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# Cognitive Disorders and Apraxia

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## Abstract

According to the Canadian Study of Health and Aging (CSHA), it is estimated that 5% of all people over the age of 65 years have evidence of vascular cognitive impairment (Rockwood et al. 2000). The risk for cognitive impairment or decline is augmented by a history of stroke. As many as two-thirds of patients experience cognitive impairment or decline following stroke and approximately 1/3 develop dementia. Risk for developing dementia may be up to 10 times greater among individuals with stroke than for those without. In this review, we examine issues around the definition, prevalence and natural history of post-stroke cognitive impairment as well as its clinical consequences. Risk factors for cognitive impairment are reviewed and the association between the treatment of hypertension and prevention of cognitive decline and dementia is explored. Identified treatment interventions include cognitive rehabilitation strategies (for the remediation of attention, memory, and executive functioning and problem-solving), electroacupuncture and TENS, music listening and pharmacotherapy. Reviews of the impact, risk factors, clinical consequences and treatment of both delirium and apraxia post-stroke are also provided.

## Key Points

**Definition & Diagnosis**

- Stroke survivors with vascular cognitive impairment but not dementia exhibit impairments of attention, executive function and processing speed, but have preservation of memory and orientation when compared to those with vascular dementia.

- At present, there is no gold standard for the diagnosis and assessment of vascular cognitive impairment.

**Incidence & Prevalence**

- As many as two-thirds of patients experience cognitive impairment or decline following stroke. The presence of cognitive impairment is associated with a substantial increase in risk for dementia.

- Risk for developing dementia may be up to 10 times greater among individuals with stroke than for those without.

- At the time of stroke, 10% of patients may have existing dementia. Another 10% may develop dementia shortly after a first-ever stroke. More than one-third of patients may experience dementia following a recurrent stroke.

- While cognitive decline may progress post stroke, approximately 16 – 20% of patients with cognitive impairment improve. While most improvements occur in the first three months, recovery may continue for at least the first year post stroke.

**Clinical Consequences**

- The presence of cognitive impairment following stroke has been associated with a 3-fold increase in risk for mortality. Mortality rates among stroke patients with dementia are 2 to 6 times greater than among stroke patients without dementia.

- Cognitive impairment is associated with decreased ADL and IADL function and patients may require longer-term, ongoing rehabilitation.

**Risk Factors**

- Depression contributes to cognitive impairment in stroke patients.

- Increasing age, lower levels of formal education and non-white race are independent risk factors for the development of dementia following stroke.

- The association between cognitive impairment or dementia and risk factors for stroke may not depend on the influence of any single risk factor, but rather upon the number and severity of risk factors.

- Overall, the effect of treatment of hypertension on risk for cognitive decline and dementia is uncertain. In individuals with previous stroke or TIA, treatment has been associated with reduced risk.

- The severity of white matter change is associated with poorer cognitive performance and increasing limitations in activities of daily living following stroke.

**Therapies & Interventions**

- Attention training may have a positive effect on specific, targeted outcomes.

- Compensatory strategies can be used to improve memory outcomes. However, more research is required particularly among individuals who have experienced stroke.

- Analogical problem-solving skills training may improve problem solving and instrumental activities of daily living in individuals with stroke.

- Although multi-modal interventions appear effective in individuals with traumatic brain injury, there is little evidence regarding the effectiveness of such programs in individuals with stroke.

- Electroacupuncture and high-intensity low-frequency TENS have no effect on cognitive functioning following stroke.

- Music listening may have a positive impact on cognitive function following stroke.

- Exercise may be associated with improvement in executive function. Further research is required.

- It is unclear whether rTMS has any effect on executive function following stroke. Further research is required.

- Anodal transcranial direct current stimulation may help to improve working memory and attention post stroke.

- ASA is a common antithrombotic therapy used in the treatment of vascular dementia and may be effective in stabilizing cognitive deficits.

- Treatment with doneprezil improves cognitive and global function in patients with vascular dementia.

- Treatment with rivastigmine may stabilize cognitive performance and improving behaviour for patients with subcortical vascular dementia. Further study is required.

- Treatment with rivastigmine does not result in improved executive function in individuals with post-stroke cognitive impairment, no dementia.

- Treatment with galantamine may be associated with cognitive and functional benefits, particularly in individuals with mixed dementia.

- Treatment with nimodipine is of benefit in the treatment of memory deficits. Among patients with subcortical vascular dementia, treatment with nimodipine may slow cognitive decline.

- Among patients with vascular dementia, treatment with memantine is associated with stabilization or improvement of cognitive function.

- Treatment with pentoxifylline may be of benefit to cognition in patients with multi-infarct dementia.

- Citicoline has no effect on cognitive function.
- Remission of depression following antidepressant therapy is associated with improved cognitive function.

- The use of escitalopram in individuals without post-stroke depression is associated with improved global cognition and memory.

**Deleirium**

- A multi-component approach targeting known risk factors may reduce the incidence and duration of delirium. Further study within the stroke population is required.

- Increased knowledge, awareness of risk and precipitating factors along with a model of individualized care may reduce the duration of delirium and result in shorter lengths of stay and a reduced risk for mortality. Further study is required.

**Apraxia**

- Strategic or compensatory training appears to be effective in the treatment of apraxia post-stroke.

- Gesture training is an effective intervention for the treatment of ideomotor apraxia post stroke.

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## 12.1 Defining Cognitive Impairments Post Stroke

Currently, there are two terms used to describe cognitive deficits occurring after stroke: vascular dementia and vascular cognitive impairment. **Vascular dementia** is defined as a loss of cognitive function resulting from ischemic, hypoperfusive, or hemorrhagic brain lesions due to cerebrovascular disease or cardiovascular pathology (Roman 2003). However, Rockwood (2002) notes that the concept of vascular dementia is being replaced by **vascular cognitive impairment**, a much broader term that encompasses all forms of cognitive loss due to cerebrovascular disease (Hachinski & Bowler 1993). One reason why the term vascular cognitive impairment is being adopted is because "*terming vascular cognitive impairment a 'dementia' falsely implies that a progressive degenerative factor is the underlying cause, which lacks definitive means of prevention and treatment, as seen in Alzheimer's disease*"(Devasenapathy & Hachinski 2000).

According to O'Brien et al. (2003) the term vascular cognitive impairment refers to all forms of cognitive impairment caused by cerebrovascular disease. The authors noted that vascular dementia, vascular cognitive impairment without dementia, and vascular mild cognitive impairment all fall within this definition. Wentzel et al. (2001) have also included the first two subgroups in their concept of vascular cognitive impairment, with an additional Alzheimer's Disease and a vascular component (mixed dementia) subgroup.

Studies by Sachdev et al. (1999) and Roman et al. (2004) suggested that the adoption of a categorical term "vascular cognitive disorder" as means to provide clarification (Table 12.2). Vascular cognitive disorder is defined as "the group of syndromes and diseases characterized by cognitive impairment resulting from a cerebrovascular etiology." Vascular cognitive impairment, vascular dementia and mixed AD plus cardiovascular disease all fall within this defined category.

**Table 12.2 Vascular Cognitive Disorder**

| Category | Definition |
|---|---|
| Vascular Cognitive Impairment (VCI) | VCI, no dementia |
| Vascular Dementia | Deficits of executive control resulting in loss of function for instrumental ADL |
| Mixed AD + Cardiovascular disease | AD worsened by stroke (pre-stroke dementia) |
| ** from Roman et al. (2004)* | |

**Table 12.1 Cognitive Syndrome of Post-Stroke dementia (Kalaria and Ballard 2001)**

| |
|---|
| Occurs in up to 30% of stroke patients |
| Progresses slowly |
| Predominantly executive dysfunction |
| Subcortical and frontal lobe functions are affected |
| Memory and language deficits are less obvious |
| Late stage memory deficits and dementia |

In a study comparing mild vascular dementia with mild Alzheimer's dementia patients, Graham et al. (2004) reported that both groups had cognitive impairments in all domains and many of the same neurological deficits were found in both groups. However, patients with vascular dementia had greater impairments of semantic memory, executive and attentional functioning as well as deficits of visuospatial and perceptual skills while the Alzheimer's dementia patients suffered greater impairment of episodic memory (Graham et al. 2004). Stroke patients with cognitive impairment, but no dementia

also exhibit less memory impairment when compared with patients with Alzheimer's disease(Ballard et al. 2003b). A comparison of features associated with vascular and Alzheimer's dementia is presented in Table 12.3.

**Table 12.3 Comparison between Vascular Dementia and Alzheimer's Disease**

| Characteristic | Vascular Dementia | Alzheimer's Disease |
|---|---|---|
| Onset | Sudden or gradual | Gradual |
| Progression | Slow, stepwise fluctuation | Constant insidious decline |
| Neurological findings | Evidence of focal deficits | Subtle or absent |
| Memory | Mildly affected | Early and severe deficit |
| Executive function | Early and severe | Late |
| Dementia type | Subcortical | Cortical |
| Neuroimaging | Infarcts or white matter lesions | Normal; hippocampal atrophy |
| Gait | Often disturbed early | Usually normal |
| Cardiovascular history | Transient Ischemic accidents, strokes, vascular risk factors | Less common |

In a study of community residents over 65 years old, Rao et al. (1999) found that those with stroke (n=25) displayed significantly poorer performance than controls (n=25) on abstract thinking, attention, calculation, language, memory, orientation, perception, praxis, and MMSE scores. Clinically, people with vascular cognitive impairment commonly present with decreased executive functioning, mental slowing and impairment of goal formulation, initiation, planning, organizing, sequencing, executing, abstracting and attention (Lesniak et al., 2008; Roman, 2003; Srikanth et al., 2003; Desmond et al., 1999; Looi & Sachdev, 1999; Hochstenbach et al., 1998). Memory however, may be relatively preserved (Roman, 2003; Desmond et al., 1999; Looi & Sachdev, 1999).

Sachdev et al. (2004b) demonstrated that patterns of impairment in patients with vascular dementia and vascular cognitive impairment differed in quantity rather than quality. Patients with vascular dementia and vascular cognitive impairment both displayed deficits of information processing speed, attention, working memory and praxis-gnosis function, but patients with vascular dementia were significantly more impaired within these cognitive domains. Deficits in abstraction, mental flexibility, information processing speed and working memory distinguished both impaired groups from a group of age-matched controls (Sachdev et al. 2004a).

Stephens et al. (2004) proposed that the concept of vascular cognitive impairment no dementia (vascular CIND) is useful in identifying stroke patients at risk for developing dementia. Ballard et al. (2002), reported that 48 of 150 stroke survivors over the age of 75 who were free of dementia at 3 months post stroke met the criteria for cognitive impairment, no dementia. The authors noted that, compared to elderly controls, the stroke survivors with cognitive impairment no dementia (CIND) had greater impairments of attention and executive function, and had preservation of memory compared to those with vascular dementia. Similarly, Stephens et al. (2004), in their study of 384 stroke patients and 66 controls, found impairments of attention and executive function in all stroke patients, including those without significant cognitive deficits. In stroke patients who met the criteria for vascular CIND, additional deficits of memory and language expression were identified. Further impairment of memory and orientation distinguished patients with vascular CIND from those with post-stroke dementia (Stephens et al. 2004). In the study by Stephens et al. (2004) and in the Canadian Study of Health and Aging, relative severity of memory impairments predicted progression to dementia (Ingles et al. 2002; Stephens et al. 2004)

***Stroke survivors with vascular cognitive impairment, no dementia, exhibit impairments of attention, executive function and processing speed, but have preservation of memory and orientation when compared to those with vascular dementia.***

### 12.1.1 Issues in the Diagnosis and Assessment of Cognitive Impairment Post Stroke

At present, there is no 'gold standard' for the diagnosis of vascular dementia (Chui 2000). While some use a modified version of the DSM-III-R criteria (Tatemichi et al. 1993), the DSM-IV criteria (Ballard et al. 2002) or the DSM-V (2013) to diagnose vascular dementia, others have used the following criteria: cognitive loss; vascular brain lesions identified by brain imaging; a temporal link between stroke and dementia; and exclusion of other causes of dementia (Roman 2003). Roman (2003) also adds that the onset of dementia must be within 3 months of a symptomatic stroke (this criterion is waived in patients with subacute VaD), and two cognitive domains other than memory be impaired for an appropriate diagnosis. Cognitive domains to be examined included: memory, praxis, language, orientation, constructional ability and executive control function. The authors suggest that while the first five cognitive domains can be assessed with the Mini-Mental State Examination, executive functioning can be examined with the Clock-Drawing Task. It should be noted that the MMSE is insensitive to executive dysfunction, an important component of vascular cognitive impairment (Royall 2000; Royall et al. 2002).

Similar to the diagnosis of vascular dementia, no gold standard exists for the diagnosis of vascular cognitive impairment. While some have used the Mini-Mental State Examination (MMSE) or the modified version (3MS) (Wentzel et al. 2001; Zwecker et al. 2002) to demonstrate cognitive decline, others have used the Montreal Cognitive Assessment (Prokopenko et al., 2013) or the Cambridge Examination for Mental Disorders in the Elderly - cognitive subscale (CAMCOG) (Ballard et al. 2003b). The CAMCOG (with a threshold of <80) has been adapted to include vascular cognitive impairment no dementia (Rockwood et al. 2000; Szatmari et al. 1999; Wentzel et al. 2001). Talelli et al. (2004) demonstrated an independent association between common carotid artery intima media thickness and cognitive impairment one year post stroke suggesting that this measurement may be useful in screening for those at increased risk for cognitive impairment

Hachinski et al. (2006) reported the results of a workshop intended to identify screening methods for the identification of individuals with possible cognitive and behavioural impairment, and to establish minimum datasets for clinical practice and research studies of vascular cognitive impairment. Participants included researchers in clinical diagnosis, epidemiology, neuropsychology, brain imaging, neuropathology, experimental models, biomarkers, genetics and clinical trials. Recommendations were produced for each working group within the following areas: clinical/epidemiology, neuropsychology, imaging, neuropathology, experimental models, biomarkers, genetics and clinical trials. The recommended 5-minute neuropsychological protocol included selected subtests of the Montreal Cognitive Assessment (5-word memory task – registration, recall, recognition, 6-item orientation and 1-letter phonemic fluency). This could be supplemented with a cube and clock drawing task, a short Trails B test and other brief attention language and abstraction tasks. Given more time, the original trails-making test, a semantic fluency test or the MMSE could be added (if administered on a different day or more than one hour following the 5-minute protocol). Inclusion of the MMSE in the abbreviated assessment was rejected as it lacks sufficient assessment of executive function and is relatively insensitive to mild memory impairment (Hachinski et al. 2006).

***At present, there is no gold standard for the diagnosis and assessment of vascular cognitive impairment.***

## 12.2 Prevalence and Natural History of Cognitive Impairment Post-Stroke

According to the Canadian Study of Health and Aging (CSHA), it is estimated that 5% of all people over the age of 65 years have evidence of vascular cognitive impairment (Rockwood et al. 2000). Forty-four percent of these individuals developed dementia over a 5-year period (Ingles et al. 2002). The risk for cognitive impairment or decline is augmented by a history of stroke. In a UK-based population study of 4,075 individuals aged 65 and over, stroke was significantly associated with an increasing risk for the development of dementia (OR = 2.1 95%CI 1.1 – 4.2) (Yip et al. 2006).

**Table 12.4 Studies included in Pendlebury and Rothwell (2009)**

| Hospital-based Studies | |
|---|---|
| Madureira et al. 2001 | Inzitari et al. 1998 |
| Henon et al. 2001 | Barba et al. 2000 |
| Pohjasvaara et al. 1997 | Barba et al. 2001 |
| Tatmichi et al. 1992 | Barba et al. 2002 |
| Desmond et al. 2000 | Arpa et al. 2003 |
| Lefebvre et al. 2005 | Del Ser et al. 2005 |
| Lin et al. 2003 | Henon et al. 1997 |
| Sachdev et al. 2006 | Henon et al. 1998 |
| Rasquin et al. 2004 | Henon et al. 2003a |
| Tatemichi et al. 1993 | Henon et al. 2003b |
| Tatemichi et al. 1994a | Cordoliani-Mackowiak et al. 2003 |
| Tatemichi et al. 1994b | Gordonnier et al. 2005 |
| Moroney et al. 1996 | Cordonnier et al. 2007 |
| Moroney et al. 1997 | Pasquier et al. 2000 |
| Desmond et al. 1998a | Altieri et al. 2004 |
| Desmond et al. 1998b | Sachdev et al. 2004 |
| Desmond et al. 2002a | Sachdev et al. 2007 |
| Desmond et al. 2002b | Zhou et al. 2004 |
| Gorelick et al. 1993 | Li et al. 2005 |
| Gur et al. 1994 | Klimkowicz et al. 2002 |
| Bornstein et al. 1996 | Klimkowicz et al. 2004 |
| Treves et al. 1997 | Klimkowicz et al. 2005 |
| Andersen et al. 1996 | Klimkowicz et al. 2006 |
| Censori et al. 1996 | Tang et al. 2004a |
| Pohjasvaara et al. 1998 | Tang et al. 2004b |
| Pohjasvaara et al. 1999 | de Koning et al. 1998 |
| Pohjasvaara et al. 2000 | de Koning et al. 2000 |
| | de Koning et al. 2005 |
| | Rasquin et al. 2004 |

In 1994, Tatemichi and colleagues (1994) examined cognitive function in 227 patients three months after admission to hospital for ischaemic stroke, and in 240 stroke-free controls. Cognitive impairment was defined as deficits in four or more areas of memory, orientation, verbal skills, visuospatial ability, abstract reasoning, and attentional skills. The authors reported that stroke patients were significantly more likely to have cognitive impairment (35.2%) compared to controls (3.8%).

**Table 12.4 (cont'd) Studies included in Pendlebury and Rothwell (2009)**

| Population-based Studies | |
|---|---|
| Kokmen et al. 1996 | House et al. 1990 |
| Kase et al. 1998 | Patel et al. 2002 |
| Ivan et al. 2004 | Patel et al. 2003 |
| Reitz et al. 2008 | Appelros et al. 2002 |
| Jin et al. 2006 | Appelros et al. 2003 |
| Srikanth et al. 2004 | Appelros et al. 2005a |
| Srikanth et al. 2006a | Appelros et al. 2005b |
| Srikanth et al. 2006b | |
| Ebrahim et al. 1985 | |

Reported prevalence rates of vascular cognitive impairment have varied substantially from 15 – 20% in various clinical settings to 39%, 35%, 30% and 32% at 3 months, one year, 2 years and 3 years post stroke, respectively as reported by Patel et al. (2003). These latter rates are similar to the 31% reported at 15 months post stroke by Ballard et al. (2003a) and at 3 months by Sundar and Adwani (2010). In a study of 451 ischemic stroke patients, Pohjasvaara et al. (1997) determined that 61.7% had some form of cognitive decline. In the groups aged 55 to 64, 65 to 74, and 75 to 85 years, the frequency of any cognitive decline was 45.7%, 53.8%, and 74.1%, respectively (p=0.0008).

The risk for cognitive impairment is greater following stroke and, while not all individuals with cognitive impairment have dementia, post-stroke cognitive impairment is associated with an increased risk for dementia. Linden et al. reported that, overall, cognitive impairments were more common among stroke patients than in age and gender matched controls (61% vs. 31%, OR = 3.5) (Linden et al. 2004). The increased risk for cognitive impairment attributable to stroke was most marked among patients less than 80 years of age (OR = 8.5). A more recent study reported that, in a sample of 327 stroke patients, 12.6% had cognitive impairment no dementia (CIND) prior to stroke (Serrano et al. 2007). Using a consistent method of assessment, the frequency of CIND was 26.9% at 3 months, 39.5% at 12 months and 36.6% at 24 months post stroke. While cognitive impairment is more common than dementia, stroke patients with CIND were at least 8 times more likely to develop delayed dementia than patients without CIND.

Pendlebury and Rothwell (2009) conducted a systematic review and meta-analysis of published studies examining prevalence and predictors of dementia in individuals with stroke. The authors included results from 73 papers providing data gathered from 22 hospital-based and 8 population-based cohorts (see Table 12.4). Reported rates of dementia following stroke varied substantially. However, the authors determined that more than 90% of this variance could be explained by study setting, inclusion/exclusion of patients with existing, pre-stroke dementia and first-ever vs. recurrent stroke. Therefore, pooled estimates were calculated based on stratification around these 3 factors.

Overall, pooled prevalence of pre-stroke dementia was 14.4% in hospital-based cohorts and 9.1% in community-based studies (Pendlebury & Rothwell 2009). Prevalence of post-stroke dementia ranged from 7.4% in population-based studies of individuals with first-ever stroke and no existing dementia to 41.3% in hospital-based studies of individuals with recurrent stroke with and without existing dementia. Rates of dementia were at least doubled following recurrent stroke when compared to first-ever stroke and were higher in hospital-based vs. population-based studies. At 3- 6 months, post-stroke incidence of dementia was approximately 20%; this increased linearly at a rate of 3.0% in hospital-based studies of either first or recurrent stroke. Incidence rates were lower in population-based studies of first-ever stroke and when cases with recurrent stroke were excluded.

Multivariate analyses were identified in 19 studies (Pendlebury & Rothwell 2009). From these 19 studies, the most commonly reported independent predictors of post-stroke dementia were older age, lower education level, previous stroke, diabetes, atrial fibrillation, existing cognitive impairment and stroke severity. In summary, Pendlebury and Rothwell (2009) suggest that approximately 10% of patients have existing dementia at the time of stroke. An additional 10% develop new dementia shortly after a first-ever stroke while more than one-third of patients may experience dementia following a recurrent stroke. Recurrent stroke was identified as an important, and commonly cited, predictor of dementia.

Kokmen et al. (1996) reported that stroke survivors have a 2 to 10-fold relative risk of developing dementia, which persists for at least 3 to 5 years. Results of the Framingham study demonstrated that, over a 10-year period, individuals with baseline stroke had twice the risk for developing dementia than age and gender-matched controls that, at baseline, had neither a history of dementia nor stroke (HR= 2.0, 95% CI 1.4 to 2.9; (Ivan et al. 2004). Age, sex, education or exposure to stroke risk factors had no effect on the reported risk. Based on a recent review, Savva et al. (2010) reported that history of stroke doubles the risk for incident dementia and that this elevated risk decreases over time.

A more recent epidemiological survey linked to the National Long-Term Care Survey in the United States confirmed a greater risk (up to 10-fold) for dementia among individuals in the first year following stroke than among stroke-free individuals (Ukraintseva et al. 2006). In addition, while stroke rates have not increased significantly over time, both stroke survival and the risk for dementia following stroke have increased substantially. The age-adjusted rates for diagnosed dementia following stroke rose from 0.043 to 0.080 from the periods 1984-1990 to 1991-2000 (relative increase = 1.87). The rate of cerebrovascular disease-related dementia increased almost 4-fold during the same time (Ukraintseva et al. 2006).

Stroke may be a major risk factor for the conversion of existing mild cognitive impairment to dementia. Gamaldo et al. (2006) demonstrated that, in a sample of 335 individuals enrolled in the Baltimore Longitudinal Study of Aging (mean age 75 years at study entry), stroke was associated with an increased risk for dementia when compared to individuals who did not experience stroke (OR = 5.55, 95% CI = 2.76-11.4). Of the individuals who were diagnosed with dementia following stroke, the majority (14/19) had evidence of mild cognitive impairment (MCI) prior to the stroke event. The OR for developing dementia in those individuals with MCI prior to stroke was reported to be 12.4 (95%CI 1.5 – 99) (Gamaldo et al. 2006).

***As many as two-thirds of patients experience cognitive impairment or decline following stroke. The presence of cognitive impairment is associated with a substantial increase in risk for dementia.***

***Risk for developing dementia may be up to 10 times greater among individuals with stroke than for those without.***

***At the time of stroke, 10% of patients may have existing dementia. Another 10% may develop dementia shortly after a first-ever stroke. More than one-third of patients may experience dementia following a recurrent stroke.***

### 12.2.1 Cognitive Recovery

In a study by Sachdev et al. (2004b), stroke survivors were assessed at 3 – 6 months post stroke and followed for a mean of 14.6 months. At both baseline and follow-up assessments, stroke patients demonstrated more cognitive impairment than healthy, age-matched controls. In patients who did not experience recurrent stroke, cognitive function declined over the follow-up period, though this decline was not significantly different from the control group when cognition was assessed globally. When domains of cognitive function were examined separately, the authors reported that stroke patients experienced significantly greater decline than controls in the areas of verbal memory and visuoconstructive function. Recurrent stroke, in this study, was associated with greater decline; patients with interval stroke experienced significantly greater decline than patients with baseline stroke only (Sachdev et al. 2004).

However, not all stroke survivors necessarily experience a progressive decline in cognitive function. In 1996, Desmond and colleagues (1996) conducted neuropsychological tests on 151 stroke patients at 3 months post stroke and annually thereafter. The authors reported that 19 of 151 stroke patients showed improvement, which, in most cases, was evident at the first annual examination. The authors also found that the probability of long-term improvement was 54.0% for a patient with a left hemisphere infarct and a major hemispheral syndrome but only 11.9% if diabetes was also present.

In a more recent study of 193 stroke patients, del Ser et al. (2005) reported that, while change in cognitive status (both improvement and deterioration) was common following stroke, by 24 months post stroke cognition had stabilized in the majority of cases (78.2%). In that study, 7.8% of cases demonstrated improvement in cognitive status at 24 months while 21.8% experienced deterioration. Deterioration in cognitive status was associated with older age, previous cognitive impairment, polypharmacy, and hypotensive episodes during admission for stroke (del Ser et al. 2005). Assessments at 3 years demonstrated that vascular mild cognitive impairment (vsMCI) following stroke may be considered progressive (Sachdev et al. 2009). Incident dementia was diagnosed in 24.4% of patients with vaMCI vs. 8.5% in patients without vaMCI. While some cognitive decline occurred in all groups, individuals without vaMCI were not at greater risk than the control subjects for development of cognitive impairment. In fact, the rates of transition from no cognitive impairment to cognitive impairment were greater in the control group than in the group of individuals without MCI following stroke (Sachdev et al. 2009).

Rasquin et al. (2005) reported that, of 118 stroke patients with mild cognitive impairment at one month post stroke, 20% had normal cognitive function on a later assessment. Most of the cognitive recovery documented by this study occurred between one and 6 months post stroke (Rasquin et al. 2005). An earlier study found that most patients who demonstrated cognitive deficits at one month following first-ever stroke, experienced improvement on at least one cognitive domain at 6 months (Rasquin et al. 2002). Patients with persistent cognitive disturbances at 6 months post stroke were more likely to be older, have a lower level of education (Rasquin et al. 2002) and a lower MMSE score on initial assessment (Rasquin et al. 2005). Similarly, Ballard et al. (2003b) reported that 50% of patients included in their study experienced some increase in Mini-Mental State Examination (MMSE) scores while 16% experienced an increase of more than 2 points and a 6.6 point increase on the CAMCOG scale between 3 and 15-month follow-up assessments ($p<0.0001$). Patel et al. (2003) reported a similar proportion of stroke patients (17.6%) regained cognitive function by one-year post stroke. Ballard et al. (2003b) suggested that, while persistent cognitive impairment and dementia are frequent, recovery may be the natural outcome in the absence of cerebrovascular or neurodegenerative disease or further cerebral insult. According to Kotila et al. (1984), the greatest improvement in cognitive function occurs from onset to 3 months after stroke, although improvement can still occur on most measures throughout the first year after stroke.

Although improvement in cognitive deficits may occur in the months following stroke, there is evidence to suggest that some functions may recover more readily than others. In a cohort study done at 2.3 and 27.7 months post stroke reported that the biggest improvement in cognition was found in the attentional domain, while the least improvement was found in memory (Hochstenbach et al. 2003). In the study by Ballard et al. (2003b), increased scores reflected improvements in orientation, language expression, abstract thinking, total memory, attention, perception and executive performance. In contrast, Lesniak et al. (2008) reported that, in the first year post stroke, the greatest improvements in cognitive function occurred in the areas of executive function, aphasia and long-term memory, while deficits in attention and short-term memory tended to persist. However, impairments in memory may also improve over time. In a recent review of studies examining memory post stroke, Snaphaan and de Leeuw (2007) reported that the prevalence of memory dysfunction varied with the interval from the event to assessment. Reported prevalence of post stroke memory impairment was 23 – 55% at 3 months following stroke while at 1 year post stroke reported prevalence ranged from 11-31%.

***While cognitive decline may progress post stroke, approximately 16 – 20% of patients with cognitive impairment improve. While most improvements occur in the first three months, recovery may continue for at least the first year post stroke.***

### 12.2.2 Mortality and Cognitive Impairment

According to the Canadian Study of Health and Aging (Wentzel et al. 2001), the overall outlook is poor for people with vascular cognitive impairment. The mean length of survival was reported as 41 months. Out of 149 people with vascular cognitive impairment no dementia (CIND), 58 (46%) progressed to dementia at the five-year follow-up. The majority of the 68 patients who had not progressed to dementia still presented with worsening cognitive deficits. Seventy-seven of the 149 people (52%) had died.

Patel et al. (2003) reported case-fatality rates at 1, 2 and 3 years for cognitively impaired versus cognitively intact stroke survivors of 23% versus 8% (p=0.006), 35% versus 15% (p=0.002) and 45% versus 24% (p=0.005) respectively. A more recent 15 year longitudinal study by Douiri et. al (2013) reported that individuals experiencing cognitive impairment 3 months following a stroke had a 53% increased risk of death when compared with individuals with no impairment (Hazard Ratio: 1.53, 95%CI 1.3-1.8). It has been reported that women with cognitive deficits post stroke have the worst prognosis; 5-year mortality rates of 60% have been reported for those aged 65–74 years and 83% for those aged over 85 years (Rockwood et al. 2000). Following stroke, the presence of cognitive impairment alone has been associated with an almost 3 times greater risk for mortality when compared to health age and sex-matched controls (RR=2.9) (Hobson & Meara 2010).

A review by Leys et al. (2005) reported that higher rates of mortality have also been found among patients with post stroke dementia in both community-based and hospital-based studies. Overall, mortality rates are reported to be 2 to 6 times higher among individuals with post stroke dementia after adjusting for demographic factors, associated cardiac disease, stroke severity and stroke recurrence (Leys et al. 2005).

***The presence of cognitive impairment following stroke has been associated with a 3-fold increase in risk for mortality.***

***Mortality rates among stroke patients with dementia are 2 to 6 times greater than among stroke patients without dementia.***

## 12.3 Clinical Consequences of Post-Stroke Cognitive Impairment

Cognitive processes include discrimination and acquisition of relevant information, understanding and retention, and the expression and application of knowledge in the appropriate situation (Cicerone et al. 2000). Cognitive impairments may reduce the efficiency, pace and persistence of functioning, decreasing effectiveness in performance of routine activities of daily living or resulting in failure to adapt to new or problematic situations. Evidence of an association between the presence of cognitive impairment at admission and rehabilitation outcomes has been reported (Heruti et al. 2002; Lesniak et al. 2008).

### 12.3.1 Impact of Cognitive Impairment on Rehabilitation Outcomes

It has been suggested that higher order cognitive abilities such as abstract thinking, judgment, short-term verbal memory, comprehension and orientation are important in predicting the stroke survivor's functional status at discharge (Jongbloed 1986; Mysiw et al. 1989; Tatemichi et al. 1994). Reduced cognition has been associated with a decreased ability to perform ADLs, with poorer physical functioning at discharge and with a greater likelihood of mortality within 1 year of discharge (Arfken et

al., 1999; Prencipe et al., 1997; Desmond et al., 2000; Lin et al., 2003; Claesson et al., 2005; Leys et al., 2005; Hinkle, 2006; Cederfeldt et al., 2010; Lichtenberg et al., 1994; Tatemichi et al., 1994; Ruchinskas & Curyto, 2003). Narasimhalu et al. (2011) found post-stroke cognitive impairment to be predictive of dependency and Zinn et al. (2004)reported fewer discharges home among patients with cognitive impairment than among cognitively intact patients (85.9% vs. 93.4%, p=0.07. A recent 15 year longitudinal study found that, on average, the relative risk of disability following stroke was twice as high for those with cognitive impairment (adjusted relative risk: 3 months, 2.4 (95%CI:1.93-3.08); 1 year, 1.9 (95%CI:1.38-2.6); 5 years, 1.8 (95%CI:1.27-2.55) than in those without (Douiri et al. 2013)

Although the presence of cognitive impairment may be associated with decreased ADL function, it has been demonstrated that it is not a significant predictor of ADL function at 6 months post stroke (Zinn et al. 2004). Rather, instrumental function may be more severely impacted by the presence of cognitive ability. At 6 months post stroke, the presence of cognitive impairment was associated with and predictive of decreased IADL function (Zinn et al. 2004). Similarly, Mok et al. (2004) determined that higher levels of cognitive impairment post stroke were associated with greater deficits in IADL function and greater levels of prestroke cognitive decline. Identified predictors of IADL performance were stroke severity, executive dysfunction, age and prestroke cognitive decline (Mok et al. 2004).

Patients with cognitive impairments may require more therapy over a longer period of time (Zinn et al. 2004). In addition, participation in rehabilitation may be adversely affected by the presence of executive dysfunction (Skidmore et al. 2010). This is, of course, associated with greater expenditure of healthcare resources (Claesson et al., 2005).

***Cognitive impairment is associated with decreased ADL and IADL function and patients may require longer-term, ongoing rehabilitation.***

### 12.3.2 Depression and Cognitive Impairment

A recent study reported that the presence of depression in patients with amnestic mild cognitive impairment (aMCI) is associated with a risk of developing dementia of the Alzheimer's type that is twice that of aMCI patients without depression (Modrego & Ferrandez 2004). Not only was the risk found to be greater, but cognitive deterioration proceeded at a more rapid (Modrego & Ferrandez 2004). Barnes et al. (2006) reported that, among 2220 participants in the Cardiovascular Health Study (Cognition Study), depressive symptoms at baseline were associated with an increased risk for MCI (moderate depression OR = 1.37 95% CI 1.00 – 1.88; moderate to severe depression OR = 2.09 95% CI 1.46 – 2.97) at follow-up 6 years later. While the presence of both small and large infarcts was also associated with increased risk for MCI (OR = 1.47 and 1.67, respectively), this association was independent of depression (Barnes et al. 2006).

It has been reported that the presence of depression is significantly and independently associated with the presence of cognitive impairment in stroke survivors one year following the stroke event (Kalaria & Ballard 2001; Talelli et al. 2004). Jaillard et al. (2010) reported a significant association between depression, left-sided stroke and cognitive dysfunction as soon as 15 days following a first-ever stroke event. Indeed, there is considerable evidence that affective disorders are associated with cognitive functioning (Burvill et al. 1995; Dam et al. 1989; Egelko et al. 1989). This phenomenon has been termed the "dementia of depression" or pseudodementia. In 1986, Robinson and colleagues found that patients with major depression after stroke had significantly greater cognitive impairment than patients with minor depression or no mood disturbance. In 2000, Murata and colleagues examined cognitive functioning in 41 patients with, and 135 patients without, major depression in the acute hospital setting

and either 3 or 6 months later. The authors noted that at follow-up, patients with major depression and improvement in mood demonstrated significantly greater recovery in cognitive functioning compared to patients with major depression without mood improvements. It is important to note, however, that a patient's score on the MMSE determined whether or not the patient had cognitive impairment.

In a recent report from the Sydney Stroke Study, Brodaty et al. demonstrated a greater frequency of dementia among stroke patients with depression (27.8%) when compared to those without depression (17.3%) at 3 months post stroke, though this difference was not significant (OR = 1.84, 95% CI 0.60-5.67,p=0.29) (Brodaty et al. 2007). By 15 months post stroke, 54.2% of patients with depression were diagnosed with dementia vs. 7.1% of non-depressed patients (OR = 15.36, 95% CI 5.1 – 46.7, p<0.001). However, logistic regression demonstrated that dementia at 3 months was a significant predictor for depression at follow-up (OR = 5.55, 95% CI 1.95 – 15.77, p=0.001) while the reverse was not true. There is evidence from one double-blind, controlled trial of nortriptyline (Kimura et al. 2000) that depression, in combination with other factors, adds to cognitive impairment in stroke patients (Haring 2002). Murata et al. (2000) also concluded that major post-stroke depression leads to cognitive impairment and not vice versa.

***Depression contributes to cognitive impairment in stroke patients.***

## 12.4 Risk Factors Associated with Post-Stroke Cognitive Impairment

Gorelick reported on the risk factors for vascular dementia in 4 categories: demographic, atherosclerotic, genetic and stroke-related (Gorelick 1997, 2004). Categorical risk factors identified in his review are listed in Table 12.5.

**Table 12.5 Risk Factors for Vascular Dementia by Category (Gorelick 1997, 2004)**

| Demographic | Atherosclerotic | Genetic | Stroke Related |
|---|---|---|---|
| Age<br>Male sex<br>Lower education level | Hypertension<br>Smoking<br>Myocardial infarction<br>Diabetes mellitus<br>Hyperlipidemia | Cerebral autosomal dominant arteriopathy with subcortical infarct<br>Leukoencephalopathy<br>Apolipoprotein | Volume of cerebral tissue loss<br>Evidence of bilateral cerebral infarction<br>Strategic infarction<br>White matter disease |

Additional risk factors may include atrial fibrillation and ethnicity (Geldmacher & Whitehouse 1996; Kalaria & Ballard 2001).

### 12.4.1 Demographic Risk Factors

As part of a prospective study of dementia and stroke, it was reported that the following patient characteristics were significantly associated with the development of dementia following ischemic stroke on logistic regression: increasing age, lower levels of education and non-white race (Desmond et al. 2000). Indeed, the importance of age and level of education as determinants of post stroke dementia has been well established (Leys et al. 2005; Mackowiak-Cordoliani et al. 2005; Yip et al. 2006). A review by Leys et al. (2005) cited no fewer than 19 independent studies supporting the association between increasing age and dementia following stroke. The association between level of education and post stroke dementia is not quite as clear; however, the authors speculate that failure to demonstrate a significant association between education and development of dementia in this review could be indicative of lack of statistical power or inadequate representation of individuals with high levels of education within the individual studies (Leys et al. 2005). However, a recent longitudinal cohort study

was able to demonstrate that education level does have an independent association with less memory impairment, Mini Mental State Exam Score, and the presence of dementia. This study was also able to demonstrate some effect of education on a decreased risk of post stroke mortality (Ojala-Oksala et al. 2012).

While the review presented by Gorelick (Table 12.4) cited male sex as a risk factor for the development of vascular dementia, more recent reviews do not support this assertion (Gorelick 1997, 2004). Leys et al. (2005) stated that the risk for post stroke dementia was not associated with sex in most studies included in their review, yet, a more recent study by Tang et al. (2006) reported female sex to be a significant independent risk factor for cognitive impairment following stroke. In their study of clinical determinants of post stroke dementia, Desmond et al. (2000) reported that sex was not a significant independent predictor of dementia. However, women with major hemispheric stroke syndrome were identified as being at a disproportionately increased risk for vascular dementia (OR=5.44) (Desmond et al. 2000). Similarly, DeRonchi et al. (2007) observed that sex did not modify the association between dementia and stroke, whereas, both age and level of education did.

***Increasing age, lower levels of formal education and nonwhite race are independent risk factors for the development of dementia following stroke.***

### 12.4.2 Atherosclerotic Risk Factors

There have been numerous studies examining the role of stroke risk factors in the prediction of the development of post stroke dementia. However, many of these studies offer conflicting results.

A study by Barba et al. (2000) identified a number of predictors for post stroke dementia including older age, atrial fibrillation, previous nephropathy, low Canadian Neurological Scale score at discharge from acute care and previous mental decline. However, established stroke risk factors such as hypertension, diabetes and history of myocardial infarction were not found to be significantly associated with the development of post stroke dementia.

Desmond et al. reported that, among known stroke risk factors, only the presence of diabetes and a history of previous stroke were associated with an increased risk for vascular dementia (2000). In addition to being a risk factor for the development of cognitive impairment or dementia, diabetes mellitus has been associated previously with a failure to exhibit cognitive improvement (Desmond et al. 1996). Furthermore, Mizrahi et al. (2010) found non-insulin-dependent diabetes mellitus was associated with an increased risk for cognitive impairment following stroke. However, a review by Mackowiak-Cordoliani (2005) presented conflicting results among studies examining the impact of diabetes on the risk for developing post stroke dementia.

It has been reported that hypertension contributes to the risk for both vascular dementia and Alzheimer's dementia (Skoog et al. 1996). In their review, Leys et al. (2005) reported that hypertension has been established as a risk factor for vascular dementia, but not necessarily for post stroke dementia, that is, "all types of dementia that happen after stroke". While diabetes mellitus and atrial fibrillation have been identified "in several studies" as independent risk factors for post stroke dementia, the role or influence of hyperlipidaemia, hyperhomocysteinaemia, alcohol consumption, and cigarette smoking has not been clearly delineated (Leys et al. 2005). Studies have reported a significant association between myocardial infarction and risk for dementia following stroke (Gorelick 1997; Gorelick et al. 1993; Leys et al. 2005).

It has been suggested that the link between atherosclerotic risk factors and the risk for dementia may be indirect. That is, stroke risk factors may increase the risk for dementia primarily by increasing the risk for stroke. In the Framingham Study, history of stroke at baseline doubled the risk for dementia (Ivan et al. 2004). Adjustment for individual risk factors such as hypertension, diabetes, atrial fibrillation and current cigarette smoking did not serve to decrease this risk. However, the association between cognitive decline and risk factors for stroke may depend on the severity and multiplicity of exposure rather than the influence of any single risk factor (Elkins et al. 2004). Elkins et al. (2004) reported that cognitive decline, as assessed by the Modified MMSE and the Digit Symbol Substitution Test, increased with each quartile increase in the Cardiovascular Health Study Stroke Risk Score. This risk score takes the following factors into consideration: age, gender, systolic blood pressure, diabetes, impaired fasting glucose, left ventricular hypertrophy, atrial fibrillation, history of heart disease, creatinine of 1.25 mg/dL and 15 foot walk time. The authors concluded that higher cognitive function was associated with a lower, overall risk for stroke (Elkins et al. 2004).

A similar conclusion was reached by Elias et al. (2004) as part of the Framingham Offspring Study. The Framingham Stroke Risk Profile (FSRP) was used to determine the 10-year risk for stroke based on the following factors; age, systolic blood pressure, antihypertensive medication, diabetes, cigarette smoking status, history of cardiovascular disease, atrial fibrillation and left ventricular hypertrophy on ECG. Among a sample of 1,011 men and 1,164 women, a 10% increment in the FSRP score was associated with declining performance on assessments of abstract reasoning, visual-spatial memory, visual organization, concentration, visual scanning and tracking, but not of verbal memory.

***The association between cognitive impairment or dementia and risk factors for stroke may not depend on the influence of any single risk factor, but rather upon the number and severity of risk factors.***

### 12.4.2.1. Treatment of Hypertension and Prevention of Dementia

The contribution of hypertension to the risk for dementia post stroke may be masked, in part, by its large contribution to the risk for stroke. The slow development of cognitive impairment related to the presence of hypertension is greatly augmented by the presence of stroke. Reduction of hypertension could reduce the risk for cognitive decline by preventing further cardio or cerebrovascular disease (Mackowiak-Cordoliani et al. 2005; Williams 2004).

In the Epidemiology of Vascular Aging Study (n=1373, aged 59 - 71), Tzourio et al. (1999) reported that 8.5% of participants experienced cognitive decline (defined as a reduction of 4 or more points on the MMSE) over the 4-year study period. The odds for cognitive decline were almost 3 times greater (OR=2.8) among individuals with high blood pressure than among normotensive participants. In individuals identified as hypertensive, treatment was associated with reduced risk for cognitive decline, particularly among patients who were identified as hypertensive both at baseline and follow-up (OR = 6.0 among individuals with untreated persistent hypertension vs. 1.3 in individuals whose hypertension was treated). Likewise, results from the Spanish COGNIPRES study suggest that control of hypertension, in individuals over the age of 60, may be associated with a significant reduction in risk for cognitive impairment (OR=0.60, 95% CI 0.39-0.94 compared to uncontrolled BP)(Vinyoles et al. 2008).

In a study of a sample of 2,212 community dwelling African Americans aged 65 years and older, Richards et al. (2000) determined that the use of medications that mediate vascular risk was associated with reduced risk for cognitive impairment after controlling for age, education and history of stroke (OR = 0.73, p=0.01). Antihypertensive medications alone were associated with a significant reduction in the risk for cognitive impairment (OR=0.66) with the exception of centrally-acting sympatholytics. This particular class of drugs was associated with a significant increase in the risk for cognitive impairment

(OR=2.24). There was no significant protective effect identified for antidiabetic, antihyperlipidemic or antithrombotic medications. A subsequent analysis confirmed that use of antihypertensive medications was protective for incident cognitive impairment when adjusting for age, sex, years of formal education, baseline cognition and history of hypertension, angina or myocardial infarction (OR=0.62) (Murray et al. 2002).

Results from the Honolulu Asia Aging Study, Peila et al. (2006) demonstrated that, in hypertensive men, duration of treatment is also associated with reduction in risk for incident dementia. In that study, treatment of midlife hypertension was associated with a decrease in the risk for the development of dementia; treatment for 12 years or more was associated with a significantly reduced risk for dementia (HR = 0.40 95% CI 0.22 – 0.78). However, when risk for vascular dementia was considered on its own, a significant trend toward risk reduction was identified with increasing duration of treatment (p=0.009) but, the reported Hazard Ratios for each treatment period (0-5 years, 5 – 12 years and >12 years) were not significant (HR = 2.04 95%CI 0.6 – 6.9; HR = 0.18 95%CI 0.10 – 1.71; HR = 0.32 95%CI 0.10-1.34, respectively).

Many blood pressure reduction trials have been conducted and, while some report the effects of treatment on cognition outcomes, cognition is typically treated as a secondary outcome or project. Blood pressure reduction trials that have addressed the effects of treatment on cognition are summarized below (Table 12.6).

**Table 12.6 Antihypertensive Medications for the Prevention of Vascular Dementia and Cognitive Decline**

| Author, Year<br>Country<br>Pedro Score | Methods | Outcome |
|---|---|---|
| SHEP Program<br>Applegate et al.<br>(1994)<br>8 (RCT) | 4,736 persons with systolic blood pressures from 160-219 mm Hg were randomized to receive active drug treatment or placebo. Patients were followed monthly until goal blood pressure or maximum level of stepped care was reached. Primary study end point was stroke. Impact of treatment on cognitive function was assessed in 6-month intervals using the Comprehensive Assessment and Referral Evaluation (CARE). Average follow-up = 4.5 years. For a subgroup of participants (n=2,034), more extensive cognitive function tests were administered in addition to CARE. | There were no significant between group differences in cognitive function at baseline. There was no significant difference with regard to change in cognitive function assessed on the CARE over time. In addition, no significant differences in change between the active treatment and placebo groups for any of the specific tests of cognitive function (digit symbol substitution, addition test, finding A's, Boston Naming Test, delayed recognition span, letter sets). |
| UK – MRC<br>Prince et al.<br>(1996)<br>UK<br>7 (RCT) | A subset of 2,584 patients enrolled in a larger clinical trial were selected for inclusion in the present analysis. Within the larger trial, 4,396 older patients (≥ 65 years of age) with moderate hypertension were randomized to receive either a placebo, atenolol 50 mg/day or HCT 25 mg plus amiloride 2.5 mg/day. Within the present study, 633 patients were assigned to diuretic group, 640 to the β-blocker group and 1,311 patients to placebo. The Paired Associate Learning test (PALT) and the Trail Making Test (TMT) were administered at baseline, 1,9,21 and 54 months. | Assignment to active treatment was associated with a significant fall in systolic blood pressure over the 54 months of the trial (p<0.0001). However, there was no evidence that treatment of blood pressure had any effect on cognitive outcomes (p=0.33 for TMT and p=0.86 for PALT). |

| | | |
|---|---|---|
| Hypertensive Old People in Edinburgh (HOPE)<br>Starr et al.<br>(1996)<br>Scotland<br>8 (RCT) | 81 subjects were randomized to receive either captopril (12.5 mg twice daily, n = 41) or bendrofluazide (2.5 mg daily, n=40) following a 2 week placebo period for both groups. Participants were >69 years of age and had mild to moderate hypertension and mild cognitive impairment (MMSE scores = 20 – 28. Treatment duration = 24 weeks. | There were no significant differences in blood pressure changes between groups at 24 weeks or at any intermediate assessment. There were no significant differences in any psychometric tests of cognitive function between groups at any assessment. There were no significant differences on any test of cognition between patients in the highest quartile of blood pressure reduction (>50mmHg systolic, >19mmHg diastolic) and the lowest quartile (<15mmHg systolic, <5 mmHg diastolic) with one exception. Patients whose diastolic pressure changed the most experienced significant improvement on the anomalous sentences repetition test when compared with patients whose diastolic BP had changed the least. |
| SYST-EUR<br>Forette et al.<br>(1998)<br>International<br>8 (RCT) | 2418 patients with hypertension were included in this double-blind placebo-controlled trial to investigate whether antihypertensive drug treatment could reduce the incidence of dementia. Active treatment consisted of nitrendipine (10-40 mg/day) with the possible addition of enalapril (5-20 mg/day), hydrochlorothiazide (12.5-25 mg/day), or both drugs, titrated or combined to reduce the systolic blood pressure by at least 20 mm Hg to reach a value below 150 mm Hg. Cognitive function was assessed by the mini mental state examination (MMSE). | Compared with placebo (n=1180), active treatment (n=1238) reduced the incidence of dementia by 50% from 7.7 to 3.8 cases per 1000 patient-years (p=0.05). In the control patients, the MMSE decreased (p=0.04) with decreasing diastolic blood pressure, whereas in the active-treatment group MMSE scores improved slightly (p=0.01) with greater reduction in diastolic blood pressure (p=0.002 for between-group difference). |
| SYST-EUR<br>Forette et al.<br>(2002)<br>International<br>6(RCT) | An open-label extension of the SYST-EUR trial. Patients in the placebo group (n=1417) began antihypertensive therapy with nitrendipine (10 – 40 mg/day) with the possible addition of enalapril (5 – 20 mg/day) and/or hydrochlorothiazide (12.5 – 25 mg/day). Patients in the treatment group (n=1485) continued treatment as they had from the beginning of the double-blinded trial (see SYST-EUR, 1998 below). Mean follow-up = 3.9 years. | Throughout follow-up, blood pressure was higher among patients in the control group than among patients in the long-term treatment group. Long-term antihypertensive therapy was associated with a reduction in the risk of dementia by 55% vs. the control group (43 vs 21 cases, p<0.001). The relative hazard ratio associated with the treatment group was 0.38 after adjusting for sex, age, education and blood pressure at study entry (p<0.001). |
| SCOPE<br>Lithell et al.<br>(2003)<br>International<br>8 (RCT) | 4937 patients aged 70 – 89 years with SBP 160 – 179 mmHg and/or diastolic blood pressure 90 – 99 mmHg and MMSE ≥24 were randomized to receive either candesartan (8 mg o.d., n=2477) or matching placebo (n=2460). Open-label anti-hypertensive therapy was used as needed. The dose of the drug could be increased to 2 tablets once per day if SBP≥160 mmHg or DBP ≥90 mmHg was observed during the study. MMSE was assessed along with blood pressure at regular follow-up visits (1 month, 3 months and every 6 months thereafter). Mean follow-up = 3.7 years. | Open-label antihypertensive therapy was used in 66% of patients in the control group. An additional 16% of control patients received low-dose HCT given at baseline. Mean blood pressure reduction was 21.7/10.8 mmHg in the treatment group and 18.5/9.2 mmHg in the control group. Mean MMSE score dropped from 28.5 to 28 in the treatment group and from 28.5 to 27.9 in the control group. The difference between groups was not significant (p=0.20). The proportion of patients who developed cognitive impairment or dementia was not significantly different between groups. |
| PROGRESS<br>Tzourio et al. | 6105 patients with stroke or transient ischemic attack within the previous 5 years were included | During a mean follow-up of 3.9 years, dementia was documented in 193 (6.3%) of the 3051 randomized |

| | | |
|---|---|---|
| (2003)<br>International<br>8 (RCT) | in this randomized, double-blind, placebo-controlled trial. There were no blood pressure criteria for study entry. Participants who tolerated and adhered to at least 4 wks of therapy with perindopril were randomly assigned, in a double-blind manner, to continued active treatment or matching placebo. Active treatment comprised a flexible treatment regimen based on perindopril with the addition of indapamide in those participants for whom the responsible study physician believed that there was no specific indication for, nor contraindication to, the use of a diuretic. | participants in the actively treated group and 217 (7.1%) of the 3054 randomized participants in the placebo group. Cognitive decline occurred in 9.1% of the actively treated group and 11.0% of the placebo group (p=0.01). The risks of the composite outcomes of dementia with recurrent stroke and of cognitive decline with recurrent stroke were reduced by 34% (*p* = .03) and 45% (*p*<.001), respectively. Combination therapy was more effective in reducing the risk for dementia than monotherapy (23% vs. –8%). |
| Fogari et al.<br>(2004)<br>Italy<br>6 (RCT) | 144 patients, 61 – 80 years of age with moderate-mild hypertension were randomly assigned to receive either valsartan 160 mg o.d. (n-73) or enalapril 20 mg. o.d. (n-71) following a 2-week period of treatment with placebo. Duration of treatment = 16 weeks. | Treatment with both valsartan and enalapril was associated with reductions in BP at all assessment points (4, 8, 12 and 16 weeks) Treatment with valsartan was associated with greater reductions in both diastolic and systolic blood pressure at the end of the treatment period (p<0.001 and p<0.01, respectively). Treatment with enalapril was not associated with any significant changes in cognition while treatment with valsartan was associated with improved scores for word list memory (p<0.05 vs. baseline, p<0.01 vs. enalapril) and word list recall tests (p<0.05 vs. baseline, p<0.01 vs. enalapril). Use of enalapril was not associated with any cognitive decline over the course of treatment. |
| SCOPE<br>Skoog et al.<br>(2005)<br>International<br>8 (RCT) | 4937 patients aged 70 – 89 years with SBP 160 – 179 mmHg and/or diastolic blood pressure 90 – 99 mmHg and MMSE ≥24 were randomized to receive either candesartan (8 mg o.d.) or matching placebo. Open-label anti-hypertensive therapy was used as needed. The dose of the drug could be increased to 2 tablets once per day if SBP≥160 mmHg or DBP ≥90 mmHg was observed during the study. Open-label antihypertensive therapy was used in 66% of patients in the control group. An additional 16% of control patients received low-dose HCT given at baseline. MMSE was assessed along with blood pressure at regular follow-up visits (1 month, 3 months and every 6 months thereafter). Low cognitive function at baseline = MMSE of 24 – 28. High cognitive function = MMSE of 29 – 30. 2070 patients had low cognitive function (LCF), 2867 had high cognitive function (HCF). Mean follow-up = 3.7 years. | Incidence of dementia was higher in LCF than HCF patients. Patients with LCF were older, had less formal education, were more often women, more often had a history of previous stroke and were more often on antihypertensive or psychopharmacologic drugs at baseline. Among patients with LCF, less cognitive decline occurred among patients treated with candesartan (p=0.04). In patients with HCF, there was no difference in cognitive decline between treatment groups. Significant cognitive decline was more frequent among patients with LCF at baseline (p<0.001) as was the onset of dementia (p<0.001); however, the proportion of patients developing dementia did not differ significantly between treatment & control groups. LCF patients were at a greater risk for nonfatal and all strokes (RR=1.40 p=0.33 and RR=1.42 p=0.012 respectively); however, when adjusted for age and education, these differences were nonsignificant. |
| MOSES study<br>Schrader et al.<br>(2005)<br>Germany/Austria<br>8 (RCT) | 1352 individuals with HTN & history of stroke were randomly assigned to receive nitrendipine (10 mg o.d., n=671) or eprosartan (600 mg o.d., n=681). Combination therapy (diuretics, β-blockers or α-blockers) was permitted if necessary to reach target BP. Primary study end | Although target blood pressures were achieved in both groups by 3 months, there were no significant differences in MMSE, Barthel or Rankin scores from baseline to end of study in either group. |

| | | |
|---|---|---|
| | points were mortality, # of cardiovascular and cerebrovascular events. Assessment of functional capacity including cognitive function was also undertaken. Mean follow-up time = 2.5 years. | |
| Starchina et al. (2007) Russia No Score | 22 patients aged 49-74, with stroke (n=18) or TIA (n=3), were treated with combined anti-hypertensive therapy, including rationally selected antihypertensive agents and 2.5-5 mg of cilazapril (an angiotensin-converting enzyme inhibitor) to normalize arterial pressure (ABP). Cognitive status was assessed before and after treatment using a number of outcomes including the Mini Mental State Examination (MMSE), the 10-word memory test and the Boston naming test. Emotional status was assessed using the Beck Depression Inventory (BDI) and the Spielberger Anxiety Scale. | Overall, patients showed a significant improvement in performance on the MMSE (p=0.05), 3 categories (number of semantic prompts, number of phonemic prompts, number of incorrect responses) of the Boston naming test (p<0.002), and all 4 categories of the Wisconsin test (p<0.004). As well, patients showed a trend towards improved performance on the 10-word memory test. Of the 2 patients with mild dementia, one showed stabilization of measures of cognitive function, while the other showed slight improvement. No changes were found in levels of anxiety or depression for the group. |
| PRoFESS Study Group Diener et al. (2008) 10 (RCT) | 20,332 patients with ischemic stroke within 90 days of within trial entry were randomly assigned to treatment (80 mg/day telmisartan, n=10,146) or matching placebo (n=10,186). All patients received open-label treatment for hypertension as necessary at the discretion of the investigators. 880 patients in the telmisartan condition and 934 patients in the placebo condition experienced recurrent stroke. Cognitive function was evaluated using the MMSE one month after randomization, at 2 years and at the next-to-last visit. | For many patients the 2-year follow-up coincided with the penultimate visit. Over time, there were no significant between group differences found in MMSE scores for individuals receiving placebo vs. telmisartan. Relative risk for MMSE score ≤24 points associated with treatment with telmisartan vs. placebo was 1.01 (95% CI 0.94-1.09). Although there were fewer individuals with MMSE decline of 3 points or more in the telmisartan group, this difference was not significant (RR=0.95, 95% CI 0.87-1.05). Results from a PRoFESS substudy of cognition are pending. |

**Discussion**

A meta-analysis of blood pressure reduction trials that included cognitive decline or dementia among study outcomes was conducted by Feigin et al. (2005). Adequate data could be obtained from only 4 trials for inclusion in the meta-analysis; PROGRESS, SCOPE, SHEP, and SYST-EUR. Based on data from these 4 trials, Feigin et al. (2005) reported that blood pressure lowering treatment was associated with a 20% risk reduction for the development of cognitive decline or dementia in patients with vascular disease. However, this reduction was non-significant (p=0.06) and there was significant heterogeneity between the trials. The lack of definitive result was attributed to insufficient power to detect modest treatment effects (only small numbers of patients developed dementia) and measurement error in the diagnosis of dementia (Feigin et al. 2005). Di Bari et al. (2001) reported that, in the case of the SHEP trial, differential group attrition may have biased both cognitive and functional evaluations toward the null effect resulting in an underestimation of treatment effect.

Of the studies summarized here, the majority reported comparisons of antihypertensive treatments rather than evaluating the efficacy of antihypertensive treatment compared with placebo (Table 12.7). Although the SCOPE and PRoFESS trials were both placebo-controlled, patients assigned to the control conditions could also receive active, open-label therapy to control blood pressure as needed.

**Table 12.7 – Summary of Treatment of Hypertension and Impact on Cognition**

| Study | Treatment(s) Assessed | Results* |
|---|---|---|
| SHEP 1994 | Chlorthalidone + atenolol vs. placebo | NS (global cognitive function, or digit symbol substitution, addition test, finding A's, Boston Naming Test, delayed recognition span, letter sets) |
| UK-MRC 1996 | Atenolol vs. HCT vs. placebo | NS (trail making, paired associate learning) |
| SYST-EUR 1998 | Nitrendipine *(+ enalapril + HCT)* vs. placebo | + (development of dementia, cognitive impairment) |
| PROGRESS 2003 | Perindopril *(+ indapamide)* vs. placebo | + (cognitive decline, dementia) |
| **Relative Efficacy of Antihypertensive therapies** | | |
| HOPE 1996 | Captopril vs. bendrofluazide | NS (cognitive function) |
| SCOPE** | Candesartan vs. placebo *(+ possible open-label therapy)* | NS (MMSE scores, dementia) |
| Fogari et al. 2004 | Valsartan vs. enalapril | NS (verbal fluency, Boston naming test, word list recognition) + (valsartan)(word list memory, word list recall tests) |
| MOSES | Nitrendipine vs. eprosartan | NS (MMSE scores) |
| PRoFESS** | Telmisartan vs. placebo *(+ possible open-label therapy)* | NS (MMSE scores) |

***Results reflect between treatment group comparisons only; NS=no significant difference, +=significant positive difference between groups ** therapy administered included additions of open-label therapies (ACE-inhibitors or α-blockers or β-blockers, and/or diuretics) as part of a treatment regimen designed to reduce BP as required.***

In the SCOPE study, a large proportion of patients in both the candesartan and placebo groups were given open-label active antihypertensive therapy to control blood pressure, making the study more of a comparison between candesartan and other antihypertensive therapy (mostly diuretic based) than candesartan versus placebo (Trenkwalder 2006; Zanchetti & Elmfeldt 2006). However, a *post hoc* comparison between patients who did not receive any add-on therapy post-randomization (n=1253 in the candesartan group and 845 in the placebo group) revealed reductions in cardiovascular events and mortality in those patients with moderate to mild hypertension receiving antihypertensive treatment (Trenkwalder 2006; Zanchetti & Elmfeldt 2006). With regard to cognition, mean MMSE scores fell in both groups, but there was no significant difference between the groups in adjusted change. However, in a subgroup of patients with low cognitive function (MMSE score of 24-28) at baseline (n=2070), adjusted decline in MMSE score was significantly smaller in the candesartan group (-0.04) than the control (-0.53) (p=0.04).

The OSCAR study (Observation Study on Cognitive function And Systolic blood pressure Reduction) was a 6-month international observational study examining the impact of treatment with eprosartan on cognitive function as assessed by the MMSE (Shlyakhto 2007). Preliminary results from 10,884 hypertensive patients in 8 countries demonstrated a significant reduction in blood pressure, as well as a significant increase in MMSE scores associated with treatment. Improvement in MMSE scores was demonstrated in all age groups, but most markedly in among individuals aged 70-80. It should be noted that the OSCAR study did not include individuals with previous history of stroke.

Of the studies appearing in Table 12.6, three (PROGRESS, MOSES, PRoFESS) were secondary prevention trials focusing on individuals with previous history of stroke or TIA. Only the PROGRESS study reported a significant association between treatment of hypertension and reduced risk for cognitive decline or dementia. Both the MOSES and PRoFESS trials compared the relative effectiveness of antihypertensive regimens. Neither reported significant between group differences on MMSE scores.

***Conclusions Regarding Medications for the Treatment of Hypertension and Prevention of Vascular Dementia***

***There is conflicting (Level 4) evidence that treatment of hypertension is associated with reduced risk for cognitive decline and dementia. Lack of definitive results may be due to differential patient attrition, insufficient power or measurement error. Further trials in which cognition is the primary study outcome are required.***

***There is moderate (Level 1b) evidence that treatment of hypertension may reduce the risk for cognitive decline or dementia in patients with history of previous stroke or TIA when compared to placebo.***

***There is no evidence that one particular antihypertensive agent is superior to another for the prevention of cognitive decline.***

***Overall, the effect of treatment of hypertension on risk for cognitive decline and dementia is uncertain. In individuals with previous stroke or TIA, treatment has been associated with reduced risk.***

### 12.4.3 Stroke-related Risk Factors

In a review of studies examining post stroke dementia, Leys et al. (2005) compiled a list of stroke characteristics and features from neuro-imaging studies associated with the development of dementia or cognitive impairment following a stroke event (Table 12.8). All characteristics listed have been reported to be associated with post stroke dementia in at least 2 previous studies. The authors note that, in the case of strategic infarcts, the original studies are either case studies or small series, are more than 20 years old and were conducted without MRI or follow-up.

**Table 12.8 Stroke-related Determinants of Post Stroke Dementia**

| Stroke Characteristics | From Neuro-imaging |
|---|---|
| Severe deficit at onset | Silent infarcts |
| Recurrent stroke | Global central atrophy |
| Supratentorial lesions | Medial-temporal-lobe atrophy |
| Left hemisphere lesions | White matter changes |
| Anterior & posterior cerebral artery territory lesions | |
| Strategic infarcts | |
| Multiple lesions | |

A recent systematic review and meta-analysis examined the incidence and prevalence of cognitive impairment following a lacunar stroke when compared with other stroke subtypes. Authors identified 24 studies, and found that the prevalence of cognitive impairment or dementia did not differ between lacumar and other stroke types (29% and 24% respecitivly). However, when broken down by hospital or community based samples, non lacunar strokes had a higher prevalence in hospital based samples (odds ratio: 0.67), and community based studies demonstrated a higher prevalence of lacunar stroke (odds ratio 1.56). It should be noted, however, that studies included in this review were found to be highly heterogeneous (Makin et al. 2013).

Prior Transient Ischemic Attach (TIA) has also recently been demonstrated to potentially have an effect on the development of dementia following an ischemic stroke. A longitudinal study on a large sample (n=1697) showed that individuals with aTIA <4 weeks prior to a stroke event had a higher risk of

developing dementia than those without TIA (adjusted odds ratio: 1.83, 96%CI: 1.32-2.52) (Jacquin et al. 2012).

#### 12.4.3.1 White Matter Changes and Cognitive Impairment

In a population study of individuals aged 59 – 71 years, Dufouil et al. determined that the prevalence of severe white matter hyperintensities (WMH) increases with age (Dufouil et al. 2001). It has also been demonstrated that, in non-disabled elderly, the number of lacunes and increasing WMH are associated with lower MMSE scores (van der Flier et al. 2005). Jokinen et al. (2005) reported that the overall degree of WMH, rather than the location of WMH, predicted poor performance on neuropsychological tests measuring speed of mental processing, executive function, visual memory, delayed recall of object learning and visuospatial tasks but not short term memory storage, story recall or verbal conceptualization. Similarly, Verdelho et al. (2007) demonstrated that individuals with severe age-related white matter changes demonstrate worse performance on tests of global cognition, executive function, speed and motor control, attention, naming and visuoconstructional praxis when compared to individuals with mild to severe white matter changes. Prins et al. (2005) suggested that stroke may play a role in worsening cognitive decline in individuals with documented white matter lesions and generalized brain atrophy by affecting both information processing speed and executive function.

A review by Leys et al. (2005) identified silent infarcts, global cerebral atrophy and white matter changes as predictors of post stroke dementia. Sachdev et al. (2004a) reported that study participants who had experienced stroke or TIA had significantly more cortical atrophy, greater ventricle/brain ratios and more extensive deep white matter hyperintensities than an age-matched control group. Stroke/TIA subjects with vascular dementia (VaD) or vascular cognitive impairment (VCI) had significantly more WMH than stroke/TIA subjects without cognitive impairment. Participants with VCI and VaD did not differ from each other in terms of WMH but did differ significantly in terms of stroke volume. A correlation between WMH and change in cognition was found such that higher WMH was associated with a greater likelihood for cognitive decline (Sachdev et al. 2004b). Similarly, Burton et al. (2004) reported a higher volume of WMH, particularly in the temporal and frontal lobes, in stroke patients when compared to controls (Burton et al., 2004). In that study, moderate WMH (2.4% of total brain volume) was associated with greater impairments of processing speed and attention than mild WMH (1.2%). Most recently, McMurtray et al. (2007) demonstrated that patients with both lacunar infarcts and white matter changes experienced significant performance deficits on cognitive testing in multiple domains including verbal fluency (category and letter) and verbal memory in addition to lower MMSE scores when compared to patients who had lacunar stroke but no associated leukoaraiosis.

The LADIS (LeukoAraiosis and DISability) study examined the impact of age-related white matter changes (WMC) on functional activities within a limited period of time (Inzitari et al. 2007). The authors determined that the severity of white matter changes was an independent predictor of 1-year transition in functional status from none to 1 activity limitation to 2 or more reported limitations. Participants with severe WMC were more than twice as likely to experience this defined transition in function when compared to participants with only mild WMC (OR=2.38, 95% CI 1.29-4.38). The impact of WMC severity on functional decline was best explained by declines in both motor and cognitive function (Inzitari et al. 2007). In the LADIS study, individuals with a history of previous stroke were more than 4 times as likely to have severe WMC. Pohjasvaara et al. (2007) examined the role of white matter lesions with regard to declines in function 3 months following ischemic stroke. In general, increasingly severe white matter changes were associated with higher age, female gender, impaired activities of daily living (both basic and extended), global cognitive status, impaired memory and executive dysfunction.

***The severity of white matter change is associated with poorer cognitive performance and increasing limitations in activities of daily living following stroke.***

## 12.5 Cognitive Rehabilitation

Cognitive rehabilitation involves "a systematic, functionally oriented service of therapeutic activities that is based on assessment and understanding of the patient's brain-behavioural deficits" (Cicerone et al. 2000). Various interventions aim to: 1) reinforce, strengthen or re-establish previously learned patterns of behaviour; 2) establish new patterns of cognitive activity through compensatory cognitive mechanisms for impaired neurological systems; 3) establish new patterns of activity through external compensatory mechanisms such as personal orthoses or environmental structuring and support; and 4) enable persons to adapt to their cognitive disability. Accordingly, cognitive rehabilitation directs itself to several areas of cognition such as attention, concentration, perception, memory, comprehension, communication, reasoning, problem-solving, judgement, initiation, planning, self-monitoring and awareness (Cumming et al. 2013).

Cicerone et al. (2000) established evidence-based recommendations for clinical practices of cognitive rehabilitation. The authors methodically reviewed the scientific literature addressing the effectiveness of cognitive rehabilitation for patients with traumatic brain injury (TBI) or stroke. After conducting an extensive MEDLINE literature search, Cicerone et al. (2000) reviewed 171 articles that met their inclusion criterion. Articles were allocated to 1 of 7 categories accordingly to the area of intervention investigated: attention, visual perception and constructional abilities, language and communication, memory, problem-solving and executive functioning, multi-modal interventions and comprehensive-holistic cognitive rehabilitation. The authors also noted evidence that supported several forms of cognitive rehabilitation. In addition, they were able to make specific recommendations for remediation of language and perception after a left and right hemisphere stroke. The literature search and recommendations were expanded and updated to include published evidence from 1998 – 2002 in 2005 (Cicerone et al. 2005).

A meta-analytic examination of the reviews conducted by Cicerone et al. (2000; 2005) reported effect sizes associated with attentions, visuospatial, language, memory and comprehensive cognitive interventions. Overall, cognitive rehabilitation interventions were associated with small, but significant treatment effects (ES=0.30). Overall treatment effect was moderated by treatment domain, etiology of injury (e.g. TBI vs. stroke) and time since injury. For studies of individuals with stroke, the reported pooled effect size associated with cognitive rehabilitation was slightly larger (ES=0.40). It should be noted, however, that studies of individuals with stroke were primarily in the areas of language and visuospatial interventions. Studies of attention or executive function, memory or comprehensive cognitive function were focussed more often on individuals with TBI or other brain injury.

In 1999, a European Task Force was created with the aim of evaluating the existing evidence for the clinical effectiveness of cognitive rehabilitation. In 2003, Cappa and colleagues published these recommendations as a set of guidelines to be used in the management of adult patients with cognitive disorders due to acquired focal neurological damage (Cappa et al. 2003). An update to these recommendations was published recently (Cappa et al., 2005). Recommendations provided by Cicerone et al. and the EFNS will be referred to where appropriate (Cicerone et al., 2005; Cappa et al., 2005).

### 12.5.1 Remediation of Attention Deficits

Cicerone et al. (2000) reviewed 13 studies examining the effectiveness of attention intervention during the acute phase of rehabilitation of traumatic brain injury (TBI) and stroke. An additional 5 studies

examining the remediation of attention deficits following TBI were added in 2005 (Table 12.9). It should be noted that none of the studies added to the review were specific to the stroke population.

**Table 12.9 Remediation of Attention Deficits**

| Cicerone et al. 2000 | |
|---|---|
| ▪ Novack et al. 1996<br>▪ Niemann et al. 1990<br>▪ Gray et al. 1992<br>▪ Ponsford et al. 1988<br>▪ Sturm et al. 1991<br>▪ Sohlberg et al. 1987<br>▪ Strache 1987 | ▪ Sturm et al. 1997<br>▪ Ethier et al. 1989<br>▪ Wilson et al. 1992<br>▪ Gansler et al. 1991<br>▪ Gray et al. 1989<br>▪ Wood 1977 |
| **Cicerone et al. 2005** | |
| • Sohlberg et al. 2000<br>• Fasotti et al. 2000<br>• Cicerone 2002 | • Palmese & Raskin 2000<br>• Park et al. 1999 |

Cicerone et al. (2005) noted that most interventions designed to improve basic attentional abilities have relied on drills and practice used within a stimulus-response paradigm. Gains made via speeded tasks appeared to be less durable that gains made via nonspeeded tasks and greater benefit was observed from attention training on complex tasks requiring selective or divided attention when compared to attention training on basic tasks of reaction time or vigilance.

The two prospective, randomized controlled trials added in the 2005 update to this review (Fasotti et al. 2000; Sohlberg et al. 2000) emphasized the development of compensatory strategies rather than the restoration of basic aspects of attention (Cicerone et al. 2005) and both reported positive results. Strategy training, focused on complex tasks requiring regulation of attention, was recommended for use during post-acute rehabilitation of adults with TBI. This recommendation was supported by Cappa et al. for the rehabilitation of attention deficits during the post-acute phase of recovery (Cappa et al., 2005).

The majority of studies included in the Cicerone et al. (2013) reviews focus primarily on individuals who have experienced traumatic brain injury rather than stroke. Studies examining the remediation of attention post stroke are presented in Table 12.10.

**Table 12.10 Remediation of Attention Deficits**

| Author, Year<br>Country<br>Pedro Score | Methods | Outcome |
|---|---|---|
| Sturm & Willmes (1991)<br>Germany<br>No Score | 27 individuals with left hemisphere damage (LHD) and 8 individuals with right hemisphere damage (RHD) of predominantly vascular etiology were provided with computer assisted attention training using 2 devices (WDG and Cognitrone). The WDG device provides visual and/or acoustic signals to which the individual must respond by pressing a response key. The Cognitrone requires the individual to match a configuration of stimuli to a multiple choice response option. The effectiveness of the training intervention was assessed using 14 | Participants demonstrated improvement for complex choice reaction (WDG), simple visual reaction time (WRG), test d2 (speeded letter cancellation – RHD only), perceptual speed and selective attention. No effects were demonstrated for choice reaction or vigilance or for any of the cognitive tests administered. Performance at 6 weeks post-training demonstrated no significant deterioration. |

| | | |
|---|---|---|
| | test variables derived from special versions of the training tasks. Training was provided in 14 30-minutes sessions (15 minutes for each device) over a 3-week period. Test variables were assessed at baseline, at the end of training and once again 6 weeks following termination of training. | |
| Gauggel & Niemann (1996) Germany No Score | 4 stroke patients with suspected problems of attention according to a percentile rank of 10 or lower on 2 of 3 tests of attention, after a 2 week waiting period of receiving PT and OT interventions, received 2 weeks of 30 minutes of computer training 5 days per week followed by 2 weeks of 45 minutes of training 5 days per week. Training was conducted individually and consisted of computer-assisted training in tasks focused on alertness, vigilance, divided attention and selective attention. Assessments included the d2-Test, Number Connection Test, Wiener Determination Apparatus, Wechsler Memory Scale subtests (IV & VII), Rey Complex Figure Test, the Satisfaction with Life Scale, the CES-D. | Only 2 patients demonstrated significant improvement on tests of attention and, for one of these patients, substantial improvement was made during the waiting period. No other significant results were reported on assessments of cognitive function, life satisfaction or mood. |
| Sturm et al. (1997) Germany 3 (RCT) | 38 patients with unilateral vascular lesions and 2 months post-onset received computer-assisted adaptive training in 2 of 4 possible aspects of attention (alertness, vigilance, selective or divided attention). Participants received training on the aspects of attention in which they demonstrated the greatest impairment. Following baseline assessment, each participant received 14, 1 hr training sessions, on the computer, on 1 of 4 tasks, then were retested before receiving another 14, 1 hour training sessions on the 2$^{nd}$ task. The order of presentation for the training tasks was randomly selected. | Rather than conducting an analysis for each possible combination of 2 attention impairments in the fashion of a 2-period crossover design, analysis of effectiveness of training was confined to the first treatment period, as only 11 of 12 possible pairs of training were present and no combination appeared more than 6 times. Using single case analysis procedures, significant training effects were observed, particularly for alertness and vigilance aspects of attention, suggesting that in patients with a localized vascular lesion, specific attention disorders need specific training. |
| Mazer et al. (2003) Canada 7 (RCT) | 84 patients with a recent hemispheric stroke (within 6 months) who had a desire to return to driving were randomized to an experimental or control group by stratified block design according to side of lesion and severity of visual processing deficits. The experimental group received visual information-processing training using the Useful Field of View (UFOV) that included training of visual processing speed, divided attention, and selective attention. The control group received traditional computerized visuoperception retraining. Both groups received 20 sessions (2 to 4 sessions per wk, 30-60 min per session). | No significant differences between groups on any outcome measure (Test of Everyday Attention, Useful Field of View (UFOV), Complex Reaction Timer, Motor-Free Visual Perception Test, single and Double Letter Cancellation Test, Money Road Map Test Of Direction Sense, Trail Making Test Parts A and B, Bell's Test, and Charron test, Functional Independence Measure). However, there was almost a 2-fold increase in the rate of success on the on-road evaluation after UFOV training for subjects with right-sided lesions. |
| Giaquinto & Fraioli (2003) Italy 5 (RCT) | 40 middle cerebral artery stroke patients were randomized to the trained group or control group in order to evaluate the effect of attentional training on the N140 component of the somatosensory event related potentials. The trained group received daily training in a discrimination task combined with | At the end of 3 weeks, N140 was present in significantly more patients in the trained group (n=16) compared to the control group (n=6) ($p<0.001$). Change in FIM scores was no greater among trained participants than control participants. However, patients in whom the N140 |

| | | |
|---|---|---|
| | cutaneous electrical stimuli for a total of 3 weeks. Controls did not receive training. A group of 20 healthy volunteers were also studied. Outcome measures included the Functional Independence Measure and Electroencephalographic (EEG) signals. | response was present at baseline experienced the most favourable outcome at discharge as assessed on the FIM. |
| Barker-Collo et al.<br>(2009)<br>New Zealand<br>8 (RCT) | 78 acute stroke patients with attention deficits identified by neuropsychological assessment. Participants were randomly allocated to standard care plus 30 hours of Attention Process Training (APT) or standard care alone. APT training consisted on 1 hour sessions prvided for a total of 4 weeks. The primary outcome was Integrated Visual Auditory Continuous Performance Test Full-Scale Attention Quotient (IVA-CPT). | Patients in the intervention group performed significantly better on the primary outcome, as compared to patients in the control group ($p < 0.05$). No other significant differences were reported between the two groups. |
| Prokopenko et. al.<br>(2013)<br>2013<br>Russia<br>8(RCT) | 24 individuals were randomized to the treament group (mean age= 61), and 19 individuals were randomized to the control group (mean age= 66). The treatment group received 15 hours of individual training on the use of computer programs (30 minutes/ day for 2 weeks) in addition to standard inpatient rehabilitation therapy, and the control group received standard inpatient rehabilitation therapy alone. Researchers completed assessments on four aspects of attention (sustained, selective, divided, and alternating) at baseline and 14-16 days post randomization. | Between group comparisons demonstrated statistically significant improvements in favour of the treatment group on the FAB test (p=0.02), the Clock drawing test (p=0.05), and Shulte's Table (p=0.01)<br>Comparisons before and after treatment demonstrated statistically significant improvements on all tests (MMSE, FAB, MoCA, Clock Drawing Test, Schulte's Tests, IADL, and SSQL) in the treatment group (all p<0.05),There were no significant differences noted on any measure in the control group. |

**Discussion**

Of the seven studies presented, five were randomized controlled trials. However, no two studies used the same interventions over similar periods of time or measured similar outcomes. All four recorded intervention effects on specific, targeted outcomes. For instance, Mazer et al. (2003) observed no significant change on a wide range of outcomes, including the MVPT and the FIM, but did note a significant change in success rates during on road driving evaluations. Barker-Collo et al. (2009) observed significant improvement in integrated visual auditory attention following 30 hours of attention process training but significant differences were not reported for any of the other outcomes assessed. A summary of RCT outcomes is presented in Table 12.11.

**Table 12.11 Summary of RCT's Evaluating Attention Remediation**

| Study | N | Treatment | Outcome |
|---|---|---|---|
| Mazer et al.<br>2003<br>Canada<br>7 (RCT) | 84 | Experimental group received visual information-processing training using the Useful Field of View (UFOV) vs. traditional computerized visuoperception retraining | Test of Everyday Attention (-)<br>Useful Field of View (UFOV) (-)<br>Complex Reaction Timer (-)<br>Motor-Free Visual Perception Test (-)<br>Single and Double Letter Cancellation Test (-)<br>Money Road Map Test Of Direction Sense (-)<br>Trail Making Test Parts A and B (-)<br>Bell's Test (-)<br>Charron test (-)<br>Functional Independence Measure (-)<br>On-road evaluation (+) |
| Giaquinto & | 41 | Daily attention training | EEG signals detecting N140 |

| | | | |
|---|---|---|---|
| Fraioli 2003<br>5 (RCT) | | (discrimination task + cutaneous electrical stimulation) vs. control/untrained group | at 3 wks (+)<br>FIM change (-) |
| Sturm et al. 1997<br>3 (RCT) | 38 | Computerized adaptive training programs for alertness, vigilance, selective and divided attention. | Performance in 4 areas (computerized attention battery): alertness, vigilance, selective attention, divided attention. Significant, specific training effects were reported, particularly for alertness and vigilance aspects of attention. |
| Barker-Collo et al. 2009 New Zealand 8 (RCT) | 78 | Attention process training verses usual care | IVA-CPT (+)<br>Trail-making part A and B (-)<br>Paced Auditory Serial Addition Test (-)<br>Bell's Test (-) |
| Prokopenko et. al. 2013 Russia 8 (RCT) | 43 | Computer Correction Program (attention training and visuo and spatial gnosis training) | MMSE (-)<br>FAB (+)<br>Montreal Cognitive Assessment (-)<br>Clock Drawing Test (+)<br>Schulte's Tests (+)<br>HADS (-) |
| *- Indicates non-statistically significant differences between treatment groups*<br>*+ Indicates statistically significant differences between treatment groups* | | | |

***Conclusions Regarding Remediation of Attention***

***Based on the results of unrated studies and two RCTs, of poor quality and one of good quality, there is evidence that computer-assisted training of attention tasks may improve performance of specific attention tasks.***

***There is moderate (Level 1b) evidence that daily attention training is associated with recovery of the N140 component of somatosensory evoked potentials.***

***There is moderate (Level 1b) evidence that visual attention retraining using the Useful Field of View is more effective than conventional computerized visuoperceptual training in improving the on-road driving performance of individuals who have experienced stroke and have right-sided lesions.***

***Based on the results of one RCT, there is limited (Level 2) evidence that Attention Process Training may improve attention deficits post stroke.***

***Attention training may have a positive effect on specific, targeted outcomes.***

### 12.5.2 Remediation of Memory Deficits

Cicerone et al. (2005) reviewed 42 studies investigating remediation of memory deficits (Cumming et al. 2013). The updated review included an additional 13 studies, only 3 were prospective RCTs (Table 12.12).

Cicerone et al. (2005) noted that, "*studies of the remediation of memory deficits have addressed a range of memory-related issues including general concerns ("everyday memory problems", impaired learning, capacity to learn during post traumatic amnesia), specific memory problems (remembering names, dates, routes, lists, faces, appointments, routines), the capacity to use effectively compensatory aids (computers, memory books) and individual subjective memory complaints* (Cumming et al. 2013). *Interventions to address these problems have included use of external compensatory aids such as*

*computers, pagers or notebooks; individualized remediation programs with heavy involvement of client input, family/social/ therapist support, and environmental adaptation; didactic lessons and homework assignments; training in compensatory strategies such as rehearsal, organization strategies, visual imagery, verbal labelling, and use of mnemonics; and implicit memory tasks*." The studies added in 2005 continued to address compensatory strategies and the use of assistive devices.

Based on 6 prospective controlled studies, Cicerone et al. (2000; 2005) found evidence for the effectiveness of compensatory strategies for patients withmemory impairments. Effective interventions included internal strategies (such as visual imagery) and the use of external strategies and devices (such as notebooks or diaries, pagers and voice organizers). Training in the use of external compensatory strategies with direct application to functional ability was recommended (Cicerone et al., 2005). It should be noted that the studies on which these recommendations were based focused on the remediation of memory following traumatic brain injury and included very few subjects who had experienced stroke.

**Table 12.12 Remediation of Memory Deficits**

| **Cicerone 2000** | |
|---|---|
| Berg et al. 1991 | Godfrey et al. 1988 |
| Ryan et al. 1988 | Goldstein et al. 1988 |
| Kerner et al. 1985 | Crosson et al. 1984 |
| Schmitter-Edgecombe et al. 1995 | Malec et al. 1983 |
| Freeman et al. 1992 | Evans et al. 1996 |
| Goldstein et al. 1996 | Finset et al. 1995 |
| Wilson et al. 1997 | Benedict et al. 1993 |
| Parente 1994 | Raskin et al. 1996 |
| Benedict et al. 1992 | Sohlberg et al. 1992 |
| Cancelliere et al. 1991 | Sohlberg et al. 1992 |
| Wilson 1982 | Furst et al. 1994 |
| Milders et al. 1998 | Malec et al. 1991 |
| Thoene et al. 1995 | Parente et al. 1983 |
| Zencius et al. 1990 | Glasgow et al. 1977 |
| Burke et al. 1994 | Laatsch et al. 1983 |
| Sohlberg et al. 1989 | Gianutsos et al. 1979 |
| Squires et al. 1996 | Malloy et al. 1984 |
| Kime et al. 1996 | Leng et al. 1991 |
| Schacter et al. 1985 | Chute et al. 1988 |
| Kirsch et al. 1992 | Fowler et al. 1972 |
| Kirsch et al. 1992 | Hersh et al. 1994 |
| **Cicerone 2002** | |
| Kaschel et al. 2002 | Evans et al. 2000 |
| Ownsworth & Mcfarland 1999 | Hart et al. 2002 |
| Wilson et al. 2001 | Van den Broek et al. 2000 |
| Hux et al. 2000 | Wade & Troy 2001 |
| Parente et al. 1999 | Wilson et al. 1999 |
| Donaghy & Williams 1998 | Wright et al. 2001 |
| | Yasuda et al. 2002 |

In the updated review by Cappa et al. (2005), strategies used to improve memory without the use of an electronic aid were judged to be "possibly effective" while specific learning strategies (e.g. errorless learning) were found to be "probably effective" depending upon the task used, the type of memory involved and the severity of impairment. Similarly, the use of external, electronic assistive devices was assessed as "probably effective". As in the earlier review (Cappa et al. 2003), there was very little evidence specifically pertaining to a stroke population. Recommendations and evaluations of treatment

were made based on studies that focused primarily on individuals who had experienced traumatic brain injury rather than stroke. Cappa et al. note a lack of evidence regarding the influence of injury etiology, injury severity, age, gender and stage of recovery (Cappa et al., 2005).

Individual studies examining the effectiveness of interventions directed at the rehabilitation of memory deficits in patients who have experienced stroke are summarized in Table 12.13.

**Table 12.13 Treatment of Memory Deficits**

| Author, Year Country Pedro Score | Methods | Outcome |
|---|---|---|
| Gasparrini & Satz (1979) USA 5 (RCT) | 30 male individuals who had experienced a cerebral vascular accident and had verbal memory deficits underwent training for the use of visual imagery mnemonic technique. 15 subjects were instructed to create an image of the two words of a pair interacting (Imagery) and the other 15 were trained to use rote memory. Each individual participated in 3 sessions during the expanse of one week. Patients' memory was assessed using the Wechsler Memory Scale (WMS) paired associates (PA) test (before before training, directly after training and one week after), a list of 10 common nouns, and 10 statements. In a second experiment, subjects then switched groups and those that originally used rote memory were told to use the visual imagery technique and those that used the imagery technique were told to imagine verbally describing certain objects but not to picture them. A list of 10 PA was used to assess memory. | No significant difference was found between the two memory techniques on any of the assessments except their memory of PA directly following training, however; those who used the imagery technique tended to have higher scores. During the second experiment, those using the visual imagery technique were able to recall significantly more word pairs than those used the verbal mediation technique ($p<0.001$) |
| Doornhein & Haan (1998) Netherlands 4 (RCT) | 12 patients who had suffered a first time cerebral stroke and were 3 to 5 months post-stroke were randomly assigned to receive no training or to receive memory strategy training for 4 weeks with 2 individual training sessions per week. | No overall difference was noted between 2 groups. The treatment group performed significantly better on target memory and Stylus Maze tests. No significant differences were found between groups for the control memory task and the subjective ratings. |
| Rose et al. (1999) UK 5 (RCT) | 48 patients with vascular brain injury and 48 control subjects (mean age = 61) were randomly assigned to an active virtual environment (VE) participation group or a passive (VE) observation group. Active participants were instructed to find their way through a layout of rooms on the computer, observing objects and locating a specific one. Passive participants observed the exploration recorded during an earlier, active session. Following the VE exploration task, participants were assessed for spatial and object recognition. | Patients in both conditions were impaired relative to the controls, but all were able to complete the VE tasks. Active participation resulted in better performance in spatial layout, but not for object recognition. In all conditions control subjects performed better than patients. |
| Wilson et al. (2001) UK 5 (RCT) | 143 patients with a traumatic head injury or a stroke were enrolled in a randomized crossover trial. All had one or more of the following: memory, planning, attention, or organisation problems. The crossover design ensured that some people | More than 80% of those who completed the 16 wk trial were significantly more successful in carrying out everyday activities (such as self care, self medication, and keeping appointments) when using the pager in comparison with baseline abilities. This significant |

| | | |
|---|---|---|
| | received a pager after a 2 wk baseline whereas others were required to wait for 7 wks after baseline before receiving the pager. Participants were assessed at three time periods namely, at baseline, 7 wks, and at 14 wks. | improvement was maintained 7 wks after returning the pager. |
| Kaschel et al. (2002)<br>Germany<br>5 (RCT) | 24 patients with brain injury in 7 rehabilitation centers were randomly allocated to receive imagery-based training or usual care in an ABA design (where A=no training and B= training). The three phases of the study were 4 weeks, 10 weeks (30 sessions) and 3 months in duration. 21 patients completed the trial. Seven of these had memory deficits subsequent to stroke. Imagery training consisted of three phases: motivation for imagery training, rapid generation of images/objects and generation and retrieval of images of simple actions. Following this period of skill acquisition, the skill was applied to problems in everyday life. Assessments included RBMT (logical memory – recall, immediate & delayed), everyday memory tests (appointments), memory assessment clinics rating scale and concentration endurance test administered at baseline and after each study phase. | Comparing measures pre and post-treatment, patients allocated to the imagery group demonstrated significant improvement in logical memory (immediate recall) while patients allocated to pragmatic intervention did not ($p=0.011$ vs. n.s.). A similar result was obtained on a measure of logical memory (delayed recall),. Ratings of patients memory in everyday life improved for patients in the imagery training condition but not the pragmatic condition when scores from post-baseline and post-follow-up were compared ($p<0.0095$ vs. n.s.) |
| Hildebrandt et al. (2006)<br>Germany<br>No Score | 62 patients with memory impairment and acquired brain injury were assigned to receive process-oriented treatment (POT), strategy training (ST) or the control condition over a period of one month. POT focussed on acquisition and recall during the sessions & spaced retrieval between sessions. ST training focussed on teaching strategies and less on encoding and retrieving information. All training was provided in a group setting. Sessions were 1 hour in length, 5 times per week for 4 weeks. Testing was administered before and after the training interval. The control group received a lower intensity version of POT (7 one hour sessions in total). Assessments included short-term free and cued recall, recognition tests, 4 subtests of the RBMT, text reproduction, map learning, categorical word fluency, & the digit/symbol test. | Compared to the control group, performance on word fluency ($p<0.01$) and in retrieval of orally presented texts ($p<0.01$) increased significantly in both treatment groups. Only the POT group demonstrated significant increases in free recall and cued recall tests vs. the control condition. Comparing the two treatments directly demonstrated a trend toward improved semantically cued retrieval and a decrease in rates of forgetting associated with participation in POT training. |
| Westerberg et al. (2007)<br>Sweden<br>6 (RCT) | 18 participants with stroke were randomly assigned to receive either home-based computerized training for working memory or to a control condition (no training). Testing was performed at study entry and following training. Participants assigned to the computer training condition received a CD containing the training software and were asked to complete the program over a 5-week period. From their home PC, participants were to complete 90 trials of the training tasks (approximately 40 minutes) per day, 5 days per week, for 5 weeks. Daily results were | There were significant between group differences reported for performance on tests of working memory (span board – ES=0.83, $p<0.05$ and digit span ES=1.58, $p<0.005$) in favour of computer training. In addition, there were similar significant differences reported for the untrained tests of attention and memory (PASAT ES=0.61, $p<0.001$ and Ruff tests ES=0.81, $p<0.005$). No treatment effects were found on the Raven, Stroop or declarative memory tests. |

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| | reported via internet. In addition, a psychologist provided feedback via telephone on a weekly basis. Assessments included span board, digit span, stroop test, Raven's matrices, PASAT and Ruff 2&7 (serial cancellation tests). | |
| Mount et al. (2007) USA 4 (RCT) | 33 individuals who experienced stroke were randomly assigned in a cross-over study to receive either error-less training first or trial and error training. Participants first performed the task of preparing a wheelchair for use and then using a sock-donner to put on socks. Training continued until retention of the task was achieved or for a maximum of 7 days. An individual's ability to carry-over the task was assessed by using modified versions of the wheelchair and sock-donner. Performance was scored according to the number of errors (verbal errors, errors of no response, errors of action or errors of sequence) an individual made while performing the task. Carry-over was assessed the day after rention in the same way but required the subject to complete a task similar to the original. | Mode of training made no difference for the incidence rate of retention in any level of memory impairment, however individuals with intact memory were more likely to achieve carry-over than those with impaired memory (OR=0.21, p=0.09, 95% CI 0.03 to 1.30). While there was no significant effect of training mode on whether an individual was able to carry-over their abilities in the wheelchair task, individuals who received trial and error were more likely to carry-over their abilities in the sock-donner task than those who received errorless training (OR=0.86, p<0.89, 95% CI 0.92 to 5.98 and OR=19.92, p<0.03, 95% CI 1.34 to 296 respectively). |
| das Nair and Lincoln (2012) UK 8 | 72 individuals who had experienced a stroke, traumatic brain injury, or who were diagnosed with multiple sclerosis, and reported memory problems as a result, were randomized to three study arms: restitution programme (exercises to practice encoding and retrieval, n=24), compensation programme (external memory aids, n=24), or a self help programme (relaxation and coping strategies, n=24). Both the restitution and compensation arms were also taught to use internal memory aids and errorless learning techniques. Participants attended 10 sessions (approx. 1.5 hours each) and were encouraged to use the skills learned in each session in their everyday lives. Assessments were completed at baseline, 5, and 7 months post randomization and included an assessment of language ability, pre-morbid intellectual level, memory, executive capabilities, mood, and disability | A significant difference in the mean group score on the Internal Memory Aids questionnaire (p=0.002) was between groups in an Intention to Treat Analysis. Per protocol analysis demonstrated significant mean group differences between compensation and self help groups on the Internal Memory Aid Questionnaire at 5 (p=0.006) and 7 (p=0.010) month followups, as well as the External Memory Aids Questionnaire at 7 month followup (p=0.049) Per protocol analysis also demonstrated significant differences between restitution and self help groups on the Internal Memory Aid Questionnaire at 5 (p=0.002) and 7 (p=0.011) month followups. |
| Chen et. al (2012) USA 5 | 11 right handed inidividuals with right brain strokes were randomized to receive either Global Processing Training treatment (n=6), or a Role Repetition Training control (n=5). All participants underwent a 90 minute training session which consisted of a pretraining phase (immediate reporoduction of a figure), a training phase (either Global Processing Training treatment or Role Repetition Training control), followed by a post training phase. Global Processing training consisted of drawing progressive subunits of the training | A significant interaction effect (F(1,9)=7.37, p=0.024) demonstrated that immediate post training recall accuracy improved more in the Global Porcessing treatment group than in the control group. The treatment group also demonstrated significantly higher retention rates after 30 minutes than in the control group (significantly different immediate post training scores on repetition #5, p=0.018). There were no signigicant differences found between groups, and improvements were not maintained, during follow up visits |

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| | figure, with each subunit presented in dashed lines to be traced with the previous subunit outlined in solid lines. The Role Repetition training involved tracing the entire figure at once. Each group repeted the task 5 times. During the post training phase, participants were asked to reproduce the figure one last time, followed by a recognition test consisting of three subtests: subunit recognition, spatial recognition, and whole figure recognition. Assessments were repeated 1 day, 2 weeks, and 4 weeks post training | |

**Discussion**

Relatively little evidence exists with regard to the use of compensatory strategies in the remediation of memory deficits post stroke. In general terms, the studies outlined above assessed the use of strategy training, electronic assistive devices and virtual environments.

**Table 12.14 Summary of RCTs Examining Rehabilitation of Memory Deficits**

| Study | N | Treatment | Outcome |
|---|---|---|---|
| Gasparrini and Satz<br>1979<br>USA<br>5 (RCT) | 30 | Visual imagery mnemonic technique vs. Rote memory | Paired associates post test (-)<br>Change in paired associated (-)<br>Word list (-)<br>Sentences (-)<br>Long term memory (-)<br>Teaching Paired Associates (+) |
| | | Visual imagery mneomic technique vs. verbal mediation technique | Paired Associates Test (+) |
| Doornhein & De Haan (1998)<br>PEDro: 4 | 12 | Memory strategy training vs. no training | Name-face paired association task (+)<br>Stylus Maze Task (+)<br>List Learning Task (-)<br>Oxford Recurring Faces Test (-)<br>Memory Questionnaire (subjective judgement) (-) |
| Kaschel et al. (2002)<br>PEDro: 5 | 24 | Imagery-based memory training vs. no training | RBMT – immediate and delayed recall (+)<br>Everyday memory tests (appointments) (+)<br>Memory assessment clinics rating scale – family (+)<br>Memory assessment clinics rating scale – self (-)<br>Concentration endurance test (-)<br>Weschler memory scale (-) |
| Rose et al. (1999)<br>PEDro: 5 | 5 | Active vs. passive participation in virtual environment training. Unimpaired control subjects were also randomized to both conditions. | Spatial Layout (+)<br>Object recognition (-) |

| | | | |
|---|---|---|---|
| Wilson et al. (2001)<br>PEDro: 5 | 143 | Pager prompting system vs. waiting period (no pager) in randomized crossover design | Personalized target behaviours (+)<br>Caregiver strain (+) |
| Westerberg et al. (2007)<br>PEDro: 6 | 18 | Home-based, computerized working memory training vs. control | Working memory and attention (+) |
| Mount et al. (2007)<br>PEDro: 4 | 33 | Trial and error vs. errorless training in randomized crossover design | Incidence rate of retention (-)<br>Carry-over for wheelchair task (-)<br>Carry-over for sock donning task (+) |
| das Nair and Lincoln (2012)<br>PEDro: 8 | 72 | Either compensation or restoration memory programme vs. self help control | Everyday memory questionnaire (-)<br>Rivermead Behavioural Memory Test (-)<br>General Health Questionnaire (-)<br>Extended Activities of Daily Living (-)<br>Internal Memory Aids Questionnaire (+)<br>External Memory Aids Questionnaire (-)<br>Wimbledon Self Report Scale (-) |
| Chen et. al. (2012)<br>PEDro: 5 | 66 | Global Processing Training vs. Rote Repetition Traning | Pre-post training performance (+)<br>Immediate Recall (+)<br>Delayed Recall (-) |

An early study of memory strategy training found no significant treatment effect on memory impairment or subjective memory complaints although there were some improvements associated with treatment on the stylus maze and target memory assessments (Doornhein & De Haan 1998). A study examining the use of imagery training produced positive results on certain target assessments; however, this study included a minority of patients who had experienced stroke (33%) (Kaschel et al. 2002).

The use of a computer as a tool in the remediation of memory has also been examined. A preliminary feasibility study of the use of virtual environments (Rose et al. 1999) suggested that the use of this technology by cognitively impaired stroke survivors would be possible and might result in improvements in spatial memory. More recently, Westerberg et al. (2007) reported improvement of both working memory and attention following an intensive, computerized training program, in a group of individuals with stroke. The training program was provided on CD and each participant completed the training tasks at home. Daily training session results were submitted via the internet and support was provided to the participants by telephone on a weekly basis.

Wilson et al. (2001) employed the use of a pager in an apparently successful strategy, which resulted in improvements in everyday tasks that persisted beyond the end of the intervention and removal of the device. In addition, use of the NeuroPage devices was associated with a reduction in carer strain (Teasdale et al. 2009). However, the participant sample in the original Wilson et al. (2001) study was comprised of individuals with ABI of various etiologies including both TBI (n=63) and stroke (n=36) as well as other disorders (n=44) (Wilson et al. 2001). Fish et al. (2008)reported the results of a specific analysis to examine the effectiveness of Wilson et al. paging system for individuals with stroke. Overall, use of the pager was associated with significant improvements in test performance; however, following pager withdrawal, performance in individuals with stroke regressed to baseline levels. In contrast, test performance remained significantly better than at baseline for participants with TBI. A further examination of between-group differences revealed that participants with stroke tended to be older, have more recent injuries and poorer executive function than participants with TBI. Further analysis of the TBI group suggested that maintenance of gains was associated with executive function. Therefore, selection of an intervention for the remediation of memory should take such factors as etiology of brain injury and executive function into consideration.

***Conclusions Regarding Treatment of Memory Deficits Post-Stroke:***

***There is strong (Level 1a) evidence that compensatory strategies are effective in improving memory outcomes post brain injury. Strategies include imagery-based training and the use of assistive, electronic devices. It should be noted that relatively few study participants had experienced stroke.***

***There is moderate (Level 1b) evidence that an intensive, computerized training program may result in improvements in both working memory and attention.***

***Compensatory strategies can be used to improve memory outcomes. However, more research is required particularly among individuals who have experienced stroke.***

### 12.5.3 Remediation of Executive Functioning and Problem Solving

Cicerone et al. (2000) investigated the remediation of executive functioning and problem solving (Cumming et al. 2013). The term executive functioning as used by Cicerone et al. referred to "*those integrative cognitive processes that determined goal directed and purposeful behaviour and are superordinate in the orderly execution of daily life functions*" (Cumming et al. 2013). Functions affected include the ability to formulate goals; to initiate behaviour; to anticipate the consequences of actions; to plan and organize behaviour according to spatial, temporal, topical or logical sequences; and to monitor and adapt behaviour to fit a particular task or context (Cicerone et al. 2000).

Cicerone et al. (2000) reviewed 14 studies addressing remediation of executive functioning and problem solving (Table 12.15). Only 3 of the identified studies could be classified as a randomized controlled trial or non-randomized cohort study. In the 2005 review by the same authors, 9 studies were added (Table 12.15). The additional studies identified included a single RCT examining the effectiveness of goal management training (Levine et al. 2000); however, no stroke patients were included in the subject population.

Based on results from the RCTs and prospective cohort studies identified in their original review, Cicerone et al. (2000) recommended "*training of formal problem-solving strategies and their application to everyday situations and functional activities*" as practice guidelines (Cumming et al. 2013). Cicerone et al. also recommended as a practice option, "*cognitive intervention that promote internalization of self-regulation strategies through use of verbal self-instruction, self questioning and self-monitoring*" (Cumming et al. 2013). While no new recommendations were made on the basis of the limited information added from RCTs, both recommendations were supported by the updated review (Cicerone et al., 2005). It should be noted here that the proposed recommendations were made based on studies examining patients suffering from traumatic brain injury and not stroke. Individual studies that have examinedinterventions aimed at improving executive functioning and problem solving are summerized in table 12.16

**Table 12.15 Remediation of Executive Functioning and Problem Solving**

| Cicerone et al. 2000 | |
|---|---|
| Von Cramen et al. 1991 | Sohlberg et al. 1988 |
| Fox et al. 1991 | Evans et al. 1998 |
| Cicerone et al. 1992 | Alderman et al. 1995 |
| Cicerone et al. 1987 | Burke et al. 1991 |
| Lawson & Rice 1989 | Rebmann & Hannon 1995 |
| Hux et al. 1994 | Youngjohn & Altman 1989 |

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|---|---|
| Webster & Scott 1983<br>Lira et al. 1983 | |
| **Cicerone et al. 2005** | |
| Levine et al. 2000<br>Medd & Tate 2000<br>Stablum et al. 2000<br>Ownsworth et al. 2000<br>Knight et al. 2002 | Tham et al. 2001<br>Schlund 1999<br>Dayus & van de Broek 2000<br>Bieman-Copeland & Dywan 2000 |

**Table 12.16 Interventions for Executive Function/Problem-Solving**

| Author, Year<br>Country<br>Pedro Score | Methods | Outcome |
|---|---|---|
| Man et al.<br>(2006)<br>China<br>(No Score) | 103 patients with acquired brain injury (>50% stroke) were assigned to one of three problem-solving skills training groups or a control group. All training groups used an analogical skills training approach and had similar structure and content. Each group received 20 sessions (each 45 minutes) in addition to homework assignments between sessions. Group 1 received a computer assisted program (interactive, patient-directed software), Group 2 received online assisted programming (video conferencing with interactive software) and Group 3 participated in face-to-face rehabilitation (therapist administered). The control group received no intervention over the 2-month study period. | All groups experienced significant gains in basic and functional problem solving skills overall. There were no significant between-group differences reported for basic, functional or overall problem-solving skills. There were significant increases in instrumental activities of daily living (Lawton) in each of the treatment groups, but not in the control group. Similarly, there were significant increases on the Category Test reported for all treatment groups, but not for the control group. There was a significant increase in problem-solving self-efficacy in group receiving face-to-face therapist-led intervention only. |
| Liu et al.<br>(2004)<br>Hong Kong<br>6 (RCT) | 46 acute stroke patients were randomized to receive 15 sessions (1 hr/day x 3 weeks) of either mental imagery or functional training designed to improve performance of ADLs. During the 3 weeks, patients were trained to perform 3 sets (5-items each) of daily tasks. Patients also received 1-hour of PT daily. The ability to perform 15 trained tasks as well as 5 untrained tasks was assessed on a 7-point Likert type scale, where higher values were associated with increasing independence. Additional outcome measures included the Fugl-Meyer and the Colour Trails Test. | The mental imagery group showed better relearning of both trained and untrained tasks compared to the control group (both at $p < 0.01$). The mental imagery group also demonstrated better retention of learned tasks and transfer of skill for untrained tasks at 1 month follow-up ($p < 0.01$). |
| Liu et al.<br>(2009)<br>Hong Kong<br>4 (RCT) | 35 acute MCA stroke patients were randomly assigned to a mental imagery or a functional rehabilitation group. The study involved 3 weeks of standardized practice of daily tasks. Patients in the mental imagery group practiced truncating tasks, self reflecting on their abilities, using video feedback, mentally rehearsing, and actually performing the task. The functional rehabilitation group engaged in conventional occupational therapy involving therapist demonstration and patient practice. Each participant also received | The mental imagery group performed significantly better on 4 out of 5 trained tasks (each at $p < 0.05$) and 3 out of 5 untrained tasks (each at $p < 0.05$), some of which involved an unpredictable and continuously changing outdoor environment. |

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| | standard care involving 1 hour of PT per day. The primary outcome was performance on trained and untrained tasks in both training and novel environments. | |
| Levine et al. (2011) International (No score) | 19 brain-injured patients (58% stroke patients) were assigned to receive either Goal Management Training (GMT) or a control treatment called brain health workshop (BHW). Interventions were carried out in the form of seven 2-hour sessions, each with specific objectives. A battery of tests including the Sustained Attention to Response Task (SART), the Delis–Kaplan executive function system (D-KEFs) Tower Test, the Hotel Task, the Dysexecutive Questionnaire (DEX), and the Cognitive Failures Questionnaire (CFQ) was used as the study's primary outcome measure. These tests were performed immediately before and after intervention and then again at 4 months follow up. | The GMT group had a significantly greater reduction in the number of omission errors made than the BHW group on the SART test ($F_{2,30}$=4.872, p<0.02). In addition, at follow-up the number of commission errors on the SART was significantly reduced and scores on the D-KEFs tower test were significantly improved when compared to baseline for the GMT group (p<0.05). No significiant changes were found in the BHW group on any of the tests post-intervention or at follow-up when compared to baseline scores however; the BHW allocated their time significantly better than the GMT group when performed the Hotel test ($F_{2,32}$=4.260 p<0.03). Scores on all other tests post-intervention and at follow-up were not significantly different between groups. |

**Table 12.17 Summary of RCTs Examining Rehabilitation of Executive Function**

| Study | N | Treatment | Outcome |
|---|---|---|---|
| Liu, 2004, Hong Kong, 6 (RCT) | 46 | Mental Imagery vs Functional Training | Score of trained tasks at 2 and 3 weeks (+)<br>Score of trained tasks at 1 month follow up (+)<br>Score of untrained tasks (+)<br>Color Trails Test (-)<br>Fugl-Meyer (-) |
| Liu 2009 Hong Kong, 7(RCT) | 35 | Mental Imagery vs Functional Rehabilitation | Score of 5 trained tasks in training environment (+)<br>Score of 5 trained tasks in novel environment (+)<br>Score of 3 untrained tasks in novel environment (+) |

**Discussion**

Little evidence exists regarding the remediation of executive functioning and problem solving post stroke. Only 2 RCTs could be identified, both of which were conducted by the same group of researchers examining Mental Imagery.

Although the order of the mental imagery protocols was different in each study, they both involved task demonstrations, reflection, mental rehersal, video feedback, and problem identification of each of the learned tasks. The control groups were similar and involved therapist directed demonstration and assistance through each task. Results from these studies suggest that mental imagery may improve task performance and transference to new tasks (of equal difficulty), even in an unpredictable outdoor enviorment.

However, some caution should be given in interpreting these finding given that the intervention was only provided for 3 weeks in both studies. Moreover, the 2009 article involves an acute stroke population (randomized at 2 weeks post stroke) with no signs of cognitive impairement at baseline, suggesting that these results may only be generalizable to acute stroke patients with minimal cognitive deficits.

***Conclusions Regarding Treatment of Executive Functioning/Problem Solving***

***There is little evidence regarding remediation of executive functioning and problem solving post-stroke.***

***There is limited (Level 2) evidence that analogical problem-solving skills training may increase problem-solving skills and performance of extended activities of daily living.***

***Based on 2 RCTs, there is strong (Level 1b) evidence that mental imagery along with actual practice may improve relearning of activities of daily living in acute stroke patients with minimal cognitive deficits.***

***Analogical problem-solving skills training may improve problem solving and instrumental activities of daily living in individuals with stroke.***

### 12.5.4 Multi-Modal Interventions

During rehabilitation, interventions may be provided to address multiple areas of cognitive function. In their 2000 review, Cicerone et al. identified 6 studies that addressed more than one deficit (Table 12.18) (Cumming et al. 2013). No additional studies were added to their 2005 update. Cicerone et al. (2000) concluded that, although there were few studies addressing multi-modal interventions, this type of intervention appears effective resulting in improved neuropsychologic performance in the targeted areas. The authors recommended that interventions be based on the evidence pertaining to individual modes of intervention. As in previous sections examining single, discrete areas of cognitive rehabilitation, it should be noted that conclusions and proposed recommendations were made based on studies examining patients with traumatic brain injury and not stroke. To date only 1 RCT examining a multi-modal intervention within a stroke population has been identified. This study demonstrated that multi-modal interventions may be of some benefit for limited outcomes. All studies examining multi-modal intervention specific to individuals with stroke are summarized in Table 12.19.

**Table 12.18 Multi-Modal Interventions**

| Cicerone et al. 2000 |
|---|
| Batchelor et al. 1988 |
| Chen et al. 1997 |
| Franzen et al. 1993 |
| Laatsch et al. 1997 |
| Middleton et al. 1991 |
| Ruff et al. 1994 |

**Table 12.19 Multi-Modal Interventions**

| Author, Year<br>Country<br>Pedro Score | Methods | Outcome |
|---|---|---|
| Pyun et al.<br>(2009)<br>Korea<br>No Score | 6 patients with cognitive impairment following haemorrhagic stroke participated in a multi-modal training program provided in their home environment. Training included structured cognitive remediation focusing on attention, memory and executive function, story retelling, recreational "cognitive games" and aerobic | All patients showed a trend toward improvement in cognitive function over the course of the intervention (MMSE, p=0.058; NCSE p=0.078). There was significant improvement over time in IADLs (p<0.05) and a non-significant trend toward improvement in ADLs (p=0.068). Domain specific improvements were most evident in areas of spatial perception (p=0.068) |

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| | exercise. The program required 2 hours per day (30 minutes for each component) over a period of 12 weeks. A consultant met with the patient and caregiver once per week to provide support and check rates of participation and progress. Assessment included the MMSE, the Neurobehavioural Cognitive Status Exam (NCSE) as well as computerized cognitive function tests. ADLs and IADLs were also evaluated. | and visual motor organization (p=0.068). |
| Rasquin et al. (2010) The Netherlands No Score | ABI patients (33% stroke) underwent a cognitive rehabilitation programme addressing verbal recall, episodic memory, attention, executive functioning, language, and abstract reasoning. Once a week for 15 weeks, 2.5 hour long group sessions were held with cognitive therapists following discharge. Specific goals were set regarding cognitive gains, exercises were performed and individuals also underwent social skills training. Individuals also had 2 separate sessions with a psychologist. Several neuropsychological tests were used to determine progress in the cognitive domains in addition to goal attainment scaling (GAS) and completion of the Cognitive Failure Questionnaire (CFQ) and the Stroke Adapted Sickness Impact Profile (SA-SIP). Assessments were performed at baseline, directly after treatment and 6 months after treatment. | Compared to baseline, GAS scores were significantly higher directly after treatment (21 weeks) and 6 months following the treatment ($F=94.705$, $p<0.05$). However, goal attainment was not associated with a significant changes on the CFQ or the SA-SIP at these times (P=NS). |
| Kim et al. (2011) South Korea 5 (RCT) | 28 stroke patients with cognitive impairments were randomly assigned to a virtual reality (VR) group or a control group. The VR group received virtual reality training (30min 3x/week) and computer based cognitive rehabilitation (30min 2x/week), whereas the control group received only computer-based cognitive rehabilitation (30min 5x/week). The intervention was provided for a total of 4 weeks and all patients where treated with usual OT/PT care. Primary outcome measures included: computerized neuropsychological test, Tower of London (TOL test), Korean-Modified Barthel Index (K-MBI), and the motricity index (MI) | Both groups showed improvements on most outcome measures, although the VR group scored significantly beter than the control group on the visual continuous performance test ($p<0.01$) as well as the backwards visual span test ($p<0.05$). |

***Conclusions Regarding Multi-Modal Interventions***

***At present, there is an absence of evidence that a multi-modal, home-based cognitive rehabilitation program may be beneficial in terms of cognitive function and instrumental activities of daily living.***

***Although multi-modal interventions appear effective in individuals with traumatic brain injury, there is an absence of evidence regarding the effectiveness of such programs in individuals with stroke.***

## 12.5.5 Alternative Therapies

### 12.5.5.1 Electroacupuncture and TENS

Data from studies in primates as well as from neurophysiological studies in human suggests that sensory stimulation may play a role in the modification "cortical maps" and, thus, influence the rehabilitation process (Johansson et al. 2001). Various studies have examined the effect of stimulation provided via acupuncture, electroacupuncture or high-intensity low-frequency transcutaneous electrical nerve stimulation (TENS) on motor function and functional ability. A single study examining the effect of electroacupuncture and high-intensity low-frequency TENS on cognitive functioning post stroke was identified (Table 12.20).

**Table 12.20 Electroacupuncture or TENS and Cognitive Functioning Post Stroke**

| Author, Year<br>Country<br>Pedro Score | Methods | Outcome |
|---|---|---|
| Rorsman & Johansson<br>(2006)<br>Sweden<br>6 (RCT) | 54 stroke patients, 5 – 10 days post stroke, were randomly allocated to treatment with acupuncture (including electroacupuncture), high-intensity low-frequency TENS or a subliminal, low-intensity high-frequency TENS (control group) condition. Each group received 20 treatment sessions over a period of 10 weeks. Outcomes were assessed at 3 & 12 weeks and included ADL function, motor function, walking abiity, depression and cognitive functioning (assessed via the MMSE, Rey Auditory Verbal Learning Test, Facial Recognition Memory, Star Cancellation Test, Time perception, Token Test and Word Fluency). | On 4 of 8 cognitive variables, there were significant between group differences noted at baseline such that control group participants demonstrated significantly worse performance than patients in the other treatment conditions. Over the period of the study, all patients demonstrated significant improvement, irrespective of treatment on all cognitive measures. There were no significant between group differences noted at 3 or at 12 weeks. There were no significant between group differences noted at any assessment time on measures of depression, although all patients demonstrated significant improvement over the period of the study. |
| Chou et al.<br>(2009)<br>China<br>6 (RCT) | 383 patients with chronic stroke (MMSE<24) were randomly assigned to receive either electroacupuncture or sham TENS (no real electrical current) treatments. Treatment was provided 20-minute sessions, twice per week for a total of 8 weeks. All patients participated in conventional rehabilitation for one month following randomization. Treatment (and sham treatments) was initiated 35-40 days from baseline. All patients continued conventional rehabilitation for the 8-week intervention period. Assessment was conducted at baseline, and following the end of intervention (8 weeks). The Loewenstein Occupational Therapy Cognitive Assessment for geriatric populations (LOTCA-G) was used to assess cognitive function. | In the treatment group, there was significant improvement from baseline to 8 weeks on the following LOTCA-G subscores; orientation (p=0.003), perception (p=0.001), praxis (p=0.002) and memory (p=0.005). At 8 weeks, comparisons between the intervention and control groups demonstrated improved cognition in favour of treatment in the following areas; orientation (p=0.001), perception (p=0.04), praxis (p=0.004) and attention (p=0.045). |

***Conclusions Regarding Electroacupuncture and TENS***

***Based on the results of two RCTs, there is conflicting (Level 4) evidence that treatment with electroacupuncture may improve cognition.***

***Based on the results of a single RCT, there is moderate (Level 1B) evidence that high-intensity low-frequency TENS has no effect on cognitive functioning following stroke.***

***It is uncertain whether electroacupuncture is a useful therapy for post-stroke cognitive impairment.***

***High-intensity low-frequency TENS has no effect on cognitive functioning following stroke.***

### 12.5.5.2 Music Listening

Evidence derived from both animal-based and human-based investigations suggests that music may exert a positive influence on cognitive and emotional functions (Sarkamo et al. 2008). Previous trials have examined the influence of music-based exercise on cognitive function in various clinical groups, including those with dementia (Van de Winckel et al. 2004) and with coronary artery disease (Emery et al. 2003), with generally positive results.

Van de Winckel et al. (2004) conducted a randomized controlled trial evaluating the impact of a music-based exercise program delivered over a period of 3 months on general cognition and behaviour in women with dementia (mean age = 81) when compared with an attention control condition (Van de Winckel et al., 2004). Overall, the group receiving music-based therapy demonstrated significant improvement in MMSE scores as well as greater gains in verbal fluency while the control group demonstrated no significant improvement over time. Unfortunately, as the control group received only attention control (daily, one-on-one conversation) with no exercise or movement requirement, it is not possible to determine the impact of music alone.

Recently, Sarkamo et al. (2008) reported the results of a randomized controlled trial designed to evaluate the impact of music on cognitive recovery following stroke. This trial is summarized in Table 12.21.

**Table 12.21 Music Listening and Cognitive Recovery**

| Author, Year<br>Country<br>Pedro Score | Methods | Outcome |
|---|---|---|
| Sarkamo et al.<br>(2008)<br>Finland<br>6 (RCT) | 60 patients with middle cerebral artery stroke were randomly allocated to music listening, language listening or control groups as soon as possible following discharge from acute care. Patients in the music and language listening groups both received portable CD players and CD's of either music or narrated audio books as appropriate & were instructed to listen to the material by themselves for a minimum of 1 hr/day for a period of 2 months. Patients assigned to the control group received no listening material. 54 patients completed the trial (music = 18, language = 19, control = 17). Follow-up neuropsychological assessments were performed at 3 and 6 months post stroke. | There were significant group X time interactions reported for the domains of verbal memory (p=0.002) and focused attention (p=0.012). Post hoc analysis of change scores demonstrated improvements in both of these areas associated with music listening at both 3 and 6 months. Separate analyses of patients with right and left hemisphere stroke demonstrated that the group X time interaction was only significant in patients with left hemisphere lesions (p=0.011). |

***Conclusions Regarding Music Listening Therapy***

***There is moderate (Level 1b) evidence that self-regulated music listening therapy may have a positive impact on verbal memory and focussed attention in individuals with left hemisphere stroke.***

***Music listening may have a positive impact on cognitive function following stroke.***

### 12.5.5.3 Exercise Programs

Evidence suggests that physical activity and physical fitness have positive benefits on cognitive processes. In a meta-analysis examining fitness effects on cognition in older adults, Colcombe and Kramer (2003) included results from 18 studies published from 1966 to 2001 (see Table 12.22).

**Table 12.22 Exercise and Cognition**

| Colcombe and Kramer 2003 | |
|---|---|
| Barry et al. 1966 | Kramer et al. 1999 |
| Blumenthal et al. 1991 | Madden et al. 1989 |
| Dustman et al. 1984 | Moul et al. 1995 |
| Emery et al. 1990 | Okumiya et al. 1996 |
| Emery et al. 1998 | Palleschi et al. 1996 |
| Hassmen et al. 1992 | Perri et al. 1984 |
| Hawkins et al. 1992 | Powell et al. 1974 |
| Hill et al. 1993 | Rikli et al. 1991 |
| Kharti et al. 2001 | Williams et al. 1997 |

**Table 12.23 Exercise and Cognition**

| Cumming et al. 2012 | |
|---|---|
| Bateman et al. 2001 | Ploughman et al. 2008 |
| Chen et al. 2006 | Pyoria et al. 2007* |
| Fang et al. 2003 | Quaney et al. 2009 |
| Mead et al. 2007 | Ruff et al. 1999* |
| Nilsson et al. 2001 | Studensky et al. 2005 |
| Ozdemir et al. 2001 | Wolfe et al. 2000* |
| *Studies not included in meta-analysis | |

In general, Colombe and Kramer (2003) reported a significant, though small, positive effect on cognitive tasks associated with exercise (ES=0.48). While all study groups tended to improve over time, improvements were significantly greater in intervention than control groups. When analyses were undertaken by task-process category, exercise appeared to have the largest impact on executive processes (ES=0.68). The authors also identified training and participant characteristics associated with improvements in cognition. Combined strength and aerobic activity had a greater impact than aerobic activity. Longer duration programs were better than brief ones and short bouts of exercise had little impact. Women experienced greater positive effects than men and participants aged 66-70 benefitted more than those aged 55-65 or 71-80.

A recent review by Cumming et al. (2011) examined the impact of exercise on cognitive performance in stroke patients. Cumming et al. (2011) identified 12 RCTs but only 9 had sufficient data to be included in the meta-analysis (see table 12.23). The large variability between study interventions prevents drawing firm conclusions regarding frequency, intensity, and type of physical activity provided. Also, the measures used to assess cognitive performance were limited (e.g., MMSE and the FIM) and were rarely the primary focus of these articles. Although this review did report a significant treatment effect favoring the use of exercise, this body of literature is methodologically limitated, which highlights the need for further research in this area. Individual studies that had examined the impact of exercise on cognition following stroke are presented in Table 12.24 below.

**Table 12.24 Exercise Programs and Cognitive Function**

| Author, Year Country Pedro Score | Methods | Outcome |
|---|---|---|
| Ploughman et al. (2008) Canada 6 (RCT) | In a randomized cross-over trial, 21 participants 6 months to 5 years post stroke (MMSE>24) were randomized to receive both conditions in either A-B or B-A sequence. Test conditions were as follows: 1) one 20-minute session of body-weight-support-treadmill-training (BWSTT) at 20% body weight support, 2) a review of home mobility and independence & updating of home exercise programs by a physiotherapist. Cognitive assessment included Trail Making Tests (A,B), symbol digit substitution, paced auditory serial addition test. | Treadmill exercise, when compared to the control condition, had no effect on cognitive performance on any of the assessments administered. |
| Quaney et al. (2009) USA/Canada 5 (RCT) | 38 individuals with chronic stroke (MMSE >23) were randomly assigned to receive either a program of aerobic exercise (n=19) or at-home stretching (n=19). The treatment condition consistent of progressive, resistive aerobic exercise (target 70% max. heart rate) for 45 minutes 3 times per week for 8 weeks. The control/stretching condition performed 45 minutes of at-home stretching over the same time period. Cognition was assessed at baseline, 8 weeks and 8 weeks following the end of intervention. Assessment of cognition included the Wiosconsin Card Sorting Task, Trail making (A,B) and the Stroop test. | There were no significant between group differences observed at either 8 weeks or at the follow-up evaluation for any of the cognition assessments. There were a significant improvements noted in the repeated serial reaction timed task and predictive grip force modulation at the end of the intervention, but these changes were not sustained at follow-up. |
| Rand et al. (2010) Canada No Score | In a single group, pre-post, study, 11 individuals with chronic stroke participated in a 6-month exercise and recreation program. All individuals attended 2 1-hour sessions per week that included stretching, balance and task-specific exercises (e.g. steppers, fast walking, repetitive sit-to-stand). For one hour per week, participants attended a recreation and leisure session that included activities such as bowling, billiards, arts and crafts, etc.) In addition, participants were introduced to existing community fitness resources. Assessment of cognition included the Stroop Test, verbal digit span backward test, trail making test (B), walking while talking (WWT) and the Rey Auditory Verbal Learning Test (RAVLT). | A significant improvement was demonstrated over time (baseline to 3 months) on the RAVLT (long delay) (ES= 0.59, p=0.03), and the WWT (ES=0.42, p=0.04). There was a small, significant improvement on the Stroop Test from baseline to 6 months (ES= 0.12, p=0.02). |
| Kluding et al. (2011) 2011 USA No score | 9 chronic stroke patients were included in this single group pretest-postest study. The study group completed a 12-week aerobic and strengthening exercise program (3x/week). Primary outcome measures examined executive function (Digit Span Backwards and Flanker tests) and secondary outcome measures examined aerobic fitness and function (V02 max, 6MWT, | Significant improvements were found in all outcome measures: Digit Span Backwards test mean change = 0.56+/- 0.9 (P<0.05); Fugl-Meyer mean change = 3.6+/-5.7 (p<0.05); Stroke Impact scale mean change =33.8+/-38.5 (p<0.05). A significant correlation was found between improved performance on the Flanker test and improved aerobic capacity (r=0.74; P<0.05) |

| | | |
|---|---|---|
| | Fugl-Meyer, and 10m walk speed) | |
| Marzolini et. al. (2013) Canada No Score | 41 individuals attending an outpatient stroke rehabilitation program participated in the study. All were >10 weeks post stroke with stroke related motor impairment. Participants attended a 90 minute exercise class once per week, and were offered nutitional and psychosocial councelling, education sessions, cardiac assessments, and plasma and glucose monitoring. They were also provided with training and information on exercising (aerobic and light weight training) at home and encouraged to keep a detailed journal of physical activity. Outcomes were assessed at baseline, and after 6 months in the program and examined cognitive functioning, cardio-pulmonsary exercise training, gas exchange anaerobic threshold, body composition, and muscular strength. | At the 6 month follow up time point, there was a statistically significant reduction in the proportion of individuals who met the criteria for mild cognitive impairment (65.9% at baseline, 36.6% at follow up; $p<0.001$).<br><br>A positive association was also found between change in fat free mass of non affected limbs and cognitive function ($p=0.005$). |

**Discussion**

In two non-randomized studies, exercise was was found to improve cognitive outcomes; however, both studies are limited due to small sample sizes and single group designs. Also, in the study by Rand et al., it is not possible to determine if the demonstrated improvements in executive function were a result of the exercise program, the leisure and recreation component, or both (Rand et al. 2010).

Neither of the identified RCTs demonstrated a significant, positive impact on executive function as evaluated. The analyses presented by Colcombe and Kramer (2003) suggested short bouts of exercise lasting less than 30 minutes such as the one provided in Ploughman et al. (2008) tend to have little impact. However, a longer program of combined training also reported no positive impact on the assessed cognitive functions.

***Conclusions Regarding Exercise Programs and Cognition***

***Based on the results of 1 meta-analysis of studies with poor quality, there is strong (level 1a) evidence that exercise may improve cognition in individuals without significant cognitive impairment post stroke. Further investigation is required.***

***Based on the results of 2 RCTs, there is strong (Level 1a) evidence that exercise does not improve executive function in individuals without significant cognitive impairment following stroke. Further investigation is required.***

***Exercise may be associated with improvement in executive function.***

### 12.5.5.4 Repetitive Transcranial Magnetic Stimulation (rTMS)

Repetitive transcranial magnetic stimulation (rTMS) is a form of non-invasive brain stimulation in which magnetic pulses are delivered to the cerebral cortex through the scalp. A number of studies have examined the potential positive impact rTMS may have on cognitive function. While the majority of studies have been conducted using young, healthy participants, a recent RCT reported that treatment high-frequency rTMS may have a positive, though transitory, effect on working memory in elderly individuals with subjective memory complaints (Sole-Padulles et al. 2006). In addition, improvements in

executive function were reported in a group of older individuals with refractory depression following 5 sessions of rTMS (Moser et al. 2002).

Two trials examining the impact of rTMS on cognitive function in individuals with stroke were identified. These studies are summarized in Table 12.25.

**Table 12.25 Repetitive Transcranial Magnetic Stimulation**

| Author, Year<br>Country<br>Pedro Score | Methods | Outcome |
|---|---|---|
| Rektorova et al.<br>(2005)<br>Czech Republic<br>6 (RCT) | 7 patients with CVD (must include at least one lacunar infarct on brain imaging in addition to clinical evidence of CVD e.g. hemiparesis, lower facial weakness, gait disorder etc.) received a 30-minute treatment session. Each session consisted of 3 rTMS blocks-- each block separated by a 10-minute interval. Sessions were conducted on day 1 and day 4 of the study. Participants received stimulation over the left dorsolateral prefrontal cortex (DLPFC) or over the left motor cortex in a randomized order. Assessments were conducted prior to an immediately following each session. Assessment consisted of Trail Making Tests (A & B), digit symbol test (WAIS-R), Rey-Osterrieth Complex Figure Test, the Stroop Test and the story and digit span tests from the Wechsler Memory Test. | Stroop test and mean digit symbol scores improved significantly following rTMS stimulation. Site of stimulation (motor cortex vs. DLPFC) did not affect improvement in digit symbol scores (p=0.04 for each site). Improvement in Stroop interference was associated with stimulation of DLPFC only (p=0.04). There was no significant improvement demonstrated on any of the other neuropsychological assessments following stimulation of either site. |
| Kim et al.<br>(2010)<br>Korea<br>8 (RCT) | 18 individuals with stroke were randomly assigned to one of three treatment groups; low-frequency (1 Hz), high-frequency (10Hz) or sham (control) rTMS stimulation to the left dorsolateral prefrontal cortex (DLPFC). Patients received 10 treatment session; 5 times per week over a 2-week period). During the study period, all participants also received conventional cognitive rehabilitation 2 or 3 times per week. Assessment was conducted at baseline and immediately following end of treatment (2 weeks). Evaluations included the Computerized Neuropsychological Test (digit span, visual span, verbal learning, visual learning, visual continuous performance, auditory continuous performance & word-colour tests) and the Tower of London Test (planning ability). | Treatment at either frequency was not associated with any significant difference on any cognitive assessment including Tower of London reaction time when compared to the control group. However, treatment was associated with lower scores on the Beck Depression Inventory. |

**Discussion**

The recent study by Kim et al. (2010) demonstrated that, in comparison to a control condition, stimulation of the dorsolateral prefrontal cortex was not associated with improvements in cognitive function. Based on the results of an earlier, smaller study which demonstrated improvements in executive function following rTMS stimulation over the DLPFC, Kim et al. (2010) included an evaluation of planning ability. No significant effect of stimulation was associated with performance of this test.

Both randomized controlled trials, to date, have been very small and assessment heterogeneous. Neither study offered assessment periods extending beyond the end of treatment and, therefore, demonstrated effects may be transient at best. Further study is required.

***Conclusions Regarding Repetitive Transcranial Magnetic Stimulation***

***There is conflicting (Level 4) evidence that repetitive transcranial magnetic stimulation over the left dorsolateral prefrontal cortex may be associated with improvements in executive function following stroke.***

***It is unclear whether rTMS has any effect on executive function following stroke. Further research is required.***

### 12.5.5.5 Transcranial Direct Current Stimulation (tDCS)

In transcranial direct current stimulation (tDCS), a weak, non-invasive electrical current is delivered to induce changes in cortical excitability (Fregni et al. 2005). Previous studies have demonstrated that anodal tDCS may be associated with improvements in cognitive function in humans (Antal et al. 2004; Fregni et al. 2005; Kincses et al. 2004; Nitsche et al. 2003). Studies examining the use of tDCS in the treatment of cognitive function post stroke are summarized in Table 12.26.

**Table 12.26 Transcranial Direct Current Stimulation**

| Author, Year<br>Country<br>Pedro Score | Methods | Outcome |
|---|---|---|
| Jo et al. (2009)<br>Korea<br>7 (RCT) | 10 patients with stroke within the past 6 months were treated with i) 30 mins. anodal tDCS applied over the left dorsolateral prefrontal cortex (DLPFC) (constant current 2mA) and ii) a 30-minute sham stimulation session. Order of sessions was randomized. All stimulation sessions were at least 48 hours apart. Assessments were conducted prior to stimulation and immediately following each session. Primary outcome was performance of on the two-back verbal working memory test (patient is presented with a series of letters and must indicate if the current presentation is the same as the one provided "two back"). A total of 30 targets were presented. Accuracy and reaction time are measured. | On repeated ANOVA, there was a significant intervention X time interaction identified (p=0.032). There was a significant improvement noted in the pre- and post- stimulation recognition accuracy scores of the anodal stimulation group (p=0.004), but not in the sham stimulation group (p=0.403). There were no significant differences in response time demonstrated for either group. |
| Kang et al. (2009)<br>Korea<br>8 (RCT) | 10 patients with previous stroke received i) 20 minute administration of anodal tDCS (2 mA) to the left DLPFC, ii) corresponding sham stimulation. The order of stimulation was randomized. Sessions were at least 2 days apart. Outcomes assessed included the "go/no go" test (subjects are presented with 30 figures and must press a button in response to the figure "1"). Number of correct responses and reaction time are evaluated. The go/no go test was administered at baseline, 1, 2 and 3 hours post | There were no significant intervention X time interactions identified for either correct responses or reaction time for the control group. In the stroke patient portion of the study, ANOVA revealed a significant intervention X time interaction (p=0.043) for number of correct responses. tDCS stimulation was associated with a significant improvement in correct responses at one hour (p=0.024) which was maintained at 3 hours post treatment (p=0.041). Active stimulation had no significant effect on response time. Assessment of subjective outcomes |

| | | |
|---|---|---|
| | stimulation. In addition, the authors collected subjective descriptions of attention, fatigue, task difficulty and sleep quality (at baseline and 3 hours only).<br>10 healthy control subjects were also recruited and participated in an identical, parallel study. | demonstrated no effect associated with the stimulation intervention. |

**Discussion**
Working memory and attention are of particular importance in motor relearning and recovery post stroke. The results of two RCTs suggest that anodal tDCS to the left dorsolateral prefrontal cortex may result in some improvement to these areas of cognitive function. However, sample size in both studies was limited. Further research is required.

***Conclusions Regarding Transcranial Direct Current Stimulation***

***Based on the results of 2 small RCTs, there is strong (level 1a) evidence that anodal tDCS to the left dorsolateral prefrontal cortex is associated with improvements in working memory and attention. Further research is required.***

***Anodal transcranial direct current stimulation may help to improve working memory and attention post stroke.***

## 12.6 Pharmacotherapy for Vascular Cognitive Impairment

Devasenapathy and Hachinski (2000) noted that, "the early manifestations of vascular cognitive impairment can be thought of as important signs of imminent future stroke that require the same urgent clinical management as symptomatic cerebrovascular disease". According to O'Brien et al. (2003), vasodilators, nootropics, and antioxidants have all been tried for vascular dementia without success.

Other medications that have been investigated include donezepil (Chui 2000), memantine (Mobius 1999), hydergine, pentoxifylline, propentofylline, piracetam, nimodipine, and ginkgo biloba. Most of these have all shown only modest and/or clinically irrelevant effects (Chui 2000). Chui (2000) also notes that the therapeutic effects are usually very similar in patients with Alzheimer's Disease and vascular dementia, suggesting that the these two types of dementia may share a common pharmacodynamic basis.

### 12.6.1 Aspirin

Daily aspirin therapy has been shown to reduce the incidence of TIAs, recurrent strokes and cardiovascular death based on its antiplatelet effects. While aspirin is commonly prescribed to patients with cognitive impairment (Molnar et al. 1998), its benefit in terms of impact on cognitive outcomes is not well studied. A single RCT was identified and is summarized in Table 12.27.

**Table 12.27 Daily Aspirin Therapy in Vascular Dementia**

| Author, Year<br>Country<br>Pedro Score | Methods | Outcome |
|---|---|---|
| Meyer et al. | 70 patients with multi-infarct dementia were | The ASA treatment group demonstrated higher levels |

| | | |
|---|---|---|
| (1989)<br>USA<br>6 (RCT) | randomized to receive either 325 mg ASA/day (n=37) in addition to usual care or just usual care (n=33). No placebo was given. Outcomes assessed were cerebral blood flow (CBF) measurements and cognitive testing via the cognitive capacity screening examination (CCSE). Patients participated for up to 3 years. Mean length of follow-up was 15.6 months for the treatment group and 14.9 months for the control group. | of cognitive performance on the CCSE than the control group ($p<0.0001$) during all three years of follow-up. Patients in ASA condition improved above baseline at all assessments while the control group experienced declines in CCSE scores. CBF values were also significantly better among ASA treated patients than among controls ($p<0.0001$). ASA treated patients experienced fewer TIAs and/or strokes and the mortality rate was lower, however, the numbers associated with these events were too small for meaningful statistical analysis. |

**Discussion**

The pilot study by Meyer et al. (1989) demonstrated benefits associated with aspirin therapy. However, the results should be interpreted taking into consideration limitations of both size and methodology.

However, no further randomized controlled trials assessing the effects of ASA on post-stroke dementia could be identified by either the present study or in a recent Cochrane Review (Rand et al. 2010).

This could be, in part, due to difficulties in designing ethical randomized controlled trials within an environment of widespread ASA use for other purposes such as the primary and secondary prevention of stroke (Devine & Rands 2003). In a recent retrospective case analysis of 78 stroke patients with a diagnosis of ischemic vascular dementia, Devine and Rands (2003) reported that aspirin use was associated with increased times to institutionalization and death, but only in cases where the patient lived with a caregiver. However, increasing age was significantly associated with decreased time to institutionalization and death and the group of patients to whom aspirin was prescribed tended to be younger. Further research into the role of aspirin in post stroke cognitive impairment is indicated.

***Conclusion Regarding Aspirin in the Treatment of Vascular Dementia***

***ASA is commonly used in the treatment of vascular dementia. There is moderate (Level 1b) evidence, based on a single, pilot RCT, that ASA is effective in stabilizing and/or improving cognitive outcomes in patients with multi-infarct dementia.***

***ASA is a common antithrombotic therapy used in the treatment of vascular dementia and may be effective in stabilizing cognitive deficit.***

### 12.6.2 Cholinesterase Inhibitors

Cholinergic agents have been used in the treatment of dementia of the of vascular dementia. While there has been evidence from large RCTs supporting the effectiveness of these compounds in the treatment of Alzheimer's Dementia, the evidence supporting their use in the treatment of vascular cognitive impairment is less clear (Craig & Birks 2005) Alzheimer's type. Three such agents, donepezil, rivastigmine and galantamine, have also been investigated for use in the treatment

### 12.6.1 Donepezil

Donepezil is a selective acetylcholinesterase inhibitor used in the treatment of mild to moderate dementia. Among patients with dementia of the Alzheimer's type, the use of donepezil has been well studied.

The effectiveness of donepezil among patients with vascular dementia has been the subject of 2 large randomized controlled trials. These trials are summarized in Table 12.28

**Table 12.28 Donepezil in the Treatment of Vascular Dementia**

| Author, Year Country Pedro Score | Methods | Outcome |
|---|---|---|
| Black et al. (2003) International 7 (RCT) | 603 Patients with probable (70.5%) or possible (29.5%) VaD were randomized to 24 weeks of treatment with donepezil 5 mg/d, donepezil 10 mg/d (5 mg/d for first 28 days), or placebo. | At week 24, both donepezil groups showed significant improvement in cognition versus placebo on the Alzheimer's Disease Assessment Scale–cognitive subscale. Significant improvements in global function were seen versus placebo at week 24, on the Clinician's Interview-Based Impression of Change–Plus version only for patients on donepezil 5 mg/d, and on the Sum of the Boxes of the Clinical Dementia Rating only for patients on 10 mg/d. Donepezil-treated patients showed significant benefits in activities of daily living over placebo on the Alzheimer's Disease Functional Assessment and Change Scale. Withdrawal rates due to adverse events were relatively low (placebo, 11.1%; donepezil 5 mg/d, 11.1%; donepezil 10 mg/d, 21.8%; *P*=0.005 versus placebo). |
| Wilkinson et al. (2003) International 7 (RCT) | 616 patients with probable or possible VaD, were randomized to receive donepezil 5 mg/day, donepezil 10 mg/day (after 5 mg/day for the first 28 days), or placebo for 24 weeks. | 76% of patients had probable VaD. Both donepezil-treated groups showed significant improvements in cognitive function on the Alzheimer's Disease Assessment Scale–cognitive subscale compared with placebo. Greater improvements on the Clinician's Interview-Based Impression of Change–plus version were observed with both donepezil groups compared to the placebo group. Withdrawal rates due to adverse events were low (placebo, 8.8%; donepezil 5 mg, 10.1%; 10 mg, 16.3%). |
| Roman et al. (2010) International 7 (RCT) | 974 patients with possible or probable VaD were randomized (2:1) to receive either treatment with donepezil 5 mg/day (n=648) or matching placebo (n=326). 77.5% and 76.7% of individuals in the treatment and control conditions, respectively, had a history of stroke or TIA at baseline. Primary outcome measures were the Vascular AD Assessment Scale – Cognitive Subscale (V-ADAS-Cog) and the Clinician's Interview-Based Impression of Change + carer's interview (CIBIC-plus). Assessments were conducted at baseline and weeks 6, 12, 18 and 24 (end of study). | Patients in the treatment condition demonstrated significant improvement from baseline when compared to the placebo condition at all assessment points except week 6 ($p<0.05$). CIBIC-plus scores were not significantly different between groups (p=0.23), but analysis of score distribution favoured treatment at 18 and 24 weeks. Examination of secondary outcomes revealed significant differences favouring donepezil at end of study on the ADAS-cog (p=0.046), MMSE (p=0.03) and NCT (p=0.039). A similar trend toward significance was demonstrated on the Disability Assessment for Dementia (DAD) (p=0.059). |

**Discussion**

Recent meta-analyses of the results from Black et al. (2003) and Wilkinson et al. (2003) reported that the use of donepezil in patients with mild to moderate vascular cognitive impairment is associated with significant improvements in cognitive and global function, including improvements in the performance of activities of daily living (Passmore et al. 2005). In a small, open label study Whyte et al. (2008) demonstrated that individuals with recent stroke demonstrated greater functional improvement

(motor-FIM) over a 12-week treatment period when compared to a historical, matched comparator group.

In the most recent and largest RCT (Roman et al. 2010), small, but significant improvements were demonstrated in cognitive but not global function outcomes. The authors suggest that mild levels of impairment may have resulted in a ceiling effect for the CIBIC-plus assessments or that this particular assessment tool is not sufficiently sensitive to detect small, but potentially important, changes.

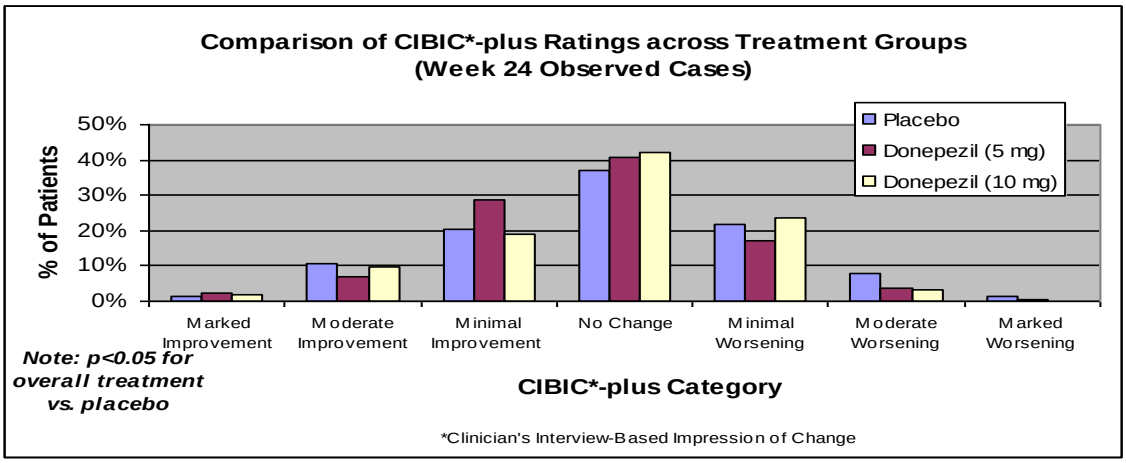
Roman et al. (2010) also conducted subgroup analyses based on the presence of hippocampal atrophy (HA). Participants with normal-sized hippocampi (NH) on MRI performed significant better than those with HA on the V-ADAS-cog, the Number Cancellation Test, ADAS-cog and DAD administered at baseline. In addition, there was a differential treatment effect identified such that NH patients treated receiving donepezil demonstrated greater improvements on the V-ADAS-cog than those with HA. Individuals with HA in the placebo group declined over time while those with NH improved slightly. The authors suggest that the presence of hippocampal atrophy plays an important role in the course of vascular dementia.

Side effects associated with the use of donepezil are mild to moderate in nature and include diarrhea, nausea, arthralgia, leg cramps, anorexia and headache (Erkinjuntti et al. 2004).

**Efficacy and tolerability of donepezil in vascular dementia: positive results of a 24-week, multicenter, international, randomized, placebo-controlled clinical trial. (Black et al. 2003).**

603 patients with probable or possible vascular dementia were randomly allocated to receive either 5 mg/day donepezil, 10 mg/day donepezil (following 5 mg/day for the first 28 days) or matching placebo for a period of 24 weeks.

Groups receiving donepezil demonstrated significant improvement in cognition when compared to patients receiving placebo. Significant improvements in global function were seen versus placebo at week 24, on the Clinician's Interview-Based Impression of Change–Plus version only for patients on donepezil 5 mg/d, and on the Sum of the Boxes of the Clinical Dementia Rating only for patients on 10 mg/d. Donepezil-treated patients showed significant benefits in activities of daily living over placebo on the Alzheimer's Disease Functional Assessment and Change Scale.




***Conclusions Regarding Donepezil for the Treatment of Vascular Dementia***

***Based on 3 RCTs, there is strong (Level 1a) evidence donepezil taken for 24 weeks improves cognitive function in patients with probable or possible vascular dementia.***

***Based on 2 RCTs and 2 meta-analyses, there is strong (Level 1a) evidence that treatment with donepezil is associated with improvement in global function for individuals with probable or possible vascular dementia.***

***Treatment with donepezil improves cognitive and global function in patients with vascular dementia.***

### 12.6.2.2 Rivastigmine

Rivastigmine is an acetylcholin-esterase inhibitor and a butyrylcholin-esterase inhibitor. In patients with mixed dementia; that is, Alzheimer's dementia patients with concurrent cerebrovascular disease or vascular risk factors, treatment with rivastigmine has been associated with significant benefits over treatment with placebo (Erkinjuntti et al. 2002; Kumar et al. 2000). In addition, it has been demonstrated that the benefits derived from treatment are greater among patients with concurrent vascular risk, such as hypertension, than among patients without such vascular risk factors (Erkinjuntti et al. 2002; Erkinjuntti et al. 2003b; Kumar et al. 2000). Given the apparent association between the presence of vascular risk factors and treatment benefit, further evaluation of rivastigmine in the treatment of vascular dementia would seem warranted.

A few studies have investigated the use of rivastigmine in the treatment of subcortical vascular dementia resulting from small vessel disease producing either lacunar infarcts or ischemic white matter changes (Moretti et al. 2001; Roman et al. 2002). None of these are randomized controlled trials. Brief summaries of these non-randomized clinical trials are presented in Table 12.29.

**Table 12.29 Rivastigmine in the Treatment of Subcortical Vascular Dementia**

| Author, Year<br>Country<br>Pedro Score | Methods | Outcome |
|---|---|---|
| Moretti et al.<br>(2001)<br>Italy<br>No Score | 16 patients with probable vascular dementia. Subcortical vascular dementia was diagnosed for patients with moderate to severe ischemic white matter changes and one or more lacunar infarcts. Patients were divided into 2 groups. Group A received rivastigmine (3-6 mg daily) while Group B received only "cardioaspirin". | After one year of treatment, cognition (assessed by MMSE, clock drawing and word fluency) remained stable among patients treated with rivastigmine (Group A). There was a trend among patients in Group B (cardioaspirin) to deteriorate on all cognitive assessments. Group B performance was significantly worse than Group A ($p<0.05$), caregivers of patients in Group B were more stressed ($p<0.05$). Scores on the Neuropsychiatric Inventory were higher among Group B patients ($p<0.01$) and they were more likely to use sedative or neurolectic medication for behavioural or social functioning than patients in Group A ($p<0.05$). |
| Moretti et al.<br>(2002)<br>Italy<br>No Score | 16 patients with subcortical vascular dementia were divided into two groups (n=8 in each group). One group received rivastigmine 3 – 6 mg/day while the other received only "cardioaspirin" 100 mg/day. Patients were followed for 22 months. Global cognitive function was assessed using the MMSE, and executive function with the ten-point clock-drawing test. Semantic and phonological fluency and ADL functioning were also assessed. *(Note: the 12-month results of this study are summarized above in Moretti et al. 2001)* | Significant improvements in executive function were noted in the rivastigmine group both over baseline ($p<0.01$) and when compared to the aspirin group ($p<0.001$). Scores on the Neuropsychiatric Inventory and on the Clinical Dementia rating were also significantly better among patients treated with rivastigmine than among those in the aspirin group ($p<0.01$ and $p<0.05$, respectively. Caregivers of patients in the rivastigmine group reported a significant reduction in stress over baseline ($p<0.05$). Scores on global performance, word fluency and ADL function were maintained among patients in the rivastigmine group. There were no improvements on any outcome measure in the aspirin group. |

| | | |
|---|---|---|
| Moretti et al. (2003)<br>Italy<br>No Score | 208 patients with subcortical vascular dementia were divided into 2 groups matched for age and education. Group A received rivastigmine 3 – 6 mg/day while Group B received 100 mg/day ASA. Length of follow-up was 12 months. | Deterioration in global cognitive function assessed on the MMSE was seen in both groups although deterioration was worse among patients in Group B. There was greater deterioration in executive function in the aspirin group ($p<0.05$). Assessment of behaviour and of depression revealed significant improvements in the rivastigmine group when compared to the ASA group ($p<0.001$ for both). No serious adverse events were reported. |
| Moretti et al. (2004)<br>Italy<br>No Score | 64 patients with probable subcortical vascular dementia were divided evenly into 2 groups matched for age and education. 32 patients were treated with rivastigmine 3 – 6 mg/day. 32 patients were treated with ASA 100 mg/day plus nimodipine 60 mg/day. Patients were followed for a total of 16 months. | Patients in both groups demonstrated deterioration in MMSE scores at 8 and 16 months. There was a non-significant trend for greater deterioration among patients treated with ASA and nimodipine. Significant benefits ($p<0.05$) were associated with rivastigmine treatment with respect to performance on assessments of attention, executive function, instrumental activities of daily living and behavioural/psychotic disturbances. Transitory adverse effects such as nausea, muscle contractions and postural instability were reported during the rivastigmine titration phase. These resolved spontaneously. No serious adverse effects were reported in either group. |
| Narasimhalu et al. (2010)<br>China<br>9 (RCT) | 50 patients with cognitive impairment no dementia (CIND, DSM-IV diagnosis) following stroke, were randomly assigned to receive either rivastigmine 9mg/day or matching placebo for 24 weeks. Primary outcome was mean change on the ten-point clock drawing test and color trails test 1 and 2. Secondary outcome assessments included the ADAS-Cog, Frontal Assessment Battery, the AD Cooperative Study ADL test, the NPI and Geriatric Depression Scale. | There were no significant between group differences on any of the primary study outcomes, although difference in mean change scores from baseline to 24 weeks approached significance for the color trails 2 test ($p=0.09$). The sole between group difference in mean change to reach significance was for the secondary outcome assessment, verbal fluency animals – part of the ADAS-Cog ($p=0.02$) |

**Discussion**

In these non-randomized, open-label clinical studies, there have been benefits associated with treatment with rivastigmine among patients with subcortical vascular dementia. In general, treatment has been associated with more stable cognitive performance and better behavioural response leading to less caregiver stress. Further studies, including large randomized controlled trials, are necessary to determine the effectiveness of rivastigmine in the treatment of vascular dementia or vascular cognitive impairment.

In a recent study focusing on cognitive impairment no dementia (CIND) post stroke, Narasimhalu et al. (2010) reported to significant improvement in executive function associated with treatment with rivastigmine. The sole significant improvement found was on the animals subtask of the test of verbal fluency included on the ADAS-Cog assessment. The authors suggest that, unlike the pencil-and-paper measures selected as tests for the primary outcome, the animals subtask is a measure of executive function not restricted by limitations in function or weakness in the dominant hand. No other treatment effects were noted for any of the other areas of cognitive function tested.

***Conclusions Regarding Rivastigmine for the Treatment of Vascular Dementia***

***There is limited (Level 2) evidence that treatment with rivastigmine is associated with more stable cognitive performance and improved behavioural outcomes among patients with subcortical vascular dementia.***

***There is moderate (Level 1b) evidence that treatment with rivastigmine has no effect on executive function in individuals with cognitive impairment no dementia following stroke.***

***Treatment with rivastigmine may stabilize cognitive performance and improving behaviour for patients with subcortical vascular dementia. Further study is required.***

***Treatment with rivastigmine does not result in improved executive function in individuals with post-stroke cognitive impairment, no dementia.***

### 12.6.2.3 Galantamine

Galantamine is an acetylcholinesterase inhibitor that also modulates nicotinic receptors (Erkinjuntti et al. 2002; Erkinjuntti et al. 2004). It has been shown to be of benefit in terms of cognition, behaviour and the performance of activities of daily living when used in the treatment of Alzheimer's dementia.

Studies examining the effectiveness of galantamine in the treatment of vascular dementia are summarized in Table 12.30.

**Table 12.30 Galantamine in the Treatment of Vascular Dementia**

| Author, Year<br>Country<br>Pedro Score | Methods | Outcome |
|---|---|---|
| Erkinjuntti et al. (2002)<br>International<br>8 (RCT) | 592 patients with probable vascular dementia or mixed dementia (AD+ cerebrovascular disease) were randomly assigned to receive either 24 mg/day galantamine (n=396) or matching placebo (n=196). Treatment continued for a period of 6 months. | Overall, patients treated with galantamine showed significant improvement on the ADAS-cog when compared to the placebo group (p<0.0001). Treatment with galantamine resulted in significant improvements when compared to placebo among patients with AD+CVD (p<0.0005) but not among patients with vascular dementia (p<0.06). The same pattern was reported for assessment on the Clinician's Interview-based Impression of Change Plus scale. 74% of treatment group patients remained stable or improved on the CIBIC-plus vs. 59% of those in the placebo group (p=0.011) However, on subgroup analysis, the change seen among treated patients was not significantly different than for untreated patients (p=0.238) when taking only patients with vascular dementia into consideration. |
| Erkinjuntti et al. (2003a)<br>International<br>(*single-blind extension of Erkinjuntti et al. 2002*) | Patients who had been treated with galantamine in the previous study (see above) continued treatment (n=295), while patients who had been allocated to the placebo condition began treatment with galantamine (n=164). Treatment continued for an additional 6 months. | After the additional 6 months , there were improvements as assessed by the ADAS-cog – 11 reported in the group receiving treatment in both phases, and in the group receiving placebo for the first 6 months followed by galantamine. Although these did not reach significance. Significant improvements were noted in functional ability for both groups (p<0.001 for the placebo/galantamine |

| | | |
|---|---|---|
| | | group vs. p<0.01 for the galantamine/galantamine group). |
| Whyte et al. (2008) USA No Score | 40 patients with recent stroke (within past 30 days) were assigned to receive either galantamine (4 mg b.i.d – titrated to 12 mg b.i.d over 12 weeks) or donepezil 5 mg/day (titrated to 10 mg/day). A historical, matched, comparator group was created via chart review (n=110). Patients were assessed on the motor-FIM, the apathy evaluation scale, the Hopkins verbal learning test, digit span and the executive interview at baseline and 12 weeks. | 14 participants withdrew from the study (7 in each group) leaving 26 patients for analysis. Of the 13 patients in the galantamine group, only 9 achieved the target dose of 12 mg b.i.d. All patients in the donepezil group reached the target dosage in the 12-week study period. FIM-motor scores improved in all groups, but at 12 weeks, patients receiving donepezil demonstrated significantly greater improvement than either individuals receiving galantamine or those in the historical comparator group (ANOVA group X time; p=0.003). There was no significant difference in 12-week FIM change in the galantamine vs. comparator groups. Tests of cognition results improved significantly over time in both the galantamine and donepezil groups with no significant group X time interactions. Similarly, there was an overall trend toward improvement in apathy over time. |

**Discussion**

While treatment with galantamine appears to be associated with benefit in terms of cognitive and functional ability, the subgroup analysis performed by Erkinjuntti et al. (2002) suggests that these effects are seen most clearly in cases of mixed dementia (AD+ cerebrovascular disease) rather than vascular dementia (Erkinjuntti et al. 2002).

In a small, open-label study of the use of acetylcholinesterase inhibitors in individuals with recent stroke, Whyte et al. (Whyte et al. 2008) reported that while all patients experienced improvements in function (assessed on the motor-FIM) over time, patients treated with galantamine did not improve significantly more than the historical, matched comparator group. Patients treated with donepezil experienced the most improvement in function (Whyte et al. 2008).

***Conclusions Regarding Galantamine in the Treatment of Vascular Dementia***

***There is moderate evidence (Level 1b), based on a single RCT of excellent quality, that treatment with galantamine is associated with improvements in cognitive and functional ability. However, the benefits associated with treatment are more clearly demonstrated among patients with mixed dementia than vascular dementia. Further study is required.***

***Treatment with galantamine may be associated with cognitive and functional benefits, particularly in individuals with mixed dementia.***

### 12.6.3 Nimodipine

Nimodipine is a calcium-channel blocker that readily crosses the blood-brain barrier. It has a vasoactive effect, which may improve blood supply to areas that are hypoperfused (Lopez-Arrieta & Birks 2002; Pantoni et al. 2000). It has been used most frequently in the treatment of Alzheimer's Dementia and multi-infarct dementia. Individual studies are summarized in Table 12.31.

**Table 12.31 Nimodipine in the Treatment of Vascular Dementia**

| Author, Year Country Pedro Score | Methods | Outcome |
|---|---|---|

| | | |
|---|---|---|
| Besson et al.<br>(1988)<br>Scotland<br>7 (RCT) | 20 patients with a history of multi-infarct dementia (Hachinski Ischaemic Scale score >9) were randomized to received either nimodipine 30 mg t.i.d. (n=10) or placebo (n=10). Treatment duration = 24 weeks. Cognition was assessed using the Mental Status Questionnaire, Sandoz Clinical Assessment – Geriatric Scale (SCAG), Royal College of Physicians Test, Katzman-memory-oreientation-concentration test and the Dementia Checklist. Assessments were conducted every 4 weeks. | There was no significant change on any measure of cognition over the 24 week study period in either group. |
| Sze et al.<br>(1998)<br>China<br>6 (RCT) | 100 acute stroke patients admitted to stroke ward were enrolled 7 – 14 days post stroke. Patients were stratified according to disability (less severe - MMSE≥24, BI>25 or severe – MMSE<24 and BI≤ 25) and, then randomized to receive oral nimodipine 30 mg 3 times/day for 12 weeks or no nimodipine. ASA and Warfarin were administered prn for secondary prevention of stroke in both groups. Assessments were performed at baseline, at 6 and 12 weeks. | Patients receiving nimodipine demonstrated greater improvement in Fuld Object-Memory Evaluation scores at 12 weeks compared to the control group (p=0.03). Patients with severe disability at baseline who received nimodipine demonstrated greater change in MMSE scores over time (p=0.05). |
| Pantoni et al.<br>(2000)<br>International (Europe)<br>8 (RCT) | 259 patients diagnosed with dementia or multi-infarct dementia and CT evidence of at least one infarct or moderate to severe ischemic white matter changes were randomly allocated to treatment with nimodipine (30 mg., times per day, n=128) or matching placebo (n=131).Treatment continued for up to 6 months. Assessments were undertaken at 4, 10, 18 and 26 weeks. | By intention-to-treat analysis, there were no significant differences between the treatment and control group from baseline to the final assessments. Serious adverse events were reported by 12.5% of the treatment group and 16.8% of the placebo group. |
| Pantoni et al.<br>(2005)<br>Italy<br>8 (RCT) | 242 patients with subcortical vascular dementia & at least one CT image consistent with lacunar infarct were randomly assigned to receive either 90 mg/day of nimodipine or matching placebo. Treatment continued for one year. Primary outcome was assessed via the Sandoz Clinical Assessment Geriatric Scale (SCAG). | There were no significant differences between groups assessed on the primary outcome measure. However, patients treated with nimodipine performed better than those in the placebo condition on lexical production (p<0.01) and semantic fluency (p<0.01). Treatment was also association with less deterioration on the MMSE (p<0.01) and the Global Deterioration Scale (p<0.05). |

**Discussion**

A recent meta-analysis reported that treatment with nimodipine among patients with vascular dementia is associated with non-significant improvements in global function and activities of daily living when compared to placebo conditions (Lopez-Arrieta & Birks 2002). Nimodipine appears to be well tolerated with few adverse effects (Lopez-Arrieta & Birks 2002). However, given the results of individual studies, it is unclear which group of patients is most likely to benefit from treatment with nimodipine. A large, multi centre, randomized controlled trial is currenly underway in China (Wang et al. 2012). This study may be able to shed some more light on the efficacy of nimodipine in the treatment of cognitive impairment following stroke.

***Conclusions Regarding Nimodipine and the Treatment of Vascular Dementia***

***There is moderate (Level 1b) evidence that treatment with nimodipine is beneficial for memory. There is also moderate (Level 1b) evidence that treatment with nimodipine may slow cognitive deterioration and improve semantic and phonetic fluency among patients with subcortical vascular dementia.***

***Treatment with nimodipine is of benefit in the treatment of memory deficits. Among patients with subcortical vascular dementia, treatment with nimodipine may slow cognitive decline.***

### 12.6.4 Memantine

Memantine is an antagonist of the N-methyl-D-aspartate (NMDA) receptor. Its use has been evaluated among patients with Alzheimer's Dementia and those with vascular dementia. Studies examining the effectiveness of treatment with memantine in vascular dementia are summarized in Table 12.32.

**Table 12.32 Memantine and the Treatment of Vascular Dementia**

| Author, Year<br>Country<br>Pedro Score | Methods | Outcome |
|---|---|---|
| Orgogozo et al.<br>(2002)<br>France<br>8 (RCT) | 321 patients with probable vascular dementia were randomly allocated to treatment (n=165) or control (n=156) groups. Patients in the treatment condition received 20 mg/day while control patients received a matching placebo. Treatment continued for 28 weeks. | At 28 weeks, patients in the treatment condition had demonstrated improvement on the ADAS-cog while patients in the control condition declined. The difference between groups was significant (95% CI 0.49 – 3.60). On the Clinician's Interview Based Impression of Change-Plus (CIBIC-plus), 60% of patients in the treatment condition were assessed as improved or stable vs. 52% in the placebo group (p=0.227). Scores on the MMSE were improved in the treatment group, but deteriorated in the placebo group (p=0.003). Assessment of intellectual function and of behaviour also demonstrated differences in favour of treatment (p=0.04 & p=0.07 respectively). A similar number of adverse events were reported in each condition. |
| Wilcock et al.<br>(2002)<br>UK<br>8 (RCT) | 548 patients with probable vascular dementia and MMSE scores of 10 –22 were randomly assigned to treatment with 20 mg/day (10 mg twice daily) memantine (n=295) or matching placebo (n=284). Treatment duration was 28 weeks. Primary efficacy outcomes were assessed via the ADAS-cog and the Clinical Global Impression of Change (CGIC). | At 6 months, scores on the ADAS-cog showed significantly less decline among patients treated with memantine vs, placebo (95% CI –3.023 to –0.49). There was no significant difference reported between groups on the CGIC. Subgroup analysis demonstrated that the largest treatment effects were among patients with baseline MMSE scores less than 15 and in those with no cerebrovascular macrolesions. No serious adverse events were reported and the frequency of reporting was similar between treatment conditions. |

**Discussion**

Among patients with probable vascular dementia, treatment with memantine appears to be beneficial and has been associated with the stabilization and improvement of cognitive outcomes relative to treatment with a placebo. Treatment effects may be larger among patients with greater cognitive impairment (MMSE <15) or with small vessel disease (Wilcock et al. 2002).

***Conclusions Regarding Memantine and Vascular Dementia.***

***There is strong (Level 1a) evidence, based on the results of 2 RCTs, that treatment with memantine is associated with stabilization or improvement of cognitive function.***

***Among patients with vascular dementia, treatment with memantine is associated with stabilization or improvement of cognitive function.***

### 12.6.5 Pentoxifylline

Pentoxifylline is a methylzanthine compound. Its use was associated with a significant increase in cerebral blood flow, which subsequently stimulated an interest in its use for the treatment of vascular dementia (Sha & Callahan 2003). A recent review by Sha and Callahan (2003) included 4 randomized controlled trials of pentoxifylline in the treatment of vascular dementia (Table 12.33).

While the authors were unable to pool data for a meta-analysis, they noted that the studies provided evidence of a trend toward improved cognitive function among patients with vascular dementia following treatment with pentoxifylline. When secondary analyses of subgroups based upon more restrictive criteria for vascular dementia were undertaken, the trends toward a positive result became significant more often(Sha & Callahan 2003).

**Table 12.33 Studies included in Sha & Callahan (2003)**

| |
|---|
| Ghose (1987) |
| Blume et al. (1992) |
| Black et al. (1992) |
| EPMID (1996) |

**Table 12.34 Pentoxifylline and the Treatment of Vascular Dementia**

| Author, Year<br>Country<br>Pedro Score | Methods | Outcome |
|---|---|---|
| Ghose<br>(1987)<br>UK<br>(RCT) | Following a 2 week washout period, in which all patients received placebo, 36 patients with either primary degenerative dementia or multi-infarct dementia were randomly allocated to groups receiving either 400 mg oxpentifylline (400 mg. 3 times/day) or matching placebo for a period of 12 weeks. | Both groups demonstrated improvement over the period of treatment, but it did not reach significance. For patients diagnosed with multi-infarct dementia, there was greater improvement associated with treatment when compared to the placebo condition ($p<0.05$). However, there were only 4 patients with multi-infarct dementia who received treatment and 7 in the control group. |
| Black et al.<br>(1992)<br>USA<br>6 (RCT) | 64 patients diagnosed with multi-infarct dementia were randomized to receive either pentoxifylline (400 mg 3 times/day) or matching placebo for 36 weeks. Randomization was stratified for length of time since diagnosis of dementia (longer than vs. less than 2 years). Assessment was undertaken with the Alzheimer's Disease Assessment Scale (ADAS) at baseline and at the study endpoint. | There was a non-significant trend toward less cognitive deterioration among patients receiving treatment with pentoxifylline when compared to placebo ($p=0.058$). This included 14 patients with neither discrete strokes nor neuroradiological evidence of CVD. In a subgroup of 40 patients with CT/MRI evidence of vascular damage, use of pentoxyfilline was associated with a significant slowing of cognitive deterioration as measured by total ADAS scores ($p=0.023$) and ADAS cognitive subscores ($p=0.020$). In 37 patients with CT/MRI evidence of at least one discrete stroke, treatment was associated with significantly less deterioration on both the total ADAS score and cognitive subscores ($p=0.002$ & $p=0.017$ respectively). |
| Blume et al. | 80 patients, aged between 55 and 75, with | Significant differences in favor of the pentoxifylline group |

| | | |
|---|---|---|
| (1992)<br>Germany<br>8 (RCT) | symptoms of vascular dementia, were randomized to receive either pentoxifylline 1200 mg daily p.o (n=40) or matching placebo (n=40). Treatment lasted for 24 weeks and was preceded by a 2 week washout period. Patients were assessed at 2, 4, 6, 8, 16, and 24 weeks. Outcomes consisted of the Figure Joint Test (FJT), Number/Letter Repetition Test (N/LRT), Sandoz Clinical Assessment Geriatric Scale (SCAG), Adjective Check List (ACL), and Clinical Global Impression (CGI). | were reported for the SCAG ($p<0.001$) and the FJT ($p<0.003$). The pentoxifylline group displayed greater improvements than placebo on the N/LRT (improvements of 13% vs. 8%) and in most scales of the ACL. Change in patients' status, as assessed by the CGI, was determined to be positive in 23% of the placebo group patients vs. 61% of those in the pentoxifylline group. Results of a subgroup analysis performed on 40 patients with "stepwise deterioration", as defined by Hachinski Ischemic Score (HIS), largely mirrored those of the total study population. Adverse events were reported in 30% of placebo group patients vs. 45% of pentoxifylline group patients. Complaints regarding adverse events were mostly mild and evenly spread between the groups, with the exception of gastro-intestinal side effects, for which a causal relationship was suspected with study medication in 15% of placebo vs. 56% of pentoxifylline reports. |
| EPMID Study Group<br>1996<br>Germany<br>7 (RCT) | 289 patients, over the age of 45, diagnosed with multi-infarct dementia were randomized to receive either oral pentoxifylline 400 mg t.i.d.(n=148) or matching placebo (n=141). Treatment lasted for 9 months and was preceded by a 4 week washout period. Patients were assessed every 3 months. Primary cognitive outcomes were assessed via the Gottfries, Brane, Steen Scale (GBS). Secondary outcomes included geriatric dysfunction, cognitive function and psychological function. These were assessed on the Sandoz Clinical Assessment Geriatric Scale (SCAG), the MMSE and a battery of psychological tests. | Patients allocated to the treatment group demonstrated an improvement in cognition and behaviour as assessed on the GBS. On intention-to-treat analysis, this represented a non-significant trend in favour of treatment when compared to the placebo condition ($p=0.065$). Similar results in favour of treatment were also reported for the intellectual functions ($p=0.06$), emotional functions ($p=0.07$) and various symptoms ($p=0.04$) subscales of the GBS. Patients in the treatment group demonstrated significant improvement on the total and cognitive function subscale of the SCAG when compared to controls ($p=0.34$ & $p=0.007$, respectively). 66 patients in the treatment condition and 62 patients receiving placebo reported adverse events. These events were assessed as "at least possibly related to" the study drug more often among patients receiving pentoxifylline, mostly due to increased incidence of gastrointestinal side effects such as nausea and vomiting. |

**Discussion**

In general, studies have demonstrated a trend toward positive effects on cognitive function associated with the use of pentoxifylline in vascular dementia.

***Conclusion Regarding Pentoxifylline and Vascular Dementia***

***There is strong (Level 1a) evidence that treatment with pentoxifylline is associated with cognitive benefit in patients with multi-infarct dementia.***

***Treatment with pentoxifylline may be benefit to cognition in patients with multi-infarct dementia.***

## 12.6.6 Alternate pharmacotherapies

### 12.6.6.1 Citicoline

Citicoline (or cytidine diphosphate choline) has been evaluated as a neuroprotective agent in

cerebrovascular disease. Previous studies have suggested that treatment with citicoline may be associated with improved cognitive function, specifically memory in elderly individuals (Cohen et al. 2003).

A single study examining the effectiveness of citicoline in the treatment of vascular dementia was identified (Table 12.35).

**Table 12.35 Citicoline and the Treatment of Vascular Dementia**

| Author, Year Country Pedro Score | Methods | Outcome |
|---|---|---|
| Cohen et al. (2003) USA 7 (RCT) | 30 patients diagnosed with vascular dementia were randomized to receive either 500 mg citicoline (n=15) or matching placebo twice per day (n=15) for 12 months. Outcomes were assessed at baseline, 6 and 12 months using a battery of neuropsychological tests. | There were no significant differences in change in overall cognitive function (MMSE or Dementia Rating Scale Scores) between groups from baseline to 6 months or baseline to 12 months. Change scores did not differ between groups on measures of memory, executive-attention, and language, visuo-spatial or motor function. Effect sizes associated with any neuro-cognitive measures were very small. |
| Alvarez-Sabin et. al. (2013)Spain 6(RCT) | Individuals who participated in the study were randomized to receive either citicoline (1g/day)(n=172) or no treatment (n=175). This study was open labeled. Participants underwent a neurophycological battery at baseline, 6 month and 12 month follow ups. Outcome assessments were combined to give an indication of attention and executive functioning, memory, language, spatial perception, motor speed, and temporal orientation. | At both 6 month and 12 month follow ups, individuals in the citicoline treatment group demonstred significantly greater odds of having no impairment in attention and executive functioning (6 month: OR 1.72 (95%CI 1.07 to 2.78, p=0.027; 12 month: OR2.38 (95%CI 1.27 to 4.46), p=-0.007) and temporal orientation (6 month: OR 1.78(95%CI 1.02 to 3.10, p=0.042; 12 month: OR2.16 (95%CI 1.02 to 4.57), p=-0.045)<br><br>No significant differences were observed between groups in memory, spatial perception, or motor speed |

***Conclusions Regarding Alternate Medications (citicoline) for the Treatment of Vascular Dementia***

***There is conflicting evidence regarding the effect of citicoline in the long term management of cognitive function post stroke.***

***Citicoline has no effect on cognitive function.***

### 12.6.6.2 Antidepressant pharmacotherapy

Tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are all used in the treatment of depression following stroke. Given the significant association between the presence of depression and cognitive impairment, the effect of antidepressant use on cognition has been investigated (Table 12.36).

**Table 12.36 Efficacy of Milnacipran on Cognitive Dysfunction**

| Author, Year Country Pedro Score | Methods | Outcome |
|---|---|---|

| | | |
|---|---|---|
| Kimura et al.<br>(2000)<br>USA<br>8 (RCT) | 47 stroke patients with major and minor depression (DSM-IV) were randomly assigned to receive either treatment with nortriptyline titrated to 100 mg (o.d.) or matching placebo. Treatment lasted 6 – 12 weeks. Outcomes assessed included changes in depression (HRSD) and cognitive impairment (MMSE). | There was no significant group or group X time interaction for MMSE scores identified. However, when patients were grouped as responders vs. non-responders in terms of change in depression, there was a significant groupXtime interaction identified (p=0.005) such that cognitive function recovered more rapidly in the responder group than in the non-responder group. Responders had significantly higher MMSE scores at doses of 75mg and 100 mg. o.d. The authors note that there were significantly more patients who had received nortriptyline in the responder group than in the nonresponder group (p=0.0032). Improvement in cognitive impairment was demonstrated only in patient with major depression at baseline. |
| Sato et al.<br>(2006)<br>Japan<br>No Score | 18 patients with post-stroke depression, approximately 3 months post-stroke, were divided into a milnacipran (n=10) and a control (n=8) group. The treatment group received between 30 and 60 mg/day of milnacipran over the treatment period, while the control received no antidepressants. Cognitive impairment and mood were measured with the Mini-Mental State Examination (MMSE) and the Hamilton Depression Rating Scale (HAM-D) at time of admission and approximately 3 months later, at discharge. | Neither the milnacipran nor the control group displayed significant change in depression symptoms, as measured by the HAM-D, from admission to discharge. A significant time-by-group interaction was found with respect to cognitive impairment (MMSE) (p=0.034), such that there was greater improvement from baseline to discharge for the milnacipran group than the control. |
| Jorge et al.<br>(2010)<br>USA<br>7 (RCT) | 129 stroke patients with no depression at baseline were randomly assigned to receive either escitalopram 10 mg. o.d., problem-solving therapy or matching placebo. In addition to assessments for depression, neuropsychological evaluations were conducted at baseline and 12 months (end of intervention). Assessments included the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Trail-making Tests (A & B), Controlled Oral Word Association, Wechsler Adult Intelligence Scale – Similarities and the Stroop Test. | To examine the effect of escitalopram on cognition, the placebo and problem-solving groups were collapsed to form a single non-escitalopram group. Controlling for change in HRSD and stroke mechanism, there was a significant between group-difference in favour of treatment for the overall RBANS score (p<0.01). In addition, there was a greater change in delayed memory scores (p<0.01) and in immediate memory scores (p=0.01)associated with escitalopram therapy (when controlling for time since stroke, change in HRSD and stroke mechanism). No treatment effect was identified for change in RBANS attention, language or visuospatial/ constructional domains, Trail-making tests, word association, Stroop test or on the Weschler similarities test. Patients who received escitalopram demonstrated greater changes on cog-FIM than those who did not (p=0.03). |

**Discussion**

According to Haring (2002), the majority of studies have failed to find a positive correlation between successful management of post-stroke depression and improved cognitive functioning (Andersen et al. 1996; Haring 2002; Lipsey et al. 1984; Robinson et al. 2000). This may be due to the inclusion of patients with minor depression (not associated with cognitive impairment) or the failure of patients with major depression to respond to treatment (Murata et al. 2000; Robinson et al. 1986). Kimura et al. (2000) demonstrated significant positive effects associated with treatment and remission of post-stroke depression, but only for those individuals who were diagnosed with major depression. Sato et al. (2006) also demonstrated improvements in cognition associated with the treatment of post-stroke depression.

As part of a study examining prevention of depression, Jorge et al. (2010) evaluated the effect of antidepressant use (escitalopram) on the cognitive function in a group of individuals with stroke, but no depression at study entry. The authors identified a significant improvement in global cognitive function and memory (immediate and delayed recall) associated with treatment. This effect was independent of the impact of treatment on depression, time since the index event and type or mechanism of stroke.

***Conclusions Regarding Alternate Medications (antidepressants) for the Treatment of Vascular Dementia***

***There is moderate (Level 1b) evidence that treatment and remission of post-stroke depression is associated with reduction in cognitive impairment.***

***There is moderate (Level 1b) evidence that use of escitalopram in individuals with no post-stroke depression is associated in improvements in global cognitive function and memory.***

***Remission of depression following antidepressant therapy is associated with improved cognitive function.***

***The use of escitalopram in individuals without post-stroke depression is associated with improved global cognition and memory.***

## 12.7 Cochrane Reviews of Cognitive Rehabilitation Following Stroke

There are currenly four Cochrane reviews in existance that examine the efficacy of treatments for cognitive impairment following stroke or cognitive impairment of a vascular nature. They investigate a range of therapeutic strategies including occupational and drug interventions, as well as interventions targeted at memory and attention deficits specifically. These Chochrane reviews are valuable in synthesizing the available evidence surrounding this impairment. Table 12.37 provides a summary of these reviews.

**Table 12.37 Summary of Cochrane Reviews for cognitve therapies following stroke**

| Author, Year<br>Country<br>Title | Description | Results |
|---|---|---|
| das Nair & Lincoln (2008)<br>UK<br><br>Cognitive Rehabilitation for Memory Deficits Following Stroke | Two idetintified studies met the criteria for inclusion in this review (total n=18 stroke patients).<br><br>Inclusion Criteria: Randomized Controlled Trials in which a treatment for memory was compared with a control. Studies included participants with memory deficts as a result of a stroke. Drug studies were not included<br><br>Obectives:<br>▪ To determine if patients who receive cognitive therapies following a stroke experience a better functional outcome | One study examined the use of memory strategies applied to specific memory problems (2 individual sessions per week for 4 weeks). The other study explored the use of an imagery mneumonic programme (30 sessions over 10 weeks) applied in 2 phases (Phase I: rapid generaration of images from given verbal information; Phase II: phase I skills applied to problems in daily life)<br><br>Authors concluded that, based on the limited number pf studies and the diversity of strategies implemented, there is little evidence to suggest that memory rehabilitation is more effective than no therapy or control. At this time, there is insfficient evidence to support or refute the use efficacy of memory rehabilitation strategies in the |

| | | |
|---|---|---|
| | then those who do not receive therapy<br>▪ To determine if individuals who receive cognitive therapy experience better memory function | treatment of cognitive impairment following stroke. |
| Loetscher & Lincoln (2013)<br>UK<br><br>Cognitive Rehabilitation for Attention Deficits Following Stroke | Six studies were included in this review (total n=223)<br><br>Inclusion Criteria: Randomized Controlled Trials in which attention therapy was compared with a placebo treatment or no therapy were included in this review. All studies included participants with attention deficits following a stroke. Drug studies were not included.<br><br>Objectives:<br>▪ To determine if individuals who receive attention treatment have improved outcomes in attentional functions than those who receive no therapy or control therapy<br>▪ To determine whether those who receive attention therapies will have better outcomes in quality of life, independence in ADLs, and mood | A trending significant effect was found in the immediate effects of treatment in global attention functioning (2 studies) when comparing treatment with usual care (Standardized mean difference: 0.53. 95%CI:-0.03 to 1.08,p=0.06). There no significant effects observed in long term improved glocal attention functioning (2 studies).<br><br>There was a positive significant effect in favour of treatment for divided attention (4 studies) (standardized mean difference 0.67, 95%CI:0.35-0.98, p<0.0001). No short term or long term effects were observed in any other domains of attention (alertness, selective attention, and sustained attention), functional abilities, mood, or quality of life.<br><br>Authors concluded that the short term and long term effectiveness of therapies for attention deficits following stroke is largely unconfirmed. Some changes were observed in short term effectiveness, howevere, further trials are needed to adequately support the benefit of cognitive rehabilitation for attention following stroke. |
| Hoffman et. al. (2010)<br>Australia<br><br>Occupational Therapy for Cognitive Impairment in Stroke Patients | One RCT was included in the review (n=33).<br><br>Inclusion Criteria: This review examined RCT's, quasi-randomized trials, and crossover trials of adult stroke survivors with confirmed cognitive deficits. Studies with therapies carried out or supervised by an occupational therapist were included. Drug trials were excluded from this review.<br><br>Objectives: To determine if occupational therapy strategies effect improvement in cognative abilities and functional ADL's in individuals with cognitive impairment following stroke. | No significant effects of the treatment were noted in the one study included. This study was significanltly biased and of low methodological quality.<br><br>Authors concluded that there is currenly a lack of evididence to either support or refute the use of occupational therapy strategies in the treatment of cognitive impairment following a stroke. |
| Birks et. al. (2013)<br>UK<br><br>Rivastigmine for Vascular Cognitive Imapirment | Three studies were included in the review (n=800)<br><br>Inclusion Criteria: Double-blind RCT's involving individuals with vascular dementia or vascular cognitive impairment were included in the review. All trials compared the drug with a placebo control.<br><br>Objective: To determine the efficacy of rivastigmine in the treatment of vascular cognitive impairment, vascular dementia, or mixed dementia | Due to heterogeneity between study designs (follow up timpoints, dose of drug, participant characteristics) a meta analysis could not be completed. One large study was able to detect a benefit of rivastigmine on cognition.<br><br>Authors concluded that sufficient evidence does not exist to make any conclusions regarding the the use of rivastigmine in the treatment of vascular cognitive impairment or vascular dementia. More trails are required. |

Overall, the four Cochrane reviews examining interventions for cognitive imprairment following a stroke event that have been conducted to date are largely inconclusive. There is an overall lack of evidence to support these therapies. Few randomized controlled trials have been conducted, and many are lacking in methodological quality. The general concensus of these four reviews is that, although various interventions for cognitive impairment following stroke appear to have some promise, more studies need to be conducted in order to support this.

## 12.8 Delirium Post Stroke

Delirium is a common neuropsychiatric syndrome in older people in all medical settings (Edlund et al. 2006; Meagher 2001). According to the Diagnostic and Statistical Manual of Mental Disorders-IV, delirium is characterized by: (i) a disturbance of conscioiusness; and (ii) change in cognition or the development of a perceptual disturbance (iii) which develops over a short period of time and fluctuates during the course of the day; and (iv) that cannot be better accounted for by pre-existing or evolving dementia (Ferro et al. 2002).

Though often mistaken for dementia, delirium differs from it particularly in its acute, fluctuating course and reversibility (Meagher 2001). Clinical features include an acute, generalized impairment of cognitive function affecting orientation, attention, and memory as well as planning and organizational skills. Sleep cycle, thought processes, affect, perception and activity levels may also be affected (Meagher 2001).

Delirium may be categorized into three basic types; hyperactive-hyperalert, hypo-active-hypoalert and mixed (Edlund et al. 2006). Symptoms associated with hyperactive-hyperalert delirium include logorrhea, motor hyperactivity, aggressiveness, stereotyped activities, hyper-reaction and delusions (Camus et al. 2000) whereas individuals with hypoactive-hypoalert delirium may experience facial inexpressiveness, motor retardation, speech retardation, decreased reactivity, perplexity and mental slowness (Camus et al. 2000).

### 12.8.1 Prevalence and Natural History of Delirium Post Stroke

According to a recent review by Inouye, the prevalence of delirium in the general community is estimated to be approximately 1 – 2% (Inouye 2006). Among individuals over the age of 85, this estimate rises to 14%. At hospital admission, 14 – 24% of individuals present with delirium, while during hospitalization estimates range from 6 – 56% (Inouye 2006). Delirium may occur in as many as 60% of individuals residing in nursing homes (Inouye 2006). In a recent study of individuals admitted to an internal medicine service that included individuals with stroke, Edlund et al. reported that 31.3% of the patients had delirium on the first day of admission (Edlund et al. 2006).

Among stroke patients, reported rates for the development of delirium have ranged from 13% (Caeiro et al. 2004) to 48% (Gustafson et al. 1991). However, the means by which delirium was assessed varied between studies. Gustafson and colleagues (1991) evaluated stroke patients 3 to 7 days after admission using the DSM-III criteria and the Organic Brain Syndrome Scale. In the 1991 and 1993 studies, delirium was detected in 48% and 42% of patients, respectively (Gustafson et al. 2010; Gustafson et al. 1991). Using the DSM-IV and the Delirium Rating Scale, Henon et al. (1999) diagnosed delirium in 24% of 202 acute stroke patients. Caeiro et al. (2004) also used the Delirium Rating Scale and reported that 13% of patients with stroke had delirium.

It has been reported that delirium was found more frequently following haemorrhagic than ischemic stroke (88% vs. 50%) (Gustafson et al. 2010). Caeiro et al. (2004) reported that delirium was significantly more frequent following intracerebral haemorrhages, as well as in patients with neglect, medical complications and older age. In a study of 68 patients with acute SAH, Caeiro et al. (2005) reported that 16% developed delirium. In these patients, delirium was associated with severity of SAH, disturbance of alertness, aphasia, older age, higher amounts of intraventricular blood and hydrocephalus.

Rates for delirium may be under-estimated, as it may be mistaken for dementia or depression (Edlund et al. 2006; Inouye 2006; Meagher 2001). If assessment of cognition is not undertaken or is undertaken on a single occasion only, fluctuations associated with delirium may be missed (Edlund et al. 2006; Inouye 2006).

While delirium may resolve within 10 – 12 days (Weber et al. 2004), it may take weeks or even months before symptoms are resolved (Inouye 2006). For older patients, recovery may be incomplete and deficits, particularly of attention and memory, may persist (Meagher 2001; Weber et al. 2004).

### 12.8.2 Risk Factors for Delirium

The causes for delirium are multi-factorial and represent an interaction between pre-disposing factors (personal vulnerability) and precipitating factors (noxious events or events related to hospitalization) (Inouye 2006; Inouye & Charpentier 1996). In a recent review, Inouye et al. (2006) presented 7 categories of risk factors as shown in Table 12.37 below, while precipitating events were placed into the following categories: drug-use, primary neurologic diseases (including stroke), intercurrent illnesses, surgery, environmental stressors and prolonged sleep deprivation. Taking this multi-factorial approach, stroke is seen as an important risk factor as well as a precipitating factor (Edlund et al. 2006; Inouye 2006).

**Table 12.38 Risk Factors for Delirium**

| Demographic | Cognitive | Functional | Sensory | Oral Intake | Drugs | Co-morbidities |
|---|---|---|---|---|---|---|
| ·Age ≥ 65<br>·Male | ·Dementia<br>·Cognitive impairment<br>·Previous delirium<br>·Depression | ·Dependency<br>·Immobility<br>·Low activity level<br>·History of falls | ·Visual or hearing impairment | ·Dehydration<br>·Malnutrition | ·Multiple psychoactive drugs<br>·Polypharmacy<br>·Alcohol abuse | ·Serious or terminal illness<br>·Chronic renal or hepatic disease<br>·Previous stroke<br>·Neurologic disease<br>·Metabolic disturbance<br>·Trauma/fracture<br>·AIDS |

Inouye (2006) suggested that dementia is the leading risk factor for delirium. A meta-analysis of studies examining delirium in patients over the age of 50 reported that the presence of dementia increased the risk for delirium 5-fold (OR = 5.2; Elie et al. 1998). In addition, the authors reported that medical illness (OR = 3.8), use of narcotics (OR= 1.5), male gender (OR = 1.9), depression (OR = 1.9), alcohol abuse (OR = 3.3), abnormal sodium (OR = 2.2), hearing impairment (OR = 1.9), visual impairment (OR = 1.7) and reduced activities of daily living (OR = 2.5) were all significant risk factors for the development of delirium. However, it was not possible to pool all results from all identified studies due to varying

methods of assessment, varying definitions of delirium and differences in study populations. The presence of delirium in patients with dementia may cause a dramatic worsening in the course of cognitive decline resulting in worsening functional status or loss of independence (Inouye 2006).

Among individuals with stroke, Henon et al. (1999) identified previous cognitive decline as the most important risk factor for delirium. In 202 acute stroke patients, 24.7% of individuals with previous cognitive decline (no dementia) developed delirium with 48 hours of admission compared to 45.5% of individuals with dementia and 13.2% of individuals with no previous cognitive decline (Henon et al. 1999). In a 2002 review, Ferro et al. cited older age, extensive motor impairment, previous cognitive decline, metabolic and infectious complications and sleep apnea as significant risk factors for delirium among individuals who experienced stroke. Caeiro et al. (2004) also found the presence of delirium to be associated with intracerebral haemorrhages, left hemi-neglect, medical complications and older age (Caeiro et al. 2004). Sheng et al. (2006) demonstrated via logistic regression analysis that older age, haemorrhagic stroke, metabolic disorders, pre-stroke dementia, Glasgow Coma Scale score <15, inability to raise both arms at the time of admission were all significant risk factors for delirium. McManus et al. reported significant determinants of delirium in acute stroke to be unsafe swallow on admission, admission Barthel score <10, elevated C-reactive protein on admission and poor pre-stroke vision (McManus et al. 2009). Pre-stroke cognitive impairment did not reach significance as an independent predictor of delirium. A recent study of 527 stroke patients(mean age =72) also identified a number of independent risk factors for delirium in stroke patients including: pre-existing cognitive decline, infection, right hemisphere stroke, carotid artery circulation large artery stroke, hight National Institutes of Health Stroke Scale Score, and brain atrophy (Oldenbeuving et al. 2011).

### 12.8.3 Clinical Consequences of Delirium

In general, delirium has been associated with longer lengths of stay in hospital, higher frequencies of in-hospital complications such as falls, infections and pressure sores, increased need for institutionalized care and increased risk for mortality (Meagher 2001). Inouye (2006) reported mortality rates associated with delirium of 22 to 76% among hospitalized patients and one-year mortality rates of 35 to 40%.

When compared to stroke patients with no delirium, the presence of delirium post stroke has been associated with longer hospitalization (Henon et al. 1999; McManus et al. 2009; Sheng et al. 2006), a reduced likelihood of discharge home (Henon et al. 1999; McManus et al. 2009; Sheng et al. 2006), poorer functional outcome at discharge on the Barthel Index and Rankin Scale (Henon et al. 1999; McManus et al. 2009) and greater losses of independence in terms of activities of daily living ($p<0.001$) (Henon et al. 1999). Long-term follow-up at 6 and 12 months following stroke has demonstrated that stroke patients who had experienced delirium were less likely to be living at home (Henon et al. 1999; Sheng et al. 2006), and had poorer functional outcomes (Henon et al. 1999; Sheng et al. 2006) and lower MMSE scores (Henon et al. 1999; Sheng et al. 2006). In addition, patients with delirium lasting more than 24 hours had significantly worse outcomes in terms of morality (6 months) and functional outcomes than patients with delirium of less than 24 hours (Sheng et al. 2006). Vida et al. (2006) demonstrated that the presence of delirium was associated with a decline in activities of daily living among patients with no dementia while among patients with dementia, the presence of delirium had no effect on the level of basic or extended activities of daily living over a period of 18 months. Among non-demented patients with delirium, stroke was one of the identified factors associated with decline in function (Vida et al. 2006).

Caeiro et al. (2004) reported that the presence of delirium was associated with an increased risk of death or dependency (OR = 6.44 95% CI 2.61 – 15.88). Sheng et al. (2006) also demonstrated that mortality at both 6 and 12 months post stroke was greater among patients who had experienced

delirium. This was further corroborated by Ka Ying Miu et. al. (2013) who observed both a higher inpatient mortality and higher 1-year morality in a study of 314 stroke patients. Shi et. al. (2012) also found a higher risk of mortality at 12 months (OR 4.91, 95%CI: 3.18 to 7.6). McManus et al. found post-stroke delirium to be significantly associated with increased inpatient mortality but not with mortality post-discharge (McManus et al. 2009). However, Henon et al. (1999) demonstrated that mortality rates both at the time of discharge from hospital and at 6 months post-discharge were not affected by the presence of delirium in stroke patients. Similarly, in their review, Ferro et al. (2002) state that delirium post stroke is associated with poor functional prognosis but not with an increased risk for mortality.

### 12.8.4 Prevention of Delirium Post Stroke

In a recent review, Inouye states that as many as 30 – 40% of cases of delirium may be preventable (Inouye 2006). Prevention is based primarily upon the recognition and aggressive management of known risk factors for its development (Weber et al. 2004). In addition, supportive and environmental measures may help protect against delirium (Meagher 2001). A single study examining the management of risk factors in the prevention of delirium was identified (Table 12.38).

**Table 12.39 Prevention of Delirium**

| Author, Year<br>Country<br>Pedro Score | Methods | Outcome |
|---|---|---|
| Inouye et al.<br>(1999)<br>USA<br>No score | 852 patients, age ≥ 70, admitted to a general medicine service received either a multicomponent risk factor intervention or usual care on the basis of a prospective matching strategy. The risk factor intervention was designed to address 6 risk factors for delirium; cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment and dehydration. Primary study outcome was delirium as assessed using the Confusion Assessment Method. | The rate of incident delirium during hospital admission was significantly lower among those individuals assigned to the risk factor management intervention when compared to usual care (OR = 0.60 95% CI 0.39 – 0.92). Total number of days of delirium was lower in the intervention group (p=0.02) as was total number of episodes (p=0.03) compared to the usual care group. In patients with delirium, there were no between group differences for severity of delirium or rate of recurrence. |

**Discussion**

The study by Inouye et al. (1996) suggests that aggressive management of known risk factors results in a reduction in the incidence and duration of delirium. However, it should be noted that this study was undertaken within a population of individuals admitted to a general medicine service. While the study exclusion criteria did not indicate stroke patients, it was not clear that any individuals with stroke were actually a part of the study.

***Conclusions Regarding Prevention of Delirium***

***There is limited (Level 2) evidence that a multi-component approach to the management of known risk factors is associated with reduced incidence and duration of delirium. However, this has not been demonstrated within the stroke population. Further study is required.***

***A multi-component approach targeting known risk factors may reduce the incidence and duration of delirium. Further study within the stroke population is required.***

### 12.8.5 Treatment of Delirium Post Stroke

There is limited information regarding effective treatment of delirium. A recent review by Weber (2004)identified 2 RCTs. One (Cole et al. 2002) evaluated the effectiveness of screening and multidisciplinary care in delirious general medicine patients while the other focused on a comparison of haloperidol, chlorpromazine and lorazepam in individuals with AIDS (Breitbart et al. 1996). Neither study included stroke patients. Studies assessing the management of delirium that included stroke patients are summarized in Table 12.39.

**Table 12.40 Management of Delirium**

| Author, Year Country Pedro Score | Methods | Outcome |
|---|---|---|
| Lundstrom et al. (2005) Sweden No Score | 400 consecutively admitted patients, over a period of 8 months were assigned to either an intervention ward (n=200) or control ward (n=200). Approximately ¼ of patients on both wards were stroke patients. Intervention consisted of training for staff on the assessment, prevention and treatment of delirium, education regarding patient-caregiver interactions, reorganization of service provision to an individualized care model, monthly guidance for nursing staff. Delirium was assessed using the Organic Brain Syndrome (OBS) scale on day 1, 3 and 7 of a patient's stay. | There were no between group differences for the prevalence of delirium within 24 hours of admission to hospital. By day 3, fewer cases of delirium were noted on both wards ($p<0.001$), but there were no differences noted between wards. By day 7, there were fewer patients remained delirious on the intervention ward than on the ward receiving usual care ($p=0.001$). 39.7% of stroke patients in the intervention group and 32.2% in the control group were diagnosed with delirium. Length of stay for patients who had experienced delirium on day 1 was shorter for those on the intervention ward than the control ward ($p<0.001$). While a larger proportion of delirious patients from the intervention ward could return home following admission than delirious control patients, the difference was not significant ($p=0.05$). Treatment on the intervention ward was also associated with lower in-hospital rate of mortality ($p=0.03$). |
| Oldenbeuving et al. (2008) Netherlands No Score | 16 patients with stroke were enrolled in this single-group study examining the use of rivastigmine in the treatment of post-stroke delirium. Patients were enrolled only if they exhibited delirium (Delirium rating scale score >12) for more than 24 hours. Study participants were treated with oral rivastigmine (dose started at 1.5 mg and increased by 3 mg every other day to a maximum of 12 mg). Increases to dose were stopped if DRS<10. Treatment continued for one week and was tapered off. | Mean DRS decreased from 14.8 to 8.5 (at maximum individual dose) and then to 5.6 after tapering off. All patients were successfully tapered off treatment with no recurrence of delirium. Mean duration of delirium = 6.7 days (range 2-17). No major side effects were reported. A randomized controlled trial is required to access the efficacy of rivastigmine in the treatment of delirium post stroke. |

**Discussion**

In general, strategies proposed for the management of delirium have been similar to those suggested for its prevention. Recognition of precipitating factors, provision of supportive and environmental care and treatment for behavioural symptoms (Ferro et al. 2002; Inouye 2006). Non-pharmacologic approaches to management can be implemented for all patients and include creating a calm and comfortable environment for the patient with orienting influences such as calendars, clocks, familiar objects and interaction with both staff and family. Changes to the environment and to routine should

be limited. Uninterrupted, quiet time should be provided at night to promote sleep and wakefulness and mobility should be encouraged during the day (Inouye 2006). The study by Lundstrom et al. (2005) seems to support the effectiveness of a program based on heightened awareness of risk and precipitating factors as well as increased individual care. However, as Lundstrom et al. noted, there were no systematic changes to treatment strategies noted and no significant differences in strategies were recorded between the intervention and control wards (Lundstrom et al. 2005).

Ferro et al. (2002) lists the use of pharmacological sedation as appropriate in the management of delirium. However, the use of drugs in the treatment of delirium should be approached with caution. Many of the compounds used to treat delirium can cause delirium, impair a patient's ability to understand and cooperate with treatment, and worsen symptoms of cognitive impairment (Meagher 2001). Drugs with anticholingeric properties, in particular, may cause symptoms of delirium. In a study of stroke patients, Caeiro et al. (2005) demonstrated that the percentage of stroke patients taking medication with anticholingeric (ACH) activity was greater among individuals with delirium and patients with delirium were often taking more than one ACH drug. In that study, identified predictors of delirium included the use of non-neuroleptic ACH drugs, medical complications, ACH drugs taken prior to stroke and intracerebral haemorrhage. Edlund et al. (2006) also noted that several neuroleptic drugs have anticholinergic properties and, as a disturbance of the cholinergic system may play a role in the development of delirium, treatment with ACH drugs may not be appropriate in its treatment.

A single, small (n=16) pilot study has examined a pharmacological approach to treatment of post stroke delirium. Following a rapid titration period, short duration oral rivastigmine was used to reduce symptoms of delirium with apparent success. All patients were weaned from the drug after a one week period with no short-term recurrence of dementia and no major side effects. A larger randomized controlled trial is needed to examine the effectiveness of rivastigmine in the treatment of delirium.

***Conclusions Regarding the Management of Delirium Post Stroke***

***There is limited (Level 2) evidence that increased knowledge and awareness of risk and precipitating factors along with individualized care is associated with reduced duration of delirium, shorter lengths of stay, and reduced mortality.***

***Based on a small, single-group pilot study, there is an absence of evidence regarding the impact of short-term treatment with rivastigmine on post-stroke delirium. Further research is required.***

***Increased knowledge, awareness of risk and precipitating factors along with a model of individualized care may reduce the duration of delirium and result in shorter lengths of stay and a reduced risk for mortality.***

## 12.9 Apraxia

Apraxia is a disorder of voluntary movement where one cannot execute willed, purposeful activity despite the presence of adequate mobility, strength, sensation, co-ordination and comprehension. Common apraxias are listed in Table 12.40.

**Table 12.41 Types of Apraxias**

| Type | Site of Lesion | Manifestation |
|---|---|---|
| Motor or Ideomotor | Often left hemisphere. | Can automatically perform a movement but cannot repeat it on demand. |

| | | |
|---|---|---|
| Ideational | Often bilateral parietal. | Can perform separate movements but cannot co-ordinate all steps into an integrated sequence. |
| Constructional | Either parietal lobe but right more often than left. | Unable to synthesize individual spatial elements into a whole (e.g., cannot draw a picture). |
| Dressing | Either hemisphere, right more often than left. | Inability to dress oneself despite adequate motor ability. |

### 12.9.1 The Importance of Apraxia Post-Stroke

Roughly 30% of patients in the acute phase of stroke show evidence of apraxia (Donkervoort et al. 2000; Faglioni & Basso 1985). However, as noted by Koski and colleagues (2002), there is considerable variability in the estimate across studies because of the lack of standardized assessment tools and the wide variations in criteria for diagnosing the disorder. Elsewhere, incidence rates of apraxia in left hemispheric stroke patients have ranged from 28% (De et al. 1980) to 57% (Barbieri & De 1988). Typically, incidence of apraxia is higher after damage to the left hemisphere (50%), than to the right hemisphere (<10%) (De et al. 1980).

Information provided by analysis of the data from the Copenhagen Study suggested that the frequency of apraxia may be substantially lower than reported previously. Out of 618 stroke patients, Pedersen et al. (2001) identified apraxia of any type in 9.1% (Pedersen et al. 2001). Manual apraxia was found in 7% of patients and oral apraxia in 6%. Manual and oral apraxia were both associated with left-sided stroke lesions and strokes of greater severity (Pedersen et al. 2001).

While it has been reported that the presence of apraxia can lead to severe disabilities in activities of daily living (Bjorneby & Reinvang, 1985; Saeki et al., 1995; Sundet et al., 1988; Foundas et al., 1995; Rothi & Heilman, 1997), results of the Copenhagen Study suggest that this is not necessarily the case. When the influence of manual and oral apraxia on functional outcome (represented by performance on the Barthel Index) was examined, taking initial Barthel Index scores, initial stroke severity, history of prior stroke, comorbidity, gender, age and handedness into account, no significant independent relationship could be found between apraxia and functional outcome. Unsal-Delialioglu et al. (2008) demonstrated that patients with apraxia may experience significant gains in function over the course of rehabilitation, although admission and discharge FIM scores may be significantly lower than their non-apraxic counterparts (Unsal-Delialioglu et al. 2008).

It has been reported that apraxia and aphasia are associated (Papagno et al. 1993). Unsal-Delialioglu et al. (2008) reported that, in a group of patients with right-sided post-stroke hemiplegia, patients with apraxia recorded lower aphasia assessment scores than non-apraxic patients (Unsal-Delialioglu et al. 2008). In the Copenhagen Study, the association between apraxia and other neurological symptoms was investigated (Pedersen et al. 2001). While apraxia was found to be significantly associated with aphasia ($r=0.28$ for manual apraxia and $r=0.36$ for oral apraxia, $p<0.001$ for both), associations with body hemineglect and anosognosia for hemiplegia were of a similar magnitude.

### 12.9.2 Anatomical Substrates of Apraxia

Although apraxia is more commonly associated with strokes affecting the left parietal lobe, it may also occur in lesions to the right parietal lobe, the temporal or frontal lobes, and even subcortical regions including white matter and the basal ganglia (Leiguarda 2001). According to Koski et al. (2002), "…the parietal cortex subserves an important component of the praxis system, especially concerned with the knowledge or representation of overlearned actions. It is recognized, however, that damage to cortical and/or subcortical regions outside the left parietal cortex, including the right hemisphere, have also been associated with apraxia and it is assumed that each of these different neural regions makes its own distinct contribution to the representation of action…"

### 12.9.3 Recovery of Apraxia Post-Stroke

While apraxia usually improves over time, spatiotemporal errors in imitation or tool use may persist (Maher & Ochipa 1997). Basso and collegues (1987) (as cited by van Heugten et al. (2000)) investigated the recovery from ideomotor apraxia (IMA) in acute stroke patients and attempted to identify predictive variables of IMA. They observed that recovery was related to the site of lesion in that patients with anterior lesions demonstrated better recovery. Recovery was not related to age, education, sex, type of aphasia and the initial severity or the size of the lesion.

### 12.9.4 Treatment of Apraxia

The presence of apraxia in the acute phase post-stroke serves as a barrier to rehabilitation since the process of motor learning may depend on imitation. Moreover, in aphasic patients, the presence of apraxia prevents the teaching of gestural communication as part of therapeutic interventions (Koski et al. 2002).

A recent review of the literature identified reports describing 10 treatment approaches; multiple cues, error reduction, six-stage task hierarchy, conductive education, strategy training, transitive/intransitive gesture training, rehabilitative treatment and errorless completion + exploration training (Buxbaum et al. 2008). Most of the reports identified are single-case, or single-case series. Only two of these treatment approaches have been investigated using randomized controlled trials and are described below. Please note that "rehabilitative treatment" is sufficiently similar to gesture training to be included with it for the purposes of the present review.

#### 12.9.4.1 Strategy Training

Strategy training provides individuals with limitations in activities of daily living with compensatory strategies to promote independence. Our review identified two trials examining the effectiveness of this technique (Table 12.41).

**Table 12.42 Treatment of Apraxias**

| Author, Year<br>Country<br>Pedro Score | Methods | Outcome |
|---|---|---|
| Van Heugten et al.<br>(1998)<br>Netherlands<br>NS | 33 stroke patients with ataxia received activity training to learn compensatory strategies (based on personal consultation with a therapist). New activities were chosen and goals set every 2 weeks. Each activity was approached in 3 stages: initiation, execution and control. Specific guidelines for instructions, assistance and feedback were provided to each occupational therapist. Therapy continued for a total of 12 weeks, The number of treatments per week was determined by each therapist. | Significant improvement was seen in motor functioning, apraxia, ADL observations, Barthel Index scores, and on the occupational therapies ADL questionnaire when baseline evaluations were compared with post-treatment evaluations. Effect sizes ranged from 0.19 for motor functioning to 1.06 for OT-ADL questionnaire results. |
| Donkervoort et al.<br>(2001)<br>Netherlands<br>8 (RCT) | 113 patients with apraxia secondary to left hemisphere stroke were randomly assigned to either strategy training integrated in usual OT or to regular OT. Strategy training involved the use of strategies to compensate | After 8 weeks of treatment, strategy training group improved significantly more than controls on ADL observations and on the Barthel ADL. No significant differences between the groups were noted at the 5 month follow-up. |

| | | |
|---|---|---|
| | for the apraxic impairment during the performance of ADL. Usual OT concentrated on sensory, motor, perceptual and cognitive deficits of the stroke patients and increasing independent functioning in ADL task. Patients underwent 8 weeks of treatment. | |
| Geusgens et al. (2006) Netherlands 8 (RCT) | 113 patients with left hemisphere stroke were randomly assigned to receive strategy training (n=56) or usual occupational therapy (n=57). Outcomes were assessed at week 8 and week 20. Note: This study represents further analysis of data collected as part of the study by Donkervoort et al. (2001). | Over time, ADL observation scores for trained tasks improved for the group as a whole (p=0.004), for the strategy training group (p=0.025), but not for the usual treatment group. Similarly, for untrained tasks, the group as a whole improved significantly (p=0.00) as did the strategy treatment group (p=0.00). Improvement on untrained tasks approached significance in the usual treatment group (p=0.05). At week 8, change scores on ADL observations on untrained tasks were larger for the strategy group than for the usual treatment group (p=0.40). There were no significant between group differences reported for change scores at 20 weeks for untrained tasks or for either assessment period for trained tasks. |

**Discussion**

Both Cicerone et al. (2005) and Cappa et al. (2005) include the above studies in their review of evidence for the remediation of apraxia. Both concluded that apraxia may be treated effectively through the use of compensatory or strategy training. Cappa et al. (2005) further recommended treatment focused on structured, functional activities. Further studies are required and assessment of transfer of training effects to untrained activities is recommended.

***Conclusions Regarding Treatment of Apraxias***

***There is strong (Level 1a) evidence that strategy training is effective in the treatment of apraxias post-stroke. Training effects may include improvement in performance of activities of daily living that appear to be sustained over time.***

***Strategic or compensatory training appears to be effective in the treatment of apraxia post-stroke.***

### 12.9.4.2 Gesture Training

Gesture training focuses on training of both transitive and intransitive gestures. Studies examining the impact of gesture training on ideomotor apraxia are summarized in Table 12.42.

**Table 12.43 Gesture Training in the Treatment of Ideomotor Apraxia**

| Author, Year Country Pedro Score | Methods | Outcome |
|---|---|---|
| Smania et al. (2000) Italy 3 (RCT) | 13 patients with "left-sided unilateral vascular lesions" were randomly assigned to receive either a behavioural training program for limb apraxia consisting of gesture production exercises(n=6) or conventional treatment (n=7) for aphasia. | No significant change was noted in performance on the Token, Raven, Oral or Constructive apraxia test in the treatment group. However, pre and post training assessments revealed significant improvement on measures of ideational and ideomotor apraxia (p=0.039 and p=0.043 respectively) for patients assigned to the |

| | | |
|---|---|---|
| | Thirty-five 50-minute treatment sessions were provided at a rate of 3/week. | treatment condition. Praxis errors were reduced significantly within the training group (p=0.001) – analysis of errors revealed improvements in awkwardness, omission, unrecognizable gestures, intrusion and position. No improvements on any of the neuropsychological tests were found for patients assigned to the control group. |
| Smania et al. (2006) Italy 5 (RCT) | 33 patients with left hemisphere stroke, limb apraxia, and aphasia were randomized to an apraxia treatment or a control (aphasia treatment) group. Before and after treatment, patients underwent tests of verbal comprehension, intelligence, oral apraxia, constructional apraxia, ideation apraxia, ideomotor apraxia, and gesture comprehension. As well, 9 patients in the apraxia group and eight in the control were assessed at a 2 month follow-up for performance on tests of ideational apraxia, ideomotor apraxia, gesture comprehension and ADL. | The apraxia treatment group displayed significant pre- to post-treatment improvements on tests of ideational apraxia (p<0.01), ideomotor apraxia (p<0.01), gesture comprehension (p<0.01) and ADL (p<0.001), while the control group displayed significant improvements on intelligence and verbal comprehension tests. Treatment effects differed significantly between the groups on tests of ideomotor apraxia (p=0.016), gesture comprehension (p=0.018) and ADL (p<0.01). Performance on limb praxic functional tests and the ADL questionnaire did not change significantly between the post-treatment evaluation and the two month follow-up. |

**Discussion**

Both studies reported significant improvement in apraxia associated with gesture training. Additionally, Smania et al. (2006) reported improvement in activities of daily living associated with treatment that appeared to be sustained for 2 months following the end of intervention. Further examination regarding the generalization and longevity of treatment effects is recommended.

***Conclusions Regarding Gesture Training***

***There is strong (Level 1a) evidence that gesture training is associated with improvement in ideomotor apraxia. Improvements may extend to activities of daily living and these effects may be sustained for at least 2 months following the end of treatment.***

***Gesture training is an effective intervention for the treatment of ideomotor apraxia post stroke.***

## 12.10 Cochrane Reviews for the Treatment of Apraxia Following Stroke

Currently, there is only one Cochrane review in existance examining the effectiveness of treatments for motor apraxia following a stroke event. This review included three randomized controlled trials.

**Table 12.43 Summary of Cochrane Reviews for apraxia treatments following stroke**

| Author, Year Country Title | Description | Results |
|---|---|---|
| West et. al. (2009) UK<br><br>Interventions for motor apraxia following stroke | Three idetintified studies met the criteria for inclusion in this review (total n=132 stroke patients).<br><br>Inclusion Criteria: Randomized Controlled Trials in which a treatment for motor apraxia compared with no intervention or an | A meta analysis of two studies found that there was a significant treatment effect at the end of the intervention period in the experimental group (mean difference 1.28, 95%CI: 0.19 to 2.38,. p=0.02)<br><br>One study examined maintenance of functional gains 6 months post stroke and did not find evidence of a lasting |

| | | |
|---|---|---|
| | alternate intervention were included.<br>Studies examining drug therapies alone were excluded.<br><br><u>Obectives:</u><br>▪ To determine if interventions targeted at the rehabilitation of apraxia post stroke have a sustained effect in the reduction of diability (6 months after treatment)<br>▪ To determine if any targeted intervention for apraxia is more effective in reducing diability for a sustained period of time | effect of treatment (mean difference 0.17, 95%CI: -1.41 to 1.75, p=0.83)<br><br>Authors concluded that there is currenlt not enough evidence to make conclusions regarding the effectiveness of treatments for motor apraxia following stroke. |

The current Cochrane review of interventions for motor apraxia following stroke was not able to provide any conclusions regarding the efficacy of these therapies.

## 12.11 Summary

1. ***There is conflicting (Level 4) evidence that treatment of hypertension is associated with reduced risk for cognitive decline and dementia. Lack of definitive results may be due to differential patient attrition, insufficient power or measurement error. Further trials in which cognition is the primary study outcome are required.***

2. ***There is moderate (Level 1b) evidence that treatment of hypertension may reduce the risk for cognitive decline or dementia in patients with history of previous stroke or TIA when compared to placebo.***

3. ***There is no evidence that one particular antihypertensive agent is superior to another for the prevention of cognitive decline.***

4. ***Based on the results of unrated studies and two RCTs of poor quality and one of good quality, there is limited (Level 2) evidence that computer-assisted training of attention tasks may improve performance of specific attention tasks.***

5. ***There is moderate (Level 1b) evidence that daily attention training is associated with recovery of the N140 component of somatosensory evoked potentials.***

6. ***There is moderate (Level 1b) evidence that visual attention retraining using the Useful Field of View is more effective than conventional computerized visuoperceptual training in improving the on-road driving performance of individuals who have experienced stroke and have right-sided lesions.***

7. ***There is strong (Level 1a) evidence that compensatory strategies are effective in improving memory outcomes post brain injury. Strategies include imagery-based training and the use of assistive, electronic devices. It should be noted that relatively few study participants had experienced stroke.***

8. ***There is moderate (Level 1b) evidence that an intensive, computerized training program may result in improvements in both working memory and attention.***

9. ***There is little evidence regarding remediation of executive functioning and problem solving post-stroke.***

10. ***There is limited (Level 2) evidence that analogical problem-solving skills training may increase problem-solving skills and performance of extended activities of daily living.***

11. ***Based on 2 RCTs, there is strong (Level 1b) evidence that mental imagery along with actual practice may improve relearning of activities of daily living in acute stroke patients with minimal cognitive deficits.***

12. ***At present, there is an absence of evidence that a multi-modal, home-based cognitive rehabilitation program may be beneficial in terms of cognitive function and instrumental activities of daily living.***

13. ***Based on a single, small study, there is limited (Level 2) evidence that a multi-modal, home-based cognitive rehabilitation program may be beneficial in terms of cognitive function and instrumental activities of daily living.***

14. ***Based on the results of a single RCT, there is moderate (Level 1b) evidence that electroacupuncture and high-intensity low-frequency TENS have no effect on cognitive functioning following stroke.***

15. ***There is moderate (Level 1b) evidence that self-regulated music listening therapy may have a positive impact on verbal memory and focussed attention in individuals with left hemisphere stroke.***

16. ***Based on the results of 2 RCTs, there is strong (Level 1a) evidence that exercise does not improve executive function in individuals without significant cognitive impairment following stroke. Further investigation is required.***

17. ***There is conflicting (Level 4) evidence that repetitive transcranial magnetic stimulation over the left dorsolateral prefrontal cortex may be associated with improvements in executive function following stroke.***

18. ***Based on the results of 2 small RCTs, there is strong (level 1a) evidence that anodal tDCS to the left dorsolateral prefrontal cortex is associated with improvements in working memory and attention. Further research is required.***

19. ***ASA is commonly used in the treatment of vascular dementia. There is moderate (Level 1b) evidence, based on a single, pilot RCT, that ASA is effective in stabilizing and/or improving cognitive outcomes in patients with multi-infarct dementia.***

20. ***Based on 3 RCTs, there is strong (Level 1a) evidence donepezil taken for 24 weeks improves cognitive function in patients with probable or possible vascular dementia.***

21. ***Based on 2 RCTs and 2 meta-analyses, there is strong (Level 1a) evidence that treatment with donepezil is associated with improvement in global function for individuals with probable or possible vascular dementia.***

22. ***There is limited (Level 2) evidence that treatment with rivastigmine is associated with more stable cognitive performance and improved behavioural outcomes among patients with subcortical vascular dementia.***

23. ***There is moderate (Level 1b) evidence that treatment with rivastigmine has no effect on executive function in individuals with cognitive impairment no dementia following stroke.***

24. ***There is moderate evidence (Level 1b), based on a single RCT of excellent quality, that treatment with galantamine is associated with improvements in cognitive and functional ability. However, the benefits associated with treatment are more clearly***

***demonstrated among patients with mixed dementia than vascular dementia. Further study is required.***

25. ***There is moderate (Level 1b) evidence that treatment with nimodipine is beneficial for memory. There is also moderate (Level 1b) evidence that treatment with nimodipine may slow cognitive deterioration and improve semantic and phonetic fluency among patients with subcortical vascular dementia.***

26. ***There is strong (Level 1a) evidence, based on the results of 2 RCTs, that treatment with memantine is associated with stabilization or improvement of cognitive function.***

27. ***There is strong (Level 1a) evidence that treatment with pentoxifylline is associated with cognitive benefit in patients with multi-infarct dementia.***

28. ***There is conflicting evidence regarding the effect of citicoline in the long term management of cognitive function post stroke.***

29. ***There is moderate (Level 1b) evidence that long-term treatment with citicoline has no effect on cognitive function.***

30. ***There is moderate (Level 1b) evidence that treatment and remission of post-stroke depression is associated with reduction in cognitive impairment.***

31. ***There is moderate (Level 1b) evidence that use of escitalopram in individuals with no post-stroke depression is associated in improvements in global cognitive function and memory.***

32. ***There is limited (Level 2) evidence that a multi-component approach to the management of known risk factors is associated with reduced incidence and duration of delirium. However, this has not been demonstrated within the stroke population. Further study is required.***

33. ***There is limited (Level 2) evidence that increased knowledge and awareness of risk and precipitating factors along with individualized care is associated with reduced duration of delirium, shorter lengths of stay, and reduced mortality. Further research is required.***

34. ***Based on a small, single-group pilot study, there is an absence of evidence regarding the impact of short-term treatment with rivastigmine on post-stroke delirium. Further research is required.***

35. ***There is strong (Level 1a) evidence that strategy training is effective in the treatment of apraxias post-stroke. Training effects may include improvement in performance of activities of daily living that appear to be sustained over time.***

36. ***There is strong (Level 1a) evidence that gesture training is associated with improvement in ideomotor apraxia. Improvements may extend to activities of daily living and these effects may be sustained for at least 2 months following the end of treatment***.

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