADS). 2. Any person with an executive disorder and activity limitation should be taught compensatory techniques. This may include internal strategies (eg self-awareness and goal setting) and/or external strategies (eg use of electronic organisers or pagers, or use of written checklists) ideally in the context of a clinical trial. 3. When a patient's activities are affected by an executive disorder, the nature and effects of the impairment and ways of supporting and helping the patient should be discussed with others involved (eg family, staff).

Guideline	Recommendations
	Psychological Care 1. Interventions for individual disorders of mood or cognition should be applied within the framework of a stepped care and comprehensive model. 2. Patients with continuing disorders should be considered for comprehensive interventions tailored towards developing compensatory behaviours and the learning of adaptive skills. 3. Within Step 1 care all patients after stroke should be screened within 6 weeks of diagnosis, using a validated tool, to identify mood disturbance and cognitive impairment. 4. Any patient assessed as having a cognitive impairment should be considered for referral to a specialist in cognitive aspects of stroke. Patients identified as having cognitive impairment or mood disorder should be reassessed before discharge decisions are taken.
Scottish Intercollegiate Guidelines Network (SIGN). Management of patients with stroke: Rehabilitation, prevention and management of complications, and discharge planning: A national clinical guideline, 2010. Edinburgh, Scotland.	• A full understanding of the patient's cognitive strengths and weaknesses should be an integral part of the rehabilitation plan (GPP). • Stroke patients should have a full assessment of their cognitive strengths and weaknesses when undergoing rehabilitation or when returning to cognitively demanding activities such as driving or work (GPP). • Cognitive assessment may be carried out by occupational therapists with expertise in neurological care, although some patients with more complex needs will require access to specialist neuropsychological expertise (GPP). **Cognitive rehabilitation**: "There is not yet sufficient evidence to support or refute the benefits of cognitive rehabilitation for patients with problems of attention or memory. When cognitive problems are suspected and relatives report personality change, the patient can be referred to a clinical psychologist to provide assessment and where appropriate, psychological intervention which may include carer education and support" (page 22)
VA/DoD clinical practice guideline for the management of stroke rehabilitation 2010.	**Assessment of cognitive function** 1. Assessment of arousal, cognition, and attention should address the following areas: a. Arousal b. Attention deficits c. Visual neglect d. Learning and Memory deficits e. Executive function and problem-solving difficulties 2. There is insufficient evidence to recommend for the use of any specific tools to assess cognition. Several screening and assessment tools exist. (See Appendix B for standard screening instruments for cognitive assessment.) **Use of standardized assessments** 1. Recommend that all patients should be screened for depression and motor, sensory, cognitive, communication, and swallowing deficits by appropriately trained clinicians, using standardized and valid screening tools. [C] 2. If depression, or motor, sensory, cognitive, communication, or swallowing deficits are found on initial screening assessment, patients should be formally assessed by the appropriate clinician from the coordinated rehabilitation team. [C] **Non-drug therapies for cognitive impairment** 1. Recommend that patients be given cognitive re-training, if any of the following conditions are present:

Guideline	Recommendations
	a. Attention deficits [A] b. Visual neglect [B] c. Memory deficits [B] d. Executive function and problem-solving difficulties [C] 2. Patients with multiple areas of cognitive impairment may benefit from a variety of cognitive re-training approaches that may involve multiple disciplines. [C] 3. Recommend the use of training to develop compensatory strategies for memory deficits in post-stroke patients who have mild short term memory deficits. [B] **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] Recommend against the use of amphetamines to enhance motor recovery following stroke. [D]
Duncan PW, Zorowitz R, Bates B, et al. Management of adult stroke rehabilitation care: a clinical practice guideline. Stroke 2005;36:e100-e143.	**Assessment of Cognition and Communication** 1. Recommend that assessment of cognition, arousal, and attention address the following areas: learning and memory, visual neglect, attention, apraxia, and problem solving. 2. The Working Group does not recommend for or against the use of any specific tools to assess cognition. Several screening and assessment tools exist. Appendix D includes standard instruments for assessment of cognition. **The use of standardized assessment tools** 1. Recommend that all patients be screened for depression and motor, sensory, cognitive, communication, and swallowing deficits by appropriately trained clinicians, using standardized and valid screening tools. 2. Recommend that if depression and motor, sensory, cognitive, communication, and swallowing deficits are found, all patients should be formally assessed by the appropriate clinician from the coordinated rehabilitation team. **Cognitive Remediation** 2. Recommend that patients be assessed for cognitive deficits and be given cognitive retraining, if any of the following conditions are present: Attention deficits, Visual neglect, Memory deficits, or Executive function and problem-solving difficulties 3. Patients with multiple areas of cognitive impairment may benefit from a variety of cognitive retraining approaches that may involve multiple disciplines. Recommend the use of training to develop compensatory strategies for memory deficits in poststroke patients who have mild short-term memory deficits.

Evidence Tables

Pharmacotherapy

Donepezil

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Roman et al. 2010 **International** **RCT**	CA: ☒ Blinding: Patient ☑ Assessor☑ ITT: ☑	974 patients with possible or probable vascular dementia. **Exclusion criteria**: age<35 or >94, recurrent stroke within the past months, and presence of unstable medical conditions. 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). **Duration of treatment:** 24 weeks	**Primary outcomes**: 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). **Timing of assessment**: Baseline and at 6, 12, 18, and 24 week follow-up.	Participants in the donepezil group demonstrated significantly greater improvement on the V-ADAS-cog than those in the placebo group (least squares mean difference= -1.16, 95% CI -1.98 to -0.33; 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). **Adverse events**: The rate 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%.
Black et al. 2003 **International** **RCT**	CA: ☒ Blinding: Patient ☑ Assessor☑ ITT: ☑	603 stroke patients with possible or probable vascular dementia of >3 months duration. **Exclusion criteria**: neurodegenerative disorders other than vascular dementia, age<40, MMSE>26 or <10, recurrent stroke with 28 day of baseline, and diagnosis with a major depression or other	Participants were randomized to receive donepezil at 5mg/day (n=198), 10mg/day (5mg/day for the first 4 weeks; n=206), or placebo (n=199). **Duration of treatment:** 24 weeks	**Primary outcomes**: the 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	As compared to those in the placebo group, participants in both the 5ml/day and 10ml/day treatment groups demonstrated significantly greater improvement on the ADAS-cog at the 24-week follow-up (p<0.01 and p<0.001, respectively). Those in the 5ml/day group, but not the 10ml/day group, were also rated as having made significantly greater improvement in global function (CIBIS-Plus) than those in the placebo group (p=0.01). **Adverse events**: The proportion of patients with treatment-emergent events was significantly

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		psychiatric disorder. 63% of those screened for eligibility were included in the study.		Rating (CDR-SB), Alzheimer's Disease Functional Assessment and Change Scale (ADFACS). **Timing of assessment**: Baseline and at 6, 12, 18, and 24 week follow-up.	higher in the 10/mg treatment group than in the placebo group (94.7% vs. 88.4%, p=0.03). The 5ml/day 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%.
Wilkinson et al. 2003 **International** **RCT**	CA: ☒ Blinding: Patient ☑ Assessor☑ ITT: ☑	616 stroke patients with probable or possible vascular dementia of >3 months duration. **Exclusion criteria**: 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. 69% of those screened for eligibility were included in the study.	Participants were randomized to receive donepezil at 5mg/day (n=208), 10mg/day (5mg/day for the first 28 days; n=215), or placebo (n=193). **Duration of treatment:** 24 weeks	**Primary outcomes**: the Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog) and the Clinician's Interview-Based Impression of Change Plus version (CIBIC-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). **Timing of assessment**: Baseline and at 6, 12, 18, and 24 week follow-up.	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). As compared to placebo, treatment with 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). **Adverse events**: 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. Although six participants died during the study period (placebo=1, 5ml=3, 10ml=2), no deaths were determined to be related to treatment condition. **Lost to follow-up**: donepezil 5m/day=19.2%, donepezil 10m/day=24.7%, placebo=16.6%.

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

Rivastigmine

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Birks et al. 2013 **Cochrane Review**	n/a	3 RCTs (n=800) examining the use of rivastigmine as compared to placebo for the treatment of vascular cognitive impairment, vascular dementia, or mixed dementia.	Studies were identified through electronic and manual search techniques. Methodological quality was assessed according to the Cochrane Collaboration handbook. Data was not pooled because of substantial between trial differences.	Measures of global impression, functional performance, behavioural disturbance, and cognitive function were considered.	A single study (n=710) demonstrated a significant treatment effect in favour of rivastigmine as compared to placebo in terms of cognitive response (change in Mini Mental State Exam score: MD 0.06, 95% CI 0.11 to 1.09, p=0.02). 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 (p>0.05).
Narasimhalu et al. 2010 **Singapore** **RCT**	CA: ☑ Blinding: Patient ☑ Assessor☑ ITT: ☑	50 patients with cognitive impairment and no dementia 3 months following an ischemic stroke. **Exclusion criteria**: Age <55 or >89 years, advanced, severe, or unstable disease, and diagnosis of major depression. 32.5% of those screened for eligibility were included in the study.	Participants were randomized to receive rivastigmine (n=25) or placebo (n=25). RIvastigmine was started at 1.5g twice per day and titrated to 3-4.5 mg twice per day after 4 weeks in those able to tolerate the starting dose. **Treatment duratio**n: 24 weeks.	**Primary outcomes**: The Ten-Point Clock Test and the Color Trails Test 1 and 2. **Secondary outcomes**: the 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). **Timing of assessment**: At baseline and at 4, 8, 12, 16, 20, and 24 weeks.	No significant between group differences were reported with respect to either primary outcome. No significant differences were reported 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 than those in the placebo group (p<0.05). **Loss to follow-up**: Rivastigmine=28%; placebo=28%.
Moretti et al. 2003 **International** **RCT**	CA: ☒ Blinding: Patient ☒ Assessor☒ ITT: ☒	208 patients with probable vascular dementia and CTs showing moderate-to-severe ischemic white matter changes and at least 1 lacunar infarct. **Exclusion criteria**: Age <55 or >80 years, MMSE<14, and evidence of non-lacunar territorial infarcts or normal	Participants were randomized to receive rivastigmine (3-6mg/day; n=104) or cardioaspirin (100 mg/day; n=104). For participants started at 3 mg/day of RIvastigmine, doses were titrated to 6 mg/day at 12 weeks.	The Clinical Dementia Rating (CDR), the Mini Mental State Exam (MMSE), the Ten-Point Clock Test, word fluency phonological tests, the Behavioral Pathology in AD Rating Scale (BEHAVE-AD), the Geriatric Depression Scale (GDS), and the Cumulative Illness	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). As compared to those who received cardioaspirin, participants in the rivastigmine condition also demonstrated significantly more improvement on the GDS and on the BEHAVE-AD total score and each of the

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		pressure hydrocephalus.	**Treatment duration**: 1 year.	Rating Scale (CIRS). **Timing of assessment**: At baseline and at 1, 3, 9, and 12 months.	subscales except delusions (all at p<0.001). **Adverse events**: Transitory nausea was reported by 21% and 27% of patients in the rivastigmine and cardioaspirin groups, respectively. Muscle contraction were reported by 14% of those in the rivastigmine group whereas 25% of those in thecardioaspirin group reported heartburn.

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

Citicoline

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Alvarez-Sabin et al. **Spain** **RCT**	CA: ☒ Blinding: Patient ☒ Assessor☑ ITT: ☒	347 patients with first-ever ischemic stroke and persistent neurological deficit. **Exclusion criteria**: age<18, infarcts in multiple locations, severe aphasia, pre-existing dementia, and history of cancer or psychopathology.	Participants were randomized to receive citicoline (1 g/day; n=172) or usual care (n=175). **Treatment duration**: 1 year.	A neuropsychological battery was used to assess 6 domains of cognitive functioning: attention / executive function, language, memory, Spatial perception, motor speed, and temporal orientation. **Timing of assessment**: At baseline and at 1, 6, and 12 months post stroke.	As compared to those in the control group, participants who received citicoline demonstrated significantly better attention/executive function (OR 2.38, 95% CI 1.27 to 4.46, p<0.01) and temporal orientation (OR 2.16, 95% CI 1.02 to 4.57, p<0.05) at the end of the study period. These differences were maintained after controlling for risk factors and stroke severity. No significant between group differences were reported with respect to the other examined cognitive domains. **Lost to follow-up**: citicoline=38%; control=47%
Alvarez-Sabin and Roman 2011 **Review**	n/a	This article presents a review of citicoline for the treatment of vascular impairment and vascular dementia following stroke.	The authors provide a description of citicoline and evidence regarding its safety and efficacy in patients with post-stroke cognitive decline	n/a	Citicoline is an intermediate in membrane phospholipid synthesis that is safe and well-tolerated. Its impact on post-stroke cognitive decline has been suggested to occur through several neuroplasticity and neurorepair mechanisms. As compared to placebo, citicoline has demonstrated an association with increased neurological and functional recovery. However, additional research is needed to assess the long-term safety and efficacy of this therapy.

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Galantamine

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Erkinjutti et al. 2002 **RCT**	CA: ☒ Blinding: Patient ☑ Assessor☑ ITT: ☑	592 patients with probable vascular dementia or possible Alzheimer's disease and evidence of stroke. **Exclusion criteria**: MMSE score of 10-25 and ADAS-cog>12, neurodegenerative disorders other than Alzheimer's disease, cognitive impairment resulting from cerebral trauma 79% of those screened for eligibility were included in the study.	Participants were randomized to receive galantamine (n=396) or placebo (n=196). Galantamine was titrated from 4mg/day to 24/mg per day, with 4mg increases per week. **Treatment duratio**n: 6 months.	**Primary outcomes**: the 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. **Timing of assessment**: Baseline, 6 weeks, and at 3 and 6 months.	As compared to those in the placebo group, 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) and the CIBIC-plus (213 [74%] vs. 95 [59%], p<0.05) at the end of the study period. The galantamine group also demonstrated significantly more improvement on the extended version of the ADAS-cog (p<0.001) and the Neuropsychiatric Inventory (p<0.05). Adverse events: The rate of adverse events was 20% in the galantamine group as compared to 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 (23.5 vs. 7.1 events) and vomiting 12.9 vs. 5.6 events). **Lost to follow-up**: galantamine=25.8%; control=16.8%

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

Nimodipine

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Pantoni et al. 2005 **Italy** **RCT**	CA: ☒ Blinding: Patient ☑ Assessor☑ ITT: ☑	230 patients with subcortical vascular dementia. **Exclusion criteria**: MMSE <13 or >24, evidence of lacunar infarct, past diagnosis of major depression or other	Participants were randomized to receive nimodipine (90 mg/day; n=124) or placebo (n=118). **Treatment Duration**: 1 year.	**Primary outcome**: the Sandoz Clinical Assessment Geriatric scale (SCAG). **Secondary outcomes**: Global Deterioration Score (GDS), Set Test, Digit	The two groups did not significantly differ on mean change in SCAG score at the end of the 1 year study period (p>0.05). As compared to placebo, nimodipine was associated with significantly greater improvement on the MMSE (p<0.01), the GDS (p<0.05), and lexical production (p<0.01).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		psychiatric illnesses, Alzheimer's disease, Parkinson's disease, Huntington's disease, and fronto-temporal dementia. 87% of those screened for eligibility were included in the study.		Span, Mini Mental State Exam (MMSE), Zahlen-Verbindungs Test (ZVT-G), Hamilton Depression Rating Scale (HDRS). **Timing of assessment**: Baseline and at 1 year.	**Adverse events**: 135 adverse events occurred in the nimodipine group as compared to 180 in the placebo group (RR 1.29, 95% CI 1.03 to 1.61). Serious adverse events were also significantly more common in the placebo group (43 vs. 66, p<0.05). **Lost to follow-up**: nimodipine=13.7%; placebo=34.7%

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

Escitalopram

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Jorge et al. 2010 **US** **RCT**	CA: ☒ Blinding: Patient ☑ Assessor☑ ITT: ☑	129 stroke patients without post-stroke depression (HAM-D <12). **Exclusion criteria**: age <50 or >90, and severe comprehension deficits or impaired decision-making capacity. 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). 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. **Treatment Duration**: 1 year.	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. **Timing of assessment**: Baseline and at 12 months	At the end of the study period, participants who received escitalopram demonstrated significantly greater improvement on the RBANS 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. **Adverse events**: No significant between group differences were reported with respect to the frequency of aggregate or specific adverse events.

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Memantine

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Wilcock et al. 2002 **UK** **RCT**	CA: ☒ Blinding: Patient ☑ Assessor☑ ITT: ☑	579 individuals with probable vascular dementia, with onset at least one-year prior to inclusion. **Exclusion criteria**: secondary dementia, depressive psuedodementia, psychomotor excitation, psychotic episodes, epilepsy, and acute or poorly controlled illnesses. 69% of those screened for eligibility were included in the study.	Participants were randomized to receive memantine (n=295) or placebo (n=284). Memantine was titrated from a starting dose of 5 mg/day to 20 mg/day. **Treatment Duration**: 28 weeks.	**Primary outcome**: the 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). **Timing of assessment**: Baseline and at 12 and 28 weeks.	As compared to placebo, memantine was associated with significantly greater mean change on the ADAS-cog at the end of the 28-week study period (mean change difference=-1.75, 95% CI -3.02 to -0.49; p<0.01). No significant between group differences were reported with respect to the CGI-C. **Adverse events**: 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 **International** **RCT**	CA: ☒ Blinding: Patient ☑ Assessor☑ ITT: ☑	321 patients with mild-moderate symptomatic vascular cognitive impairment **Exclusion criteria**: age <60, MMSE score <23 or >20, and secondary dementia. 79.7% of those screened for eligibility were included in the study.	Participants were randomized to receive memantine (n=165) or placebo (n=156). Memantine was titrated from a starting dose of 5 mg/day to 20 mg/day. **Treatment Duration**: 28 weeks.	**Primary outcome**: the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) and the Clinical Global Impression of Change (CGI-C) **Secondary outcomes**: Mini Mental State Exam (MMSE), Gottfries-Brane-Steen Scale (GBS), and Nurse's Observation Scale for Geriatric Patients (NOSGER). **Timing of assessment**: Baseline and at 2, 4, 12, 20, and 28 weeks and 24 weeks.	At the end of the study period, participants who received memantine demonstrated significantly greater improvement on the ADAS-cog than did those who received placebo (mean change difference=2, 95% CI 0.49 to 3.60, p<0.05). Although a greater number of participants in the memantine group were rated as improved or stable on the CGI-C (60% vs. 52%), this difference was not significant. **Adverse events**: 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

Selected Reviews

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Ankolekar et al. 2010 **Review**	n/a	This article presents a review of clinical trials examining the prevention and treatment of post-stroke cognitive impairment.	The authors summarize published literature with respect to lowering blood pressure, lowering blood cholesterol, choline esterase inhibitors, and other interventions for post-stroke cognitive decline.	n/a	The reduction of high blood pressure to prevent post-stroke cognitive decline has been investigated in several large trials, with pooled analysis suggesting a significant treatment effect (OR 0.92, 95% CI 0.85 to 1.00). Prevention of post-stroke cognitive decline through lipid lowering has been examined in 2 large RCTs but was not reported to have a significant treatment effect. With respect to choline esterase inhibitors, evidence from a meta-analysis of 2 trails suggests that donepezil is associated with significant improvement in cognitive functioning, whereas evidence for galantamine was reported to be inconclusive. The authors conclude that although several trials have investigated the efficacy of various pharmacological agents, “there is no convincing evidence as yet that such interventions prevent post-stroke cognitive impairment or post-stroke dementia”.
Nyenhuis and Gorelick 2007 **Review**	n/a	This article presents a review of topics related to the diagnosis and management of vascular cognitive impairment	The authors consider published literature relating to the management of VCI risk factors and pharmacological agents that have been investigated for the management of vascular cognitive impairment.	n/a	The authors identify the following risk factors as potential targets for the management of VCI: hypertension, diabetes, dyslipidemia, atrial fibrillation, smoking and excessive alcohol consumption. Several pharmacological agents have been investigated for the management of vascular cognitive impairment in RCTs, with evidence supporting the efficacy of donepezil, galantamine, and memantine. Nevertheless, the authors conclude that “current VCI treatment options demonstrate statistical improvement but not consistent global clinical efficacy.”
Black 2007 **Review**	n/a	This article presents a review of therapeutic issues in vascular dementia	The author considers published literature relating to the design of therapeutic trials for vascular dementia.	n/a	The author describes several issues that should be considered in the design of future therapeutic trials for vascular dementia: 1. Trials should target all stages and subgroups of vascular dementia. 2. Subgroup homogeneity should be reduced. 3. Trials should examine both disease modifying

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					and symptomatic strategies and should be of sufficient duration (at least one year). 4. Diagnostic and inclusion criteria should reflect current evidence. 5. Additional attention should be given to executive functioning in terms of inclusion criteria and outcome assessment. Neuroimaging should be used for both participant selection and for assessing change.

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

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