Abstract
Vascular cognitive impairment is the current term that reflects the range of cognitive deficits due to the impact of cerebrovascular disease, including stroke. According to the Canadian Study of Health and Aging (2000), it is estimated that 5% of all people over the age of 65 years have evidence of vascular cognitive impairment. 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 one third 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 regarding the definition, prevalence, and natural history of post-stroke cognitive impairment as well as its clinical consequences. Risk factors for cognitive impairment as related to demographics, atherosclerosis, and stroke are explored. Treatment interventions are identified, including: cognitive rehabilitation strategies for remediation of deficits in attention, memory, executive function, and problem solving; nerve and brain stimulation; exercise programs; music listening; and pharmacotherapy. The impact, risk factors, clinical consequences, and treatment of delirium following stroke are also reviewed.
Key Points

Cognitive Impairment Post Stroke

- Vascular cognitive impairment (VCI) is the current term that reflects the range of cognitive deficits due to the impact of cerebrovascular disease, including stroke. VCI without dementia reflects deficits in one or more domains not severe enough to cause functional decline reflecting a single strategic lesion or multiple infarcts that impact functional activities.

- Impairments of attention, executive function, and processing speed appear to be a consistent pattern of deficits in all subtypes of VCI. Given that 30% of all stroke survivors progress to a dementia syndrome, more research is needed to identify biomarkers for those at risk.

- At present, there is no gold standard for the diagnosis and assessment of VCI. Harmonized standards for brief and more extensive testing protocols have been developed for clinical and research use.

- Following stroke, as many as two-thirds of patients experience cognitive impairment or decline. 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 33% of patients may experience dementia after 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.

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

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

- Cognitive impairment is associated with decreased activities of daily living (ADL) and instrumental activities of daily living (IADL) function, and patients may require longer-term, ongoing rehabilitation.

- It is unclear whether depression is associated with cognitive impairment post stroke.

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

- The effect of treatment for hypertension on risk for cognitive decline and dementia is uncertain. In individuals with previous stroke or transient ischemic attack (TIA), treatment has been associated with reduced risk.
• There is no evidence that one particular antihypertensive agent is superior to another for the prevention of cognitive decline post stroke.

• The severity of white matter change is associated with poorer cognitive performance and increasing limitations in ADL post stroke.

Cognitive Rehabilitation Post Stroke

• Attention training may have a positive effect on specific, targeted outcomes. Further research within the stroke population is required using like outcome measures to better evaluate comparisons between studies.

• Useful Field of View (UFOV) training may be recommended over conventional computerized visuoperceptual training in the remediation of on-road driving ability.

• Compensatory strategies can be used to improve memory outcomes. Further research within the stroke population is required.

• There is limited research investigating group therapy, and little evidence supporting the use of group based interventions for the improvement of memory.

• The standardization of both intervention and outcome measures would help resolve the conflicts seen between individual studies regarding the rehabilitation of executive functioning and problem solving.

• Analogical problem-solving skills training may improve problem solving abilities and instrumental activities of daily living, but there is conflicting evidence.

• Tailored interventions to improve return to work are not effective in improving cognition.

• Acupuncture is an effective intervention for cognitive remediation.

• Although multi-modal interventions appear effective in individuals with traumatic brain injury (TBI), there is a lack of evidence regarding the effectiveness of such programs in individuals with stroke.

• Acupuncture combined with nimodipine can be an effective treatment for improving cognitive functioning.

• Physical therapies in combination with mindful interventions may not improve cognition.

• Virtual reality training may be a suitable supplemental treatment to currently existing computerized cognitive training in improving cognitive performance.

• Limited evidence suggests that electroacupuncture and transcutaneous electrical nerve stimulation (TENS) may be useful for improving cognitive function. Further research is required.

• Music therapy may have a positive impact on cognitive function. Further research is required.

• Structured exercise programs which focus on resistance, balance, and aerobics can improve cognitive function.

• Verticalization provided by a robotic table is more effective than verticalization therapy provided by a therapist.

• Further evidence is required to examine the value of specific exercise interventions compared to more general exercise interventions.
RTMS has a positive effect on executive function following stroke. Further research is required to determine if this effect is a result of a specific placement or frequency of the rTMS therapy.

Anodal transcranial direct current stimulation (tDCS) to the dorsolateral prefrontal cortex (DPC) may help to improve working memory and attention. Further research is required.

**Pharmacotherapy for Post-Stroke Cognitive Impairment**

- Aspirin is a common antithrombotic therapy used in the treatment of vascular dementia and may be effective in stabilizing cognitive deficit. Further research is required.
- There is insufficient evidence to make a conclusion about the effectiveness of GABA agonists to remediate cognitive deficits.
- Treatment with donepezil may improve cognitive and global function in patients with vascular dementia.
- Treatment with rivastigmine may stabilize cognitive performance and improve behaviour for patients with vascular dementia. Further research is required.
- Treatment with galantamine may improve cognitive and global function in patients with mixed dementia. However, its impact on patients with post-stroke cognitive impairments is less clear. Further research is required.
- Treatment with nimodipine may not be beneficial in the treatment of memory deficits in patients with vascular dementia. Further research is required.
- Treatment with memantine may be associated with stabilization or improvement of cognitive function in patients with vascular dementia.
- Treatment with pentoxifylline may improve cognitive function in patients with multi-infarct dementia.
- More research is required to determine the effect of citicoline on post-stroke cognitive function.
- Antidepressants may be useful at improving cognitive function in patients without post-stroke depression.
- Selegiline may be effective in improving post-stroke cognitive function. Further research is required.
- Although XXMT has been shown to improve memory, further research is needed in order to determine the robustness of XXMT in treating cognitive deficits.
- Vinpocetine has demonstrated in one RCT that it can be effective in the rehabilitation of cognitive deficits. Further research is needed to determine the extent of its effectiveness and potential limits on more specific elements of cognition such as attention, memory and executive functioning.
Post-Stroke Delirium

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

- Increased knowledge and awareness of predisposing and precipitating factors, along with a model of individualized care, may reduce the duration of delirium and result in shorter lengths of stay and reduced risk for mortality.
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12.1 Defining Cognitive Impairment Post Stroke

Over the past years, the definition and nomenclature describing cognitive impairments have changed to include a vast yet specific selection of cognitive disorders. Today, the Diagnostic and Statistical Manual of Mental Disorders (DSM)-V defines neurocognitive disorders (NCD) as a group of acquired disorders with a primary cognitive deficit that alters one’s level of functioning. NCDs are further classified into mild or major subtypes: major but not mild NCDs reach the threshold for diagnosis of dementia. However, this threshold is difficult to define since both types of NCDs exist on a continuum of cognitive/functional impairment and the distinction between the two NCD types is often arbitrary (Simpson, 2014).

The DSM-V diagnostic criteria for mild NCDs include (Simpson, 2014):

1. Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual motor, or social cognition) based on:
   1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function; and
   2. A modest impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.
2. The cognitive deficits do not interfere with capacity for independence in everyday activities (i.e., complex instrumental activities of daily living such as paying bills or managing medications are preserved, but greater effort, compensatory strategies, or accommodation may be required.)

According to Simpson (2014), a key difference between the DSM-IV and the DSM-V pertains to the diagnostic criteria of major NCDs, where memory impairment is no longer required for a diagnosis of major NCD. In essence, impairment in any one cognitive domain is enough to satisfy the diagnosis of major NCD, although NCDs resulting from Alzheimer’s disease require two domains (including memory).

Vascular cognitive impairment (VCI) refers to all forms of cognitive impairment caused by cerebrovascular disease (O’Brien et al., 2003). It has been adopted to reflect the wide range of potential etiologies that reflect the vascular burden on brain function, including but not limited to vascular dementia (Erkinjuntti & Gauthier, 2009). Currently, there are three terms used to describe VCI, as summarized in Table 12.1.1. **VCI-no dementia** (VCI-ND) describes individuals “whose symptoms are not associated with substantial functional impairment, including a high proportion with subcortical ischemia with cognitive impairment of presumed vascular cause” (Moorhouse & Rockwood, 2008). **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) and includes disorders that are in the original vascular dementia construct, such as post-stroke dementia and multi-infarct dementia (Moorhouse & Rockwood, 2008). **Mixed dementia** describes the “presentation of individuals with clinical, and commonly neuro pathological, features of Alzheimer’s disease and vascular dementia” (Moorhouse & Rockwood, 2008).

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Vascular Cognitive Impairment</td>
<td>VCI without dementia, and mild VCI</td>
</tr>
<tr>
<td>Vascular Dementia</td>
<td>Deficits of executive control resulting in loss of function for instrumental activities of daily living</td>
</tr>
<tr>
<td>Mixed Dementia</td>
<td>Alzheimer’s worsened by stroke; equivalent to pre-stroke dementia</td>
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Adapted from Roman et al. (2004)
Clinical presentation of VCI commonly includes 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). In a study of elderly residents, Rao et al. (1999) found that individuals with VCI displayed significantly poorer performance than controls on abstract thinking, attention, calculation, language, memory, orientation, perception, praxis, and Mini Mental State Examination (MMSE) scores.

As suggested by Rockwood et al. (2000), the concept of VCI-ND is useful in identifying patients with stroke at risk for developing vascular dementia. Ballard et al. (2003; 2002) reported that a third of elderly stroke survivors who were free of dementia at 3 months post stroke met the criteria for VCI-ND. Compared to elderly controls, the stroke survivors with VCI-ND had greater impairments of attention and executive function, but had preservation of memory compared to those with dementia. Cognitive syndrome of vascular dementia post stroke, as reported by Kalaria and Ballard (2001), is summarized in Table 12.1.2.

**Table 12.1.2 Cognitive Syndrome of Post-Stroke Vascular Dementia (Kalaria & Ballard 2001)**

| Occurs in up to 30% of patients with stroke |
| 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 |

Sachdev et al. (2004) demonstrated that patients with VCI-ND and vascular dementia had deficits in similar domains of cognition, including attention, working memory, information processing speed, and praxis-gnosis function. However, 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. Stephens et al. (2004) found impairments of attention and executive function in all patients with stroke, including those without significant cognitive deficits. In those who met the criteria for VCI-ND, additional deficits of memory and language expression were identified. Further impairment of memory and orientation distinguished patients with VCI-ND from those with vascular dementia. The authors concluded that the relative severity of memory impairments can predict progression to vascular dementia and may reflect the criteria associated with mixed dementia.

In a study comparing patients with mild vascular dementia and patients with mild Alzheimer’s disease, 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 patients with Alzheimer’s disease suffered greater impairment of episodic memory. A comparison of features associated with vascular dementia and Alzheimer’s disease is presented in Table 12.1.3.
Table 12.1.2 Comparison between Vascular Dementia and Alzheimer’s Disease

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

Conclusions Regarding Vascular Cognitive Impairment

Vascular cognitive impairment (VCI) is the current term that reflects the range of cognitive deficits due to the impact of cerebrovascular disease, including stroke. VCI without dementia reflects deficits in one or more domains not severe enough to cause functional decline, reflecting a single strategic lesion or multiple infarcts that impact functional activities.

Impairments of attention, executive function, and processing speed appear to be a consistent pattern of deficits in all subtypes. Since 30% of all stroke survivors progress to a dementia syndrome, more research is needed to identify biomarkers for those at risk.

12.1.1 Issues in the Diagnosis and Assessment of Cognitive Impairment

At present, there is no gold standard for the diagnosis of VCI. While some have used the MMSE or the modified version to demonstrate cognitive decline (Wentzel et al., 2001), others have used the Montreal Cognitive Assessment (Prokopenko et al., 2013) or the Cambridge Examination for Mental Disorders in the Elderly - Cognitive Subscale (CAMCOG) (O’Brien et al., 2003) that has been adapted to include VCI-ND (Szatmari et al., 1999). Similarly, no gold standard exists for the diagnosis of vascular dementia (Chui, 2000). In the past, some have used a modified version of criteria from the DSM-III-R (Tatemichi et al., 1994) or DSM-IV (Ballard et al., 2002). Roman (2003) used the following criteria for diagnosis: cognitive loss; vascular brain lesions; temporal link between stroke and dementia; and exclusion of other causes of dementia. For an appropriate diagnosis, the onset of dementia must be within 3 months of a symptomatic stroke, except in subacute vascular dementia, and two cognitive domains other than memory must be impaired for an appropriate diagnosis.

Based on a consensus meeting sponsored by the National Institute for Neurological Disorders and Stroke and the Canadian Stroke Network, Hachinski et al. (2006) produced a set of harmonized criteria for cognitive screening and assessment to define the spectrum of VCI subtypes. The authors proposed that the following neuropsychological domains be examined: executive function, attention, memory, visuospatial, language, depression, and pre-morbidity. They produced screening and assessment methods for the identification of individuals with possible cognitive and behavioural impairment to establish minimum datasets for clinical practice and research studies of VCI. The recommended 5-minute neuropsychological protocol included selected subtests of the Montreal Cognitive Assessment (5-word memory, 6-item orientation, and 1-letter phonemic fluency), which could be supplemented with other tasks (e.g. cube and clock drawing, short trail-making test). Given more time, the full trail-
making test, a semantic fluency test, or the MMSE could be added, but only if administered more than one hour following the 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. Further 30-minute and 60-minute neuropsychological testing protocols were recommended for more extended assessment.

Conclusions Regarding Issues in the Diagnosis and Assessment of Cognitive Impairment

**At present, there is no gold standard for the diagnosis and assessment of VCI. Harmonized standards for brief and more extensive testing protocols have been developed for clinical and research use.**

12.2 Prevalence and Natural History of Cognitive Impairment Post Stroke

According to the Canadian Study of Health and Aging, it is estimated that 5% of all people over the age of 65 years have evidence of vascular cognitive impairment (VCI) (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 older, stroke was significantly associated with an increased risk for the development of dementia (OR=2.1, 95% CI 1.1-4.2) (Yip et al., 2006).

Tatemichi et al. (1994) examined cognitive function in 227 patients 3 months after admission to hospital for ischemic stroke and in 240 stroke-free controls. Cognitive impairment was defined as deficits in four or more areas of attention, memory, orientation, language, visuospatial ability, and abstract reasoning. The authors reported that patients with stroke were significantly more likely to have cognitive impairment (35.2%) compared to controls (3.8%). Patel et al. (2003) reported prevalence rates of VCI have varied substantially from 15-20% in various clinical settings to 39%, 35%, 30% and 32% at 3 months, 1 year, 2 years, and 3 years post stroke, respectively. These latter rates are similar to the 31% reported at 15 months post stroke by Ballard et al. (2003) and at 3 months by Sundar & Adwani (2010). In a study of 451 patients with ischemic stroke, 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 patients with stroke 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). Another study reported that, in a sample of 327 patients with stroke, 12.6% had VCI-no dementia (VCI-ND) prior to stroke (Serrano et al., 2007). Using a consistent method of assessment, the frequency of VCI-ND was 26.9% at 3 months, 39.5% at 12 months and 36.6% at 24 months post stroke. While cognitive impairment was more common than dementia in patients with stroke, patients with VCI-ND were at least 8 times more likely to develop delayed dementia than those without VCI-ND.

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. 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 of variables associated with dementia 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 ten-fold increase in 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 1.4-2.9) (Ivan et al. 2004). Age, sex, education or exposure to stroke risk factors had no effect on the reported risk. Based on a review, Savva et al. (2010) reported that history of stroke doubles the risk for incident dementia and that this elevated risk decreases over time.

An 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 (RR=+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 (MCI) 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 MCI prior to the stroke event. The odds ratio for developing dementia in those individuals with MCI prior to stroke was reported to be 12.4 (95%CI 1.5-9.9) (Gamaldo et al., 2006).

Conclusions Regarding Prevalence and Natural History of Cognitive Impairment
Following stroke, as many as two-thirds of patients experience cognitive impairment or decline. 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 33% of patients may experience dementia after a recurrent stroke.

12.2.1 Cognitive Recovery

In a study by Sachdev et al. (2004), 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, patients with stroke 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 patients experienced significantly greater decline than controls in 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 et al. (1996) conducted neuropsychological tests on patients at 3 months post stroke and annually thereafter. The authors reported that 19 of 151 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 study of 193 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 mild vascular cognitive impairment (mVCI) following stroke may be considered progressive (Sachdev et al. 2009). Incident dementia was diagnosed in 24.4% of patients with mVCI vs. 8.5% in patients without mVCI. While some cognitive decline occurred in all groups, individuals without mVCI 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 patients with MCI 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.,
Similarly, Ballard et al. (2003) reported that 50% of patients included in their study experienced some increase in MMSE scores while 16% experienced an increase of more than 2 points and a 6.6 point increase on the Cambridge Examination for Mental Disorders in the Elderly - cognitive subscale between 3 and 15-month follow-up assessments (p<0.0001). Patel et al. (2003) reported a similar proportion of patients (17.6%) regained cognitive function by one-year post stroke. Ballard et al. (2003) 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. (2003), 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 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%.

### Conclusions Regarding Cognitive Recovery

*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 CSHA (Wentzel et al., 2001), the overall outlook is poor for people with VCI. The mean length of survival was reported as 41 months. Out of 149 people with VCI-ND, 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 (HR=1.53, 95%CI 1.3-1.8). Women with cognitive deficits post stroke had 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 three 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 two to six 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).

Conclusions Regarding Mortality and Cognitive Impairment

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

12.3 Clinical Consequences of Post-Stroke Cognitive Impairment

Global 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 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 activities of daily living (ADL), 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 than in those without: 3-month RR=2.4, 95%CI 1.93-3.08; 1-year RR=1.9, 95%CI 1.38-2.6; 5-year RR=1.8, 95%CI 1.27-2.55 (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 instrumental ADL (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 pre-stroke cognitive decline. Identified predictors of IADL
performance were stroke severity, executive dysfunction, age and pre-stroke 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 attention and executive dysfunction (Robertson et al., 1997; Skidmore et al., 2010). However, this is associated with greater expenditure of healthcare resources (Claesson et al. 2005).

Conclusions Regarding Impact of Cognitive Impairment on Rehabilitation Outcomes

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

Among 2220 participants in the Cardiovascular Health Study (Cognition Study), Barnes et al. (2006) reported that depressive symptoms at baseline were associated with an increased risk for mild cognitive impairment (moderate depression OR=1.37, 95%CI 1.00-1.88; moderate to severe depression OR=2.09, 95%CI 1.46-2.97). While the presence of both small and large infarcts was also associated with increased risk for mild cognitive impairment (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 pseudo-dementia. In (1986), Robinson et al. 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 et al. examined cognitive functioning in 41 patients with and 135 patients without major depression in the acute hospital setting at 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 Mini Mental State Exam determined whether or not the patient had cognitive impairment.

In a report from the Sydney Stroke Study, Brodaty et al. (2007) demonstrated a greater frequency of dementia among 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). By 15 months post stroke, 54.2% of patients with depression were diagnosed with dementia compared to 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 patients (Haring, 2002). Murata et al. (2000) concluded that major post-stroke depression (PSD) leads to cognitive impairment and not vice versa.
A longitudinal study conducted by De Ryck et al. (2014) revealed that patients with PSD scored significantly worse on assessments of cognition. These results are to be interpreted with caution as this association does not necessarily reflect causation. It is known that such clinical tests may be greatly affected by states of motivation and the cognitive slowing of depression. The scores may reflect the cognitive slowing as a result of an existing state of depression rather than the actual neurocognitive disorder itself. It is therefore possible that cognitively impaired individuals may be more depressed due to their impairments rather than the depression leading to impairment. The study provided further evidence that states of cognitive impairment were significantly more prevalent at 6 and 18 months among patients with PSD compared to patients without PSD. De Ryck et al. (2014) noted that stroke severity, physical disability and stroke outcome were also significantly associated with PSD during the study period. The authors suggest that early screening will help to identify patients experiencing PSD and potentially improve quality of life post stroke, along with long-term monitoring. It could also be argued based on these findings that early diagnosis of PSD and subsequent treatment or support could potentially prevent poor outcomes in the future.

However, in comparing patients with stroke to those without, Pustokhanova and Morozova (2013) reported significantly poorer performance on cognitive and functional assessments but no difference in depression scores was observed between groups. At six-month follow-up, the patients demonstrated a decrease in depression scores and were significantly lower than the control’s baseline score. Cognitive assessment scores were also significantly lower at follow-up compared to baseline for these patients. Although significant correlations were reported between scores of depression and cognitive assessment scores at baseline, depression was significantly correlated with attention only at follow-up. Pustokhanova and Morozova (2013) suggest that mood disorder does not directly affect cognitive decline, however the authors note that elderly female patients exhibited significantly higher neurological and deficits and were at higher risk of depression.

**Conclusions Regarding Depression and Cognitive Impairment**

*There is conflicting level 5 evidence regarding the link between post-stroke depression and cognitive and functional impairment.*

**It is unclear whether depression is associated with cognitive impairment post stroke.**

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

Gorelick (1997, 2004) reported on the risk factors for vascular dementia in 4 categories: demographic, atherosclerotic, genetic and stroke-related. Categorical risk factors identified in the review are listed in Table 12.4.1.

**Table 12.4.1 Risk Factors for Vascular Dementia by Category (Gorelick 1997, 2004)**

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

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 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 more recent longitudinal cohort study was able to demonstrate that education level does have an independent association with less memory impairment, Mini Mental State Exam (MMSE) 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 reviews presented by Gorelick (see Table 12.4.1) cited male gender as a risk factor for the development of vascular dementia, subsequent reviews do not support this assertion. Leys et al. (2005) stated that the risk for post-stroke dementia was not associated with gender in most studies included in their review, while a study by Tang et al. (2006) reported female gender to be a significant independent risk factor for cognitive impairment post stroke. In their study of clinical determinants of post-stroke dementia, Desmond et al. (2000) reported that gender 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, De Ronchi et al. (2007) observed that gender did not modify the association between dementia and stroke, whereas both age and level of education did.

Conclusions Regarding Demographic Risk Factors

Increasing age, lower levels of formal education, and non-white race are independent risk factors for the development of dementia post 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. (2000) 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. 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 et al. (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 is a risk factor for vascular dementia, but not necessarily for post-stroke dementia, as in “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.

Conclusions Regarding Atherosclerotic Risk Factors

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 Cognitive Decline

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.
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 four or more points on the MMSE) over the 4-year study period. The odds for cognitive decline were almost three 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 for untreated persistent hypertension vs. 1.3 for treated hypertension) (Tzourio et al., 1999). 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) (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, >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. Studies examining the effects of blood pressure treatment on cognition are summarized in Table 12.4.2.1.1.

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Study Design (Pedro Score)</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PROFESS Study Group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diener et al., (2008)</td>
<td>RCT (10)</td>
<td>NStart=20332 NEnd=18712</td>
<td>E1: Telmisartan (80mg/d) + Aspirin (25mg 2/d) + Extended-release Dipyridamole (200mg 2/d) E2: Telmisartan (80mg/d) + Clopidogrel (75mg/d) E3: Placebo + Aspirin (25mg 2/d) + Extended-release Dipyridamole (200mg 2/d) E4: Placebo + Clopidogrel (75mg/d)</td>
<td>• MMSE (-) • Barthel Index (-)</td>
</tr>
<tr>
<td><strong>SHEP Program</strong></td>
<td></td>
<td></td>
<td>E: Chlorthalidone (12.5-25mg/d) + Atenolol (25-50mg/d)</td>
<td>• Boston Naming Test (-)</td>
</tr>
</tbody>
</table>

(Mackowiak-Cordoliani et al., 2005; Williams, 2004).
<table>
<thead>
<tr>
<th>Study</th>
<th>Authors</th>
<th>Study Design</th>
<th>Number of Participants</th>
<th>Intervention</th>
<th>Comparator</th>
<th>End Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-Stroke Cognitive Disorders</td>
<td>Applegate et al. (1994)</td>
<td>RCT (8)</td>
<td>8736/1564</td>
<td>50mg/d or Reserpine (0.05-0.1mg/d) C: Placebo</td>
<td></td>
<td>Digit symbol substitution (-) Delayed recognition span (-) Addition test (-) Finding A’s (-) Letter sets (-)</td>
</tr>
<tr>
<td></td>
<td>Forette et al. (1998)</td>
<td>RCT (8)</td>
<td>2418/2061</td>
<td>E: Nitrendipine (10-40mg/d) + Enalapril (5-20mg/d) + HCT (12.5-25mg/d) C: Placebo</td>
<td></td>
<td>MMSE (+) Incidence of Dementia (+)</td>
</tr>
<tr>
<td></td>
<td>Starr et al. (1996)</td>
<td>RCT (8)</td>
<td>81/69</td>
<td>E1: Captopril (12.5mg 2/d) E2: Bendrofluzide (2.5-5mg/d) C: Placebo</td>
<td></td>
<td>Trail-Making Test A (-) Raven’s Progressive Matrices (-) Paired Associates Recall (-) Anomalous Sentences Repetition Recall (-) Immediate and Delayed Logical Memory (-)</td>
</tr>
<tr>
<td></td>
<td>Litthell et al. (2003)</td>
<td>RCT (8)</td>
<td>4964/4956</td>
<td>E: Candesartan (8-16mg/d) C: Placebo</td>
<td></td>
<td>MMSE (-) Incidence of Dementia (-) Blood pressure (+)</td>
</tr>
<tr>
<td></td>
<td>Tzourio et al. (2003)</td>
<td>RCT (8)</td>
<td>6105/5888</td>
<td>E: Perindopril (4mg/d) (+ Indapamide 2-2.5mg/d) C: Placebo</td>
<td></td>
<td>MMSE (+) Incidence of Dementia (-) Incidence of Dementia with recurrent stroke (+)</td>
</tr>
<tr>
<td></td>
<td>Schrader et al. (2005)</td>
<td>RCT (8)</td>
<td>1405/1352</td>
<td>E1: Nitrendipine (10mg/d) E2: Eprosartan (600mg/d) C: Placebo</td>
<td></td>
<td>MMSE (-)</td>
</tr>
<tr>
<td></td>
<td>Skoog et al. (2005)</td>
<td>RCT (8)</td>
<td>4937/4937</td>
<td>E: Candesartan (8-16mg/d) C: Placebo</td>
<td></td>
<td>Incidence of Dementia (-)</td>
</tr>
<tr>
<td></td>
<td>Ihle-Hansen et al. (2014)</td>
<td>RCT (8)</td>
<td>195/178</td>
<td>E: Pharmacological support including antihypertensive, anti-diabetic, statin, and vitamin B complex prescriptions; nutritional advice and optimised medical treatment C: Usual Care</td>
<td></td>
<td>Trail-Making Test A (-) 10 Word Test (-)</td>
</tr>
<tr>
<td></td>
<td>Prince et al. (1996)</td>
<td>RCT (7)</td>
<td>2584/2392</td>
<td>E1: Atenolol (50mg/d) E2: HCT (25mg/d) + Amiloride (2.5mg/d) C: Placebo</td>
<td></td>
<td>Trail-Making Test A (-) Paired Associate Learning Test (-)</td>
</tr>
<tr>
<td></td>
<td>Forette et al. (2002)</td>
<td>RCT (6)</td>
<td>3228/2902</td>
<td>E: Nitrendipine (10-40mg/d) + Enalapril (5-20 mg/d) and/or Hydrochlorothiazide (12.5-25mg/d) C: Placebo</td>
<td></td>
<td>Incidence of Dementia (+)</td>
</tr>
</tbody>
</table>
Word List Recognition (+)
Boston Naming Test (-)
Verbal Fluency (-)

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 four trials for inclusion in the meta-analysis; PROGRESS, SCOPE, SHEP, and SYST-EUR. Based on data from these four 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. A recent meta-analysis by Parsons et al. (2016) on 14 studies revealed a significant prevention of stroke with the use of antihypertensive medications but no significant reduction in the incidence of dementia and cognitive decline; however it was noted that short follow-up times had occurred. Long-term usage may allow for greater preventative efficacy, but further research is required to investigate this notion.

Of the studies summarized here, the majority reported comparisons of antihypertensive treatments rather than evaluating the efficacy of antihypertensive treatment compared with placebo (see Table 12.4.2.1.1). 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.

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_candesartan=1253, n_placebo=845) 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 (Observation Study on Cognitive function And Systolic blood pressure Reduction) study 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 eight 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 summarized studies (Table 12.4.2.1.1), four (PROGRESS, MOSES, PRoFESS, and Ihle-Hansen et al. (2014) were secondary prevention trials focusing on individuals with previous history of stroke or transient ischemic attack (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. Ihle-Hansen et al. (2014) not only optimised medical treatments such as antihypertensives, antiplatelet agents, statins, vitamin B complex supplements, and anti-diabetic medications, but also offered nutritional advice. Although the intervention did succeed in improving cognitive performance, these improvements did not differ significantly compared to a control group. The authors speculate that a follow-up time of one year may be insufficient as dementia develops over several years and therefore longitudinal study designs may allow for greater observations.

Conclusions Regarding Medications for Treatment of Hypertension and Prevention of Vascular Dementia and Cognitive Decline

There is level 1a evidence indicating no statistical association between lowering of blood pressure and a reduction in the risk for the development of dementia.

There is level 1a evidence that antihypertensive medication may prevent recurrence of stroke, but not reduce cognitive decline or dementia.

There is level 1b evidence that reducing risk factors detrimental to brain health such as cholesterol levels, blood pressure, and BMI may have no significant effect on cognitive performance.

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

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

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 (see Table 12.4.3.1). All characteristics listed have been associated with post-stroke dementia in at least two previous studies. The authors note that, in the case of strategic infarcts, the original studies are either case studies or small series more than 20 years old and conducted without MRI or follow-up.

Table 12.4.3.1 Stroke-Related Determinants of Post-Stroke Dementia

<table>
<thead>
<tr>
<th>Stroke Characteristics</th>
<th>From Neuro-imaging</th>
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<tbody>
<tr>
<td>Severe deficit at onset</td>
<td>Silent infarcts</td>
</tr>
<tr>
<td>Recurrent stroke</td>
<td>Global central atrophy</td>
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<tr>
<td>Supratentorial lesions</td>
<td>Medial-temporal-lobe atrophy</td>
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<td>Left hemisphere lesions</td>
<td>White matter changes</td>
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<tr>
<td>Anterior &amp; posterior cerebral artery territory lesions</td>
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<tr>
<td>Strategic infarcts</td>
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<tr>
<td>Multiple lesions</td>
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</table>
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 (Makin et al., 2013). Authors identified 24 studies, and found that the prevalence of cognitive impairment or dementia did not differ between lacunar and other stroke types (29% and 24% respectively). However, when broken down by hospital or community based samples, non-lacunar strokes had a higher prevalence in hospital based samples (OR=0.67), and community based studies demonstrated a higher prevalence of lacunar stroke (OR=1.56). It should be noted, however, that studies included in this review were found to be highly heterogeneous (Makin et al., 2013).

Prior TIA has also 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 TIA <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. (2001) determined that the prevalence of severe white matter hyperintensities (WMH) increases with age. 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 (WMC) 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 WMC. Prins et al. (2005) suggested that stroke may play a role in worsening cognitive decline in individuals with documented white matter lesions (WML) 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 WMC as predictors of post stroke dementia. Sachdev et al. (2004) reported that study participants who had experienced stroke or TIA had significantly more cortical atrophy, greater ventricle/brain ratios and more extensive deep WMH than an age-matched control group. Stroke/TIA subjects with vascular dementia or vascular cognitive impairment (VCI) had significantly more WMH than stroke/TIA subjects without cognitive impairment. Participants with vascular dementia VCI 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., 2004). Similarly, Burton et al. (2004) reported a higher volume of WMH, particularly in the temporal and frontal lobes, in patients with stroke 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%). McMurtry et al. (2007) demonstrated that patients with both lacunar infarcts and WMC 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 WMC on functional activities within a limited period of time (Inzitari et al., 2007). The authors determined that the severity of WMC was an independent predictor of 1-year transition in functional status from none to one activity limitation to two 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 four times as likely to have severe WMC. Pohjasvaara et al. (2007) examined the role of WML with regard to declines in function 3 months following ischemic stroke. In general, increasingly severe WMC were associated with higher age, female gender, impaired activities of daily living (both basic and extended), global cognitive status, impaired memory and executive dysfunction. Furthermore, recent evidence suggests that WMH correlate with the neuropsychology components of the National Institute of Neurological Disorders and Stroke-Canadian Stroke Network VCI (Wong et al., 2015).

Conclusions Regarding White Matter Changes and Cognitive Impairment

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

In 1999, a European Task Force was created with the aim of evaluating the existing evidence for the clinical effectiveness of cognitive rehabilitation for stroke, traumatic brain injury (TBI), and other brain injuries. In (2003), Cappa et al. 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, and an updated version of these guidelines was published in 2005.

In (2000), Cicerone et al. established evidence-based recommendations for clinical practices of cognitive rehabilitation in stroke and TBI. Articles were allocated to one of the following categories according to the area of intervention investigated: attention; memory; visuospatial; language and communication; executive function and problem solving; multi-modal interventions; comprehensive-holistic cognitive rehabilitation. The literature search and recommendations were expanded and updated to include published evidence from 1998-2002 and 2003-2008 (Cicerone et al., 2005; Cicerone et al., 2011).

A meta-analytic examination of the reviews conducted by Cicerone et al. (2000; 2005) reported effect sizes associated with attention, memory, language, visuospatial, executive function, and comprehensive
cognitive interventions (Rohling et al., 2009). The analysis showed that 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 and time since injury. For studies of patients with stroke, the reported pooled effect size associated with cognitive rehabilitation was slightly larger (ES=0.40).

For the purpose of this chapter, only interventions for the remediation of attention, memory, executive function, and multiple modalities are reviewed, as other areas are addressed in subsequent chapters. However, studies of patients with stroke were primarily in the areas of language and visuospatial interventions, while studies of attention, memory, executive function, and comprehensive cognitive function were more often focused on patients with TBI or other brain injury. Therefore only the studies with stroke populations reviewed by Cicerone et al. (2000; 2005; 2011) are addressed here, as well as additional studies not included in their reviews.

### 12.5.1 Remediation of Attention Deficits

Cicerone et al. (2000) noted that most interventions designed to remediate impairments of attention have “relied on drill and practice, with exercises designed to address specific aspects of attention (eg, processing speed, focused attention, divided attention)” and have often used “stimulus-response paradigms, which required subjects to identify and select among relevant auditory or visual stimuli.” Many of the reviewed studies “incorporated and/or evaluated therapeutic interventions such as feedback, reinforcement, and strategy teaching into the attention remediation programs.” Of these studies, only a few focused on patients post stroke (Sturm & Willmes, 1991; Sturm et al., 1997), with additional stroke-oriented studies added to the updated reviews in 2005 (Niemeier, 1998) and 2011 (Mazer et al., 2003; Vallat et al., 2005).

Cicerone et al. (2000) found evidence supporting the effectiveness of specialized training for patients with attention deficits. They recommended exercises that involve on complex tasks requiring selective or divided attention rather than basic tasks of intensity or reaction time. They also suggested the development of compensatory strategies focused on complex tasks requiring regulation of attention, rather than the restoration of basic aspects of attention. These recommendations were supported by their subsequent reviews (Cicerone et al., 2005; Cicerone et al., 2011) and by Cappa et al. (2005) for the rehabilitation of attention deficits during the post-acute phase of recovery. However, it should be noted that all of these recommendations were primarily based on studies examining patients post TBI rather than post stroke.

Trials examining the remediation of post-stroke attention deficits, including but not limited to those from Cicerone et al. (2000; 2005; 2011), are presented in Table 12.5.1.2.

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Study Design (Pedro Score)</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wentink et al. (2016)</td>
<td>RCT (10)</td>
<td>N\text{Start}=115 N\text{End}=107</td>
<td>E: Luminosity computer training 5 days a week for 8 weeks C: Stroke Info group</td>
<td>• Forward block span test (+) • Incongruent Reaction time (+) • Backwards span test (-) • Time A-Attention (-) • Time B-Attention (-) • Flanker Task (-) • Raven’s Progressive Matrices (-)</td>
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<tr>
<td>Study</td>
<td>Design</td>
<td>N Start</td>
<td>N End</td>
<td>E</td>
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</table>
| **Barker-Collow et al. (2009)** | RCT (8) | 78      | 66    | E: Attention Process Training | C: Usual care | Integrated Visual and Auditory Continuous Performance Test (+)  
|                             |        |         |       |                             |              | Trail-Making Test Parts A & B (-)  
|                             |        |         |       |                             |              | Paced Auditory Serial Addition Test (-)  
|                             |        |         |       |                             |              | Bell’s Test (-)  
| **Mazer et al. (2003)**     | RCT (7) | 97      | 84    | E: Useful Field of View (UFOV) training | C: Traditional computerized training | UFOV (-)  
|                             |        |         |       |                             |              | Functional Independence Measure (-)  
|                             |        |         |       |                             |              | Test of Everyday Attention (-)  
|                             |        |         |       |                             |              | Complex Reaction Time (-)  
|                             |        |         |       |                             |              | Motor-Free Visual Perception Test (-)  
|                             |        |         |       |                             |              | Single & Double Letter Cancellation Test (-)  
|                             |        |         |       |                             |              | Money Road Map Test of Direction Sense (-)  
|                             |        |         |       |                             |              | Trail Making Test Parts A & B (-)  
|                             |        |         |       |                             |              | Bell’s Test (-)  
|                             |        |         |       |                             |              | Charron test (-)  
|                             |        |         |       |                             |              | On-road evaluation (+)  
| **Westerberg et al. (2007)** | RCT (6) | 21      | 18    | E: Computerized working memory training | C: No treatment | Working memory and attention (+)  
| **Giaquinto & Fraioli (2003)** | RCT (5) | 60      | 60    | E: Daily attention training (computerized discrimination task + cutaneous electrical stimulation) | C: Untrained | EEG signals detecting N140 at 3 wks (+)  
|                             |        |         |       |                             |              | Functional Independence Measure (-)  
| **Sturm et al. (1997)**     | RCT Crossover (3) | 38     | 38    | E: Computerized Adaptive Testing for specific disorders | C: Standardized attention test battery | Alertness training task (+)  
|                             |        |         |       |                             |              | Vigilance training task (+)  
|                             |        |         |       |                             |              | Selective attention training task (-)  
|                             |        |         |       |                             |              | Divided attention training task (-)  
| **Sturm & Willmes (1991)**  | PCT (No Score) | 35      | 35    | E1: Left Hemispheric stroke (early) + Weiner Determinationsgerat (WDG) & Cognitrone | E2: Left Hemispheric stroke (late) + WDG & Cognitrone | WDG scores (+)  
|                             |        |         |       |                             |              | WDG-error scores (+)  
|                             |        |         |       |                             |              | Visual Reaction Task (+)  
|                             |        |         |       | E3: Right Hemispheric stroke + WDG & Cognitrone |              |  
| **Niemeier (1998)**         | PCT (No Score) | 31      | 31    | E: Lighthouse strategy training | C: Standard training | Mesulam Verbal Cancellation Test (+)  
|                             |        |         |       |                             |              | Sheltering Arms Functional Autonomy Rating Scale (+)  

+ Indicates statistically significant differences between treatment groups  
- Indicates no statistically significant differences between treatment groups

**Discussion**

Of the eight studies presented, seven are RCTs investigating computerized training. Both Barker-Collow et al. (2009) and Mazer et al. (2003) saw non-significant improvements on the Trail-Making Test Parts A & B and the Bells Test, although they utilized different treatment approaches. With the exception of these two outcome measures, no two studies used the same interventions over similar periods of time or measured similar outcomes. All seven recorded intervention effects on specific, targeted outcomes.
Sturm & Wilmes (1991) found that patients demonstrated improvements for attention-related reaction times after training with two computer programs, though performance had deteriorated by 6 weeks post training. In a later study using Computer Adaptive Testing, Sturm et al. (1997) reported significant improvements in specific training tasks for alertness and vigilance compared to a non-specific training task, though no significant differences were reported for selective or divided attention. As well, Giaquinto & Fraioli (2003) found that a combination of computer training and electrical stimulation resulted in enhancement of spatial attention through evoked potentials of the N140 neurological component. However, these studies of computer-based intervention on attention conflict with the results of Wentink et al. (2016). Wentink and colleagues found no significant results when examining the effects of a specific cognitive-based program (Luminosity) on attention. Although the results of these studies conflict, it bears repeating that no two studies used similar interventions or executed them over similar timelines.

After Useful Field of View (UFOV) training, Mazer et al. (2003) observed no significant change on the Test of Everyday Attention, Motor-Free Visual Perception Test, and the Functional Independence Measure, but noted a significant change in success rates on road driving evaluations. Westerberg et al. (2007) reported improvement in both attention and working memory following a home-based computer training program. Barker-Collow et al. (2009) found significant improvement in integrated visual auditory attention after Attention Process Training, but significant differences were not reported for any of the other outcomes assessed.

A meta-analysis by Loetscher and Lincoln (2013) examining six RCTs comparing cognitive rehabilitation with a usual care control group did not reveal any significant improvements in global measures of attention and standardised attentional assessments but divided attention was found to benefit significantly. The authors also note that although there was limited evidence for short-term effects of cognitive rehabilitation, there is currently a lack of evidence that determines both short and long-term efficacy. They recommend that further studies be conducted within the stroke population and at a higher methodological level.

Conclusions Regarding Remediation of Attention Deficits Post Stroke

There is mixed level 1a and level 2 evidence regarding the effect of computerized training for attention tasks on the performance of specific attention tasks.

There is mixed level 1a evidence that cognitive rehabilitation may improve divided attention but not global measures of attention and standardised attentional assessments.

There is level 1b evidence that Attention Process Training may improve aspects of visual and auditory attention.

There is level 1b evidence that an intensive, computerized training program may result in improvements in both working memory and attention.

There is level 1b evidence that visual attention retraining using the Useful Field of View may be more effective than conventional computerized visuoperceptual training at improving the on-road driving performance of individuals with right-sided lesions.
12. Post-Stroke Cognitive Disorders

Attention training may have a positive effect on specific, targeted outcomes. Further research within the stroke population is required using like outcome measures to better evaluate comparisons between studies.

Useful Field of View (UFOV) training may be recommended over conventional computerized visuoperceptual training in the remediation of on-road driving ability.

12.5.2 Remediation of Memory Deficits

Cicerone et al. (2000) noted that many studies regarding the remediation of memory deficits have encompassed “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.” In terms of the interventions used to address these problems, studies have examined the “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.” Of these studies, only a few focused on patients post stroke (Gianutsos & Gianutsos, 1979; Squires, 1996; Wilson, 1982); additional studies added in 2005 (Kaschel et al., 2002; Wilson et al., 2001) and 2011 (Fish et al., 2008; Hildebrandt et al., 2006; Thickpen-Davis & Barker-Collo, 2007) included a mixture of patients post stroke and post TBI.

Cicerone et al. (2000) found evidence supporting the effectiveness of compensatory strategies for patients with memory impairments, including internal strategies (e.g. visual imagery) and assistive devices (e.g. diaries and pagers). They recommended training that involves external strategies with direct application to functional ability, which was reiterated in their subsequent reviews (Cicerone et al., 2005; Cicerone et al., 2011). Cappa et al. (2005) determined that strategies used to improve memory without the use of an electronic aid were judged to be “possibly effective”, while specific learning strategies (e.g. trial-and-error 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”. The authors noted a lack of evidence regarding the influence of injury etiology, injury severity, stage of recovery, age, and gender. As well, it should be noted that all of these recommendations were primarily based on studies examining patients post TBI rather than post stroke.

Trials examining the remediation of post-stroke memory deficits, including those from Cicerone et al. (2005, 2011), are presented in Table 12.5.1.2.

Table 12.5.2.2 Summary of RCTs Evaluating Remediation of Post-Stroke Memory Deficits

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Study Design (Pedro Score)</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aben et al. (2014)</td>
<td>RCT (8)</td>
<td>NStart=153, NEnd=139</td>
<td>E: Memory self-efficacy training program, C: Educational program</td>
<td>• Memory Self-Efficacy Score (+) • WHO Quality of Life (-) • Social Support List (-) • Center for Epidemiological Studies Depression Scale (-)</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>N Start</td>
<td>N End</td>
<td>E/Training Method</td>
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<tr>
<td>Liu et al. (2004)</td>
<td>RCT (6)</td>
<td>49</td>
<td>46</td>
<td>Mental imagery training</td>
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<tr>
<td>Hildebrandt et al. (2006)</td>
<td>RCT (6)</td>
<td>62</td>
<td>62</td>
<td>Process-oriented memory training</td>
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<td>Strategy-based memory training</td>
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<td>Low dose memory training</td>
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<tr>
<td>Gasparrini &amp; Satz (1979)</td>
<td>RCT (5)</td>
<td>30</td>
<td>30</td>
<td>Visual imagery mnemonic technique</td>
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<tr>
<td>Rose et al. (1999)</td>
<td>RCT crossover (5)</td>
<td>96</td>
<td>96</td>
<td>Stroke, active participation in virtual environment training</td>
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<tr>
<td>Chen et al. (2012)</td>
<td>RCT (5)</td>
<td>11</td>
<td>9</td>
<td>Global processing training (global to local encoding)</td>
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<tr>
<td>Ostwald et al. (2014)</td>
<td>RCT (5)</td>
<td>159</td>
<td>134</td>
<td>Home visits from nurses and therapists, plus mailed letters containing information and resources</td>
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<tr>
<td>Wilson et al. (2001)</td>
<td>RCT Crossover (5)</td>
<td>198</td>
<td>143</td>
<td>Pager prompting system</td>
</tr>
<tr>
<td></td>
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<tr>
<td>Fish et al. (2008)</td>
<td>RCT (5)</td>
<td>36</td>
<td>63</td>
<td>Mailed letters containing information and resources</td>
</tr>
<tr>
<td></td>
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<tr>
<td>Liu et al. (2009)</td>
<td>RCT (4)</td>
<td>35</td>
<td>33</td>
<td>Mental imagery training</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>E: Training Method</td>
<td>C: Control Method</td>
<td>Outcomes</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>--------------</td>
<td>--------------------------------------------------------</td>
<td>-----------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Mount et al. (2007)</td>
<td>RCT Crossover (4)</td>
<td>E: Trial and error training</td>
<td>C: Errorless training</td>
<td>• Incidence rate of retention (-)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Carry-over for wheelchair task (-)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Carry-over for sock donning task (+)</td>
</tr>
<tr>
<td>Doornhein &amp; De Haan (1998)</td>
<td>RCT (4)</td>
<td>E: Memory strategy training</td>
<td>C: Drill and practice exercises, no strategy training</td>
<td>• Name-face paired association task (+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Stylus Maze Task (+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• List Learning Task (-)</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>• Oxford Recurring Faces Test (-)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Memory Questionnaire (subjective judgement) (-)</td>
</tr>
<tr>
<td>Miller et al. (2014)</td>
<td>PCT</td>
<td>E: Group-based memory intervention</td>
<td>C: Late treatment group</td>
<td>• Comprehensive Assessment of Prospective Memory-Self (-)</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td>• Comprehensive Assessment of Prospective Memory-Other (-)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Rey Auditory Verbal Learning Test-Delayed Recall (-)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Rey Auditory Verbal Learning Test-Total (-)</td>
</tr>
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<td></td>
<td></td>
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<td></td>
<td>• Royal Prince Alfred Prospective Memory Test (-)</td>
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<td></td>
<td></td>
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<td></td>
<td>• Complex Figure Tests (-)</td>
</tr>
</tbody>
</table>

+ Indicates statistically significant differences between treatment groups
- Indicates no statistically significant differences between treatment groups

Discussion

Of the ten studies presented, nine are RCTs. The studies evaluated the use of various compensatory strategies for memory training. 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). The use of a computer as a tool in the remediation of memory deficits was examined in a study by Rose et al. (1999), which suggested that patients may experience improvements in spatial memory following the use of virtual technology post stroke.

Hildebrandt et al. (2006) examined patients undergoing Process-Oriented Training, which aimed to improve recall during sessions and retrieval between sessions, and Strategy-Based Training, which focused on taught strategies over encoding. Both groups showed significant improvement on word fluency and verbal retrieval compared to control, though only the former group showed improvement on free and cued recall. As well, Process-Oriented Training demonstrated a trend toward improved cued retrieval and decreased rates of forgetting. In (2007), Mount et al. conducted a crossover trial in which patients received trial-and-error and errorless training on two different tasks. Mode of training had no significant effect on rate of retention or carryover ability, though patients with intact memory were more likely to achieve carryover than those with impaired memory. In (2012), Chen et al. evaluated progressive Global Process Training as a treatment alternative to Rote Repetition Training. While the treatment significantly improved immediate recall and delayed retention, these improvements were not maintained at later follow-up.

An early study showed improved scores on Paired Associates Tests when using mental imagery techniques compared to rote memory and verbal mediation, although no other outcome measures showed improvements by (Gasparrini, 1979). In (2004) and (2009), Liu et al. conducted studies evaluating mental imagery training that involved reflection, mental rehearsal, video feedback, problem identification, and therapist-directed demonstration on each learned task. Their results suggested that mental imagery may improve task performance and transference to new tasks of equal difficulty, even in an unpredictable outdoor environment. However, some caution should be given in interpreting these findings, given that the intervention was provided for only 3 weeks in both studies. Moreover, the latter
study involved an acute stroke population with no signs of cognitive impairment at baseline, suggesting that these results may only be generalizable to patients with acute stroke and minimal cognitive deficits.

Miller et al. (2014) provided patients with a group-based memory intervention with a focus on mental strategies, external aids, homework tasks, and group exercises. Although the intervention and control groups both improved significantly from baseline to follow-up on Total and Delay scores on the Rey Auditory Verbal Learning Test, the two groups did not differ significantly at post treatment on all outcome measures assessed. The authors stated that although a lack of differences between groups was disappointing, the follow-up results suggest that patients with non-acute stroke can benefit from strategy training and group interventions. Aben et al. (2014) evaluated a memory self-efficacy training programme focusing on psychoeducation in addition to compensatory memory techniques, while the control group received educational support. The intervention group demonstrated significantly greater gains on the Memory Self-Efficacy Scale compared to the control group. The authors suggested that combining compensatory techniques with psychoeducation with an emphasis on self-efficacy results in positive improvements in memory.

Ostwald et al. (2014) adopted a community outreach approach in which two groups of patients were sent letters containing information, resources, and advice. The intervention group received home visits from therapists and nurses as well. Both groups improved significantly on the Functional Independence Measure–Cognitive and Stroke Impact Scale Memory subscales but no significant differences between the two groups were found. Caregivers in the intervention group reported better health than the control group but these differences did not reach statistical significance. The authors concluded that personalised information via mail can assist patients post stroke.

Wilson et al. (2001) employed the use of a pager as a memory aid, which resulted in improvements in everyday tasks and reduction in carer strain that persisted beyond the end of the intervention. However, a post-hoc analysis found that performance regressed to baseline levels after removal of the device in patients post stroke but not post TBI (Fish et al., 2008). Further examination of between-group differences revealed that patients with stroke tended to be older, more recently injured, and have poorer executive function compared to those with TBI. The authors suggested that these factors be considered when selecting an intervention for the remediation of memory deficits.

Conclusions Regarding Remediation of Memory Deficits Post Stroke

There is level 1a evidence that compensatory strategies may be effective at improving memory outcomes, including imagery-based, process-oriented, and self-efficacy training.

There is level 1b evidence that home visits combined with mailed letters containing resources and information may result in an improvement of self-reported health status for both patients and caregivers after 6 months compared to mailed letters only.

There is level 1b and level 2 evidence that mental imagery may improve relearning of activities of daily living in patients with acute stroke and minimal cognitive deficits.

There is limited level 2 evidence that patients in group-based interventions may not improve memory abilities any better than patients who did not receive intervention while on a waiting list.

Compensatory strategies can be used to improve memory outcomes post stroke. Further research within the stroke population is required.
There is limited research investigating group therapy post stroke, and little evidence supporting the use of group based interventions for the improvement of memory.

12.5.3 Rehabilitation of Executive Function and Problem Solving

Cicerone et al. (2000) defined the term executive function as “those integrative cognitive processes that determine goal directed and purposeful behaviour and are superordinate in the orderly execution of daily life functions.” The 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.” The studies reviewed by Cicerone et al. (2000; 2005; 2011) involved interventions that sought to establish “external structure and/or internalization of control” over various “cognitive structures and processes that control the use of these [discrete] skills.” Of the studies, only a few focused on patients post stroke (Evans et al., 1998; Schweizer et al., 2008; Stablum et al., 2000; Tham et al., 2001), while others included a mixture of patients post stroke and post TBI (Man et al., 2006; Ownsworth et al., 2000).

Cicerone et al. (2000) found evidence supporting the effectiveness of executive function and problem solving rehabilitation. They recommended cognitive interventions that promote internalization of self-regulation strategies through use of verbal self-instruction, self-questioning, and self-monitoring. They also suggested that such training be applied to everyday situations and functional activities. While these recommendations were primarily based on studies examining patients post TBI, they were supported by a systematic review of ten studies involving patients in the subacute and chronic stages post stroke (Poulin et al., 2012). However, only two of those studies had not already been included in the former reviews (Honda, 1999; Rand et al., 2009).

Studies examining interventions aimed at improving executive function and problem solving post stroke, including one from Cicerone et al. (2011), are summarized in Table 12.5.3.1.

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Study Design (Pedro Score)</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Man et al. (2006)</td>
<td>RCT (9)</td>
<td>N_start=109, N_end=103, N_stroke=55, N_TBI=48</td>
<td>E1: Online training (videoconferencing)  E2: Computer-assisted training software  E3: Therapist-administered training  C: No treatment</td>
<td>• Problem-solving self-efficacy scale (+)  • Lawton instrumental activities of daily life (-)  • Category Test (-)</td>
</tr>
<tr>
<td>Hadidi et al. (2015)</td>
<td>RCT (8)</td>
<td>N_start=22, N_end=22</td>
<td>E: 1.5 hours of problem-solving therapy for 10 weeks  C: No additional therapy</td>
<td>• Depression (-)  • FIM (-)  • Comfort applying PST (+)</td>
</tr>
<tr>
<td>Chen et al. (2016)</td>
<td>RCT (8)</td>
<td>N_start=250, N_end=241</td>
<td>E: Acupuncture therapy 6 days a week for 3 weeks  C: Standard rehabilitation care</td>
<td>• NIHSS (+)  • FMA (-)  • VFSS (+)  • MoCA (+)  • MMSE (+)</td>
</tr>
</tbody>
</table>
**Discussion**

Of the eight studies presented, six are RCTs. In a PCT by Levine et al. (2011), Goal Management Training (GMT) showed significant improvements in self-regulation when compared to a Brain Health Workshop (BHW). Patients in the GMT group showed significant improvements in planning post-intervention, while no significant changes were found in the BHW group on any test post-intervention or at follow-up. A similar improvement in cognition was seen in Chen (2015), with the use of visual training. In (2014), Liu et al. investigated the use of self-regulation through feedback provided by video playback in order to identify strategies and reflect on performance. Although the intervention group improved to a significantly greater degree compared to the control group on the FIM motor, no differences were reported regarding FIM cognition. The authors noted that the patients in the study demonstrated adequate cognitive abilities at admission, and so results may have been biased.

RCTs by Jiang et al. (2016) and Chen et al. (2016) both examined the effects of acupuncture on cognition and executive functions. Both studies conducted their interventions a similar amount of times through the week, however, Jiang et al. (2016) conducted their study for a much longer period of time over all. As expected, both studies found similar results on like measures, such as significant improvements on the Mini-Mental State exam and Montreal Cognitive Assessments. General functionality was also improved in both participant groups. These studies provide reliable evidence to the growing body of work which demonstrates the potential effectiveness of alternative therapies on cognitive rehabilitation.

In a high quality RCT, Man et al. (2006) compared three forms of problem solving training with an untreated control group. Patients received training that was either patient-directed via computer
software, online-assisted via video conference, or therapist-administered in person. All training groups utilized an analogical skills approach and were similar in both content and structure. After twenty 45-minute sessions over the course of two months, all intervention groups experienced significant improvements on the Category Test, Instrumental Activities of Daily Living, and both basic and functional problem solving skills compared to baseline and control. While there was no significant difference between intervention groups on overall problem solving skills, patients who received face-to-face therapy showed significant improvements in problem solving self-efficacy compared to patients from the other intervention groups. Another high quality RCT by Hadidi et al. (2015) examined the effects of Problem Solving Therapy directly on cognitive measures. However, in this study, participants in the experimental group did not see significant improvements on functionality compared to controls. Participants did note that their comfort level when applying the skills they learning during problem solving therapy improved significantly over time. A standardized regime for problem solving therapy would be required to further elaborate on the conflicting results of these two studies.

A specific workplace intervention was used by Ntsiea et al. (2015) to measure how tailored cognitive interventions could impact a patient’s ability to return to work. Each patient received specific cognitive rehabilitation based on their functional ability, and return to work, cognition, and quality of life were measured. There was no significant difference between groups in the number of patients who returned to work over the period of the study, however, the experimental group significantly increased their Barthel Index scores. In contrast to the improvement in Barthel index scores, other measures of cognition and quality of life showed no significant improvement between groups. The outcomes in Ntsiea et al. (2015) are just one of many examples that demonstrates how different measures with similar face validity can show conflicting results.

**Conclusions Regarding Rehabilitation of Executive Function and Problem Solving Post Stroke**

*There is level 1b evidence that an analogical problem solving skills approach may increase problem solving abilities and performance of extended activities of daily living.*

*There is level 1b evidence that self-regulation training may increase executive control over motor but not cognitive function, although these findings may be biased.*

*There is level 2 evidence that goal management training may be beneficial in the rehabilitation of executive function.*

*There is level 1b and level 2 evidence that acupuncture can be an effective intervention in the remediation of cognitive deficits.*

*There is level 1b evidence that problem-solving therapy is not an effective intervention for the improvement of executive functioning.*

*There is level 1b evidence that tailored occupational cognitive interventions do not significantly affect return to work or executive functions.*

*There is level 2 evidence that visual training in combination with other interventions can improve executive functions.*
The standardization of both intervention and outcome measures would help resolve the conflicts seen between individual studies.

Analogical problem-solving skills training may improve problem-solving abilities and instrumental activities of daily living, but there is conflicting evidence.

Tailored interventions to improve return to work are not effective in improving cognition.

**Acupuncture is an effective intervention for cognitive remediation.**

### 12.5.4 Multi-Modal Interventions

During rehabilitation, interventions may be provided to address multiple areas of cognitive function. In (2000), Cicerone et al. identified studies that addressed more than one deficit, though no additional studies were added to their updates in (2005) and (2011). Despite the few studies addressing multi-modal interventions, the authors concluded that this type of intervention is effective in improving neuropsychologic performance in the targeted areas. The authors recommended that interventions be based on the evidence pertaining to individual modes of intervention and discrete areas of rehabilitation. However, it should be noted that these conclusions and recommendations were based only on studies examining patients with TBI. Two RCTs examining multi-modal interventions within a stroke population have been identified and are summarized in Table 12.5.4.2.

**Table 12.5.4.2 Summary of RCTs Evaluating Multi-Modal Interventions Post Stroke**

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Study Design (Pedro Score)</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Prokopenko et al. (2013) | RCT (7) | N
Start=43 N
End=43 | E: Computer-based training + Standard care C: Standard care | FAB (+)  Clock Drawing Test (+)  Schulte’s Tests (+)  MMSE (-)  MOCA (-)  HADS (-) |
| Wang et al. (2016) | RCT (7) | N
Start=126 N
End=119 | E: Acupuncture + nimodipine E: Acupuncture E: Nimodipine | Within Montreal Cognitive Assessments (+)  6mo post-intervention MoCA in NA group (+)  MoCA in NA compared to N and A (+) 3 mo post-intervention  MoCA in NA compared to N and A (-) 6 mo post-intervention |
| Matz et al. (2015) | RCT (7) | N
Start=202 N
End=146 | E: Motivational therapy + healthy diet + physical activity + cognitive training C: Standard care | Alzheimer Disease Assessment Scale (-)  NIH Stroke Scale (-)  Modified Rankin Scale (-)  Quality of Life (-) |
| Kongkasuwan et al. (2016) | RCT (6) | N
Start=118 N
End=113 | E: Physical therapy and art therapy C: Physical therapy only | Abbreviated Mental Test (-)  Hospital Anxiety and Depression Scale, depression portion (+)  Hospital Anxiety and Depression Scale, anxiety portion (-)  Barthel Index (+) |
Discussion

While there is limited literature regarding the use of multi-modal interventions, there is still room for debate as to whether these approaches result in successful prevention or improvement of cognitive decline. Studies conducted by Pyun et al. (2009) and Rasquin et al. (2010) involved broad training programs addressing multiple cognitive modalities. Significant improvements were noted for functional performance in completing activities of daily living and goal attainment respectively, but improvements in cognitive function failed to achieve statistical significance. However, Pyun et al. (2009) noted a trend toward significant improvements in visuospatial, visuomotor, and overall cognitive abilities. As well, Rasquin et al. (2010) found the majority of the goals attained were in the cognitive domain. The authors speculated that this was due to goals having been subjectively set by the patient, while other measures were based upon performance within the intervention. Therefore multi-modal interventions may prove beneficial from a patient perspective as opposed to a clinical viewpoint.

Matz et al. (2015) and Kongkasuwan et al. (2016) both incorporated physical therapy and mindfulness based interventions such as art therapy, motivational, and cognitive therapy. However, conflicting results were found with Matz et al. (2015) demonstrating no significant improvements in cognition or quality of life measures, and Kongkasuwan et al (2016) seeing a significant improvement on measures of depression, quality of life, and cognitive functioning. It should be noted that neither study used the same outcome measure, this could account for the difference in observable outcomes.

Wang et al. (2016) was the only multimodal RCT to examine the effectiveness of alternative therapies in combination with more traditional interventions on cognitive rehabilitation. The combination of acupuncture and nimodipine was seen to be effective in significantly improving cognitive scores compared to each intervention alone.

In an RCT, Kim et al. (2011) reported that a 30-minute virtual reality (VR) intervention in combination with computer-based cognitive rehabilitation led to greater improvements on the Visual Continuous Performance Test and the backward Visual Span Test compared to computer-based training alone. Kim et al. (2011) suggested that the interactive games of the VR training program may have resulted in enhanced procedural memory and motivation, thereby increasing attention. More recently, a RCT by Prokopenko et al. (2013) revealed greater improvements on the Clock Drawing Test, Schulte’s Tables Test, and Frontal Assessment Battery in favour of computer-based training and standard care, rather than standard care alone. The authors suggested that computer programs and games can be used at home, especially given the simplicity of using a computer, and can be used for correcting neuropsychological deficits.

Conclusions Regarding Multi-Modal Interventions Post Stroke

There is mixed level 1b evidence that physical therapy in combination with mindful interventions can improve cognition and quality of life post-stroke.
There is level 1b evidence that acupuncture combined with nimodipine can improve cognitive functioning short term.

There is level 1b evidence that standard care combined with computerized training may improve cognitive performance more than standard care alone.

There is limited level 2 evidence that virtual reality training combined with computerized training may improve cognitive performance more than computerized cognitive training alone.

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

Acupuncture combined with nimodipine can be an effective treatment for improving cognitive functioning.

Physical therapies in combination with mindful interventions may not improve cognition.

Virtual reality training may be a suitable supplemental treatment to currently existing computerized cognitive training in improving cognitive performance.

12.5.5 Electroacupuncture and Transcutaneous Electrical Nerve Stimulation (TENS)

Data from studies in primates and 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. Studies examining the effects of electroacupuncture and TNS on cognitive function post stroke are summarized in Table 12.5.5.1.

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Study Design (Pedro Score)</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rorsman &amp; Johansson</td>
<td>RCT (6)</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=54 N&lt;sub&gt;End&lt;/sub&gt;=51</td>
<td>E1: Electroacupuncture E2: High-intensity low-frequency TENS C: Low-intensity high-frequency TENS</td>
<td>Mini Mental State Exam (-) Rey Auditory Verbal Learning Test (-) Facial Recognition Memory (-) Star Cancellation Test (-) Token Test (-) Word Fluency (-)</td>
</tr>
</tbody>
</table>
• SF-36 Mental Component (+)
• SF-36 Mental Health (+)

+ Indicates statistically significant differences between treatment groups
- Indicates no statistically significant differences between treatment groups

Discussion
Despite limited literature concerning the effects of TENS on post-stroke cognitive functioning, there is still mixed findings regarding the effectiveness of this treatment. Of the two studies identified, Rorsman et al. (2006) reported that both groups in their study who received TENS (high intensity vs low intensity) demonstrated significant cognitive improvement, as did the electroacupuncture group, but no significant differences were found between all three groups. Although the low-intensity TENS group had significantly lower cognitive scores at baseline, they were comparable after three and 12 weeks of treatment. While these results may suggest that low-intensity TENS is a preferable treatment approach, the authors of the study believed that high-intensity TENS and electroacupuncture were ineffective in improving cognitive performance.

One observation from Rorsman et al. (2006) study was the lack of a control group who received usual care only, or a sham treatment. Chou et al. (2009) compared the use of electroacupuncture with a group who received usual care and sham TENS. It was reported that patients who received acupuncture demonstrated significantly greater cognitive gains than those who received usual care with sham TENS on four of the seven Lowenstein Occupational Therapy Cognitive Assessment-Geriatric (LOCTA-G) subscales and on the Short Form Health Survey, Mental Component. The authors highlighted that although the patients did not demonstrate significant differences on the LOTCA-G Thinking Operation and Visuomotor Organisation subscales, these subscales often score lower in patients with stroke. As well, it has been suggested that higher-level cognitive abilities are required to complete these tests in order to achieve an improvement in scores. Future research should observe the long-term benefits of electroacupuncture.

Conclusions Regarding Electroacupuncture and TENS Post Stroke

There is level 1b evidence that electroacupuncture may improve attention, praxis, perception and orientation, but not thinking, organization memory and mental health.

There is level 1b evidence that high-intensity TENS may not be more effective than low-frequency TENS at improving cognitive function.

Limited evidence suggests that electroacupuncture and TENS may be useful for improving cognitive function. Further research is required.

12.5.6 Music Therapy
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 coronary artery disease (Emery et al., 2003), with generally positive results.
Van de Winckel et al. (2004) conducted a RCT evaluating the impact of a music-based exercise program delivered over a period of 3 months on general cognition and behaviour in elderly women with dementia compared to an attention control condition. Overall, the group receiving music-based therapy demonstrated significant improvement in Mini Mental State Exam 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 daily conversation without exercise, it is not possible to determine the impact of music alone.

Sarkamo et al. (2008) reported the results of a RCT designed to evaluate the impact of music on cognitive function post stroke, which is summarized in Table 12.5.6.1.

Table 12.5.6.1 Summary of RCT Evaluating Music Therapy for Cognitive Function

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Study Design (Pedro Score)</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarkamo et al. (2008)</td>
<td>RCT (6)</td>
<td>E1: Music listening</td>
<td>• Verbal memory (+)</td>
</tr>
<tr>
<td></td>
<td>NStart=60</td>
<td>E2: Language listening</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NExp=54</td>
<td>C: No listening material</td>
<td>• Focused attention (+)</td>
</tr>
</tbody>
</table>

+ Indicates statistically significant differences between treatment groups
- Indicates no statistically significant differences between treatment groups

Discussion

Sarkamo et al. (2008) compared three conditions: listening to music, listening to narrated audiobooks, and no treatment. Although no significant effect of group was found between groups, a significant time-by-group interaction was revealed for verbal memory and focused attention. Post-hoc analysis revealed that the music group performed significantly better than the audiobook and control groups in verbal memory recovery, and the control group on focused attention recovery. No significant difference was noted between the music listening group and the audiobook group for focused attention, but the difference approached statistical significance in favour of the music listening group. The authors suggested that listening to music, especially with lyrics, activates a wider and broader range of neural networks and therefore increasing neural plasticity. Patients in the music-listening group reported lower levels of depression and confused mood as well, suggesting that music may also help alleviate emotional issues experienced post-stroke.

Conclusions Regarding Music Listening Therapy Post Stroke

There is level 1b evidence that self-regulated music therapy may have a positive impact on verbal memory and focused attention in individuals with left hemisphere stroke.

Music may have a positive impact on cognitive function. Further research is required.

12.5.7 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 healthy but sedentary older adults, Colcombe and Kramer (2003) included results from 18 studies from 1966 to 2001 (see Table 12.5.7.1).
In general, Colcombe 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 review by Cumming et al. (2011) examined the impact of exercise on cognitive performance in patients with stroke. The authors identified 12 RCTs but only nine had sufficient data to be included in meta-analysis (see Table 12.5.7.2). The large variability between study interventions prevents drawing firm conclusions regarding frequency, intensity, and type of physical activity provided. As well, the measures used to assess cognitive performance were limited and were rarely the primary focus of these articles. Although the authors reported a significant treatment effect favoring the use of exercise, this body of literature is methodologically limited, which highlights the need for further research in this area. Studies examining the impact of exercise on cognitive function post stroke, including but not limited to those from Cicerone et al. (2011), are presented in Table 12.5.7.3.

### Table 12.5.7.1 Exercise and Cognition

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Barry et al. 1966</td>
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<tr>
<td>Blumenthal et al. 1991</td>
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<tr>
<td>Dustman et al. 1984</td>
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<td>Emery et al. 1990</td>
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<td>Emery et al. 1998</td>
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<td>Hassmen et al. 1992</td>
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<td>Hawkins et al. 1992</td>
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<tr>
<td>Hill et al. 1993</td>
</tr>
<tr>
<td>Khartli et al. 2001</td>
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<tr>
<td>Kramer et al. 1999</td>
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<tr>
<td>Madden et al. 1989</td>
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<td>Moul et al. 1995</td>
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<tr>
<td>Okumiya et al. 1996</td>
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<tr>
<td>Palleschi et al. 1996</td>
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<tr>
<td>Perri et al. 1984</td>
</tr>
<tr>
<td>Powell et al. 1974</td>
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<tr>
<td>Riki et al. 1991</td>
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<tr>
<td>Williams et al. 1997</td>
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</tbody>
</table>

### Table 12.5.7.2 Exercise and Cognition

<table>
<thead>
<tr>
<th>Cumming et al. (2011)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bateman et al. 2001</td>
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<tr>
<td>Chen et al. 2006</td>
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<tr>
<td>Fang et al. 2003</td>
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<tr>
<td>Mead et al. 2007</td>
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<tr>
<td>Nilson et al. 2001</td>
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<tr>
<td>Ozmeker et al. 2001</td>
</tr>
<tr>
<td>Ploughman et al. 2008</td>
</tr>
<tr>
<td>Pyoria et al. 2007*</td>
</tr>
<tr>
<td>Quaney et al. 2009</td>
</tr>
<tr>
<td>Ruff et al. 1999*</td>
</tr>
<tr>
<td>Studensky et al. 2005</td>
</tr>
<tr>
<td>Wolfe et al. 2000*</td>
</tr>
</tbody>
</table>

*Studies not included in meta-analysis

Table 12.5.7.3 Summary of RCTs Evaluating Exercise Programs for Cognitive Function

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Study Design (Pedro Score)</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu-Ambrose &amp; Eng (2015) RCT (9)</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=28 N&lt;sub&gt;End&lt;/sub&gt;=24</td>
<td>E: Exercise sessions with a key focus on resistance, balance and aerobic training C: Waiting list, no treatment</td>
<td>Trail-Making Test Parts A &amp; B (+) Stroop Test (+) Verbal digits backwards test (+) Verbal digits forwards test (+)</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>N Start</td>
<td>N End</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>-----------</td>
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</tr>
</tbody>
</table>
| Calabro et al. (2015)                     | RCT (8)   | 20      | 20     | Patients received standard physical exercise plus 30 sessions of robotic tilt table training | • Raven Colored Progressive Matrices (+)  
• Electrophysiological measures (+)  
• BP, HR, pO2 (-) |
|                                           |           |         |        | C: Patients received standard physical exercise plus verticalization training by a physiotherapist |                                                                                  |
| Moore et al. (2015)                       | RCT (7)   | 40      | 40     | E: Structured exercise  
C: Standard care                                                                 | • Walking test (+)  
• Walking speed (+)  
• Balance (+)  
• Addenbrooke’s Cognitive Scale (+) |
| Tang et al. (2016)                        | RCT (6)   | 50      | 47     | E: High intensity aerobic exercise  
C: Balance/Flexibility Control Group                                                   | • Berg Balance Scale (-)  
• Verbal Digit Span (-)  
• Stroop Test (-) |
| Ploughman et al. (2008)                   | RCT Crossover (6) | 21      | 21     | E: Bodyweight-support Treadmill Training  
C: Home exercise program                                                               | • Action Research Arm Test (+)  
• Trail-Making Test Parts A & B (-)  
• Symbol Digit Substitution Test (-)  
• Paced Auditory Serial Addition Test (-) |
| Quaney et al. (2009)                      | RCT (5)   | 40      | 38     | E: Progressive, resistive aerobic exercise program  
C: Stretching exercises program                                                        | • Serial Reaction Time Task (at post-treatment only) (+)  
• Predictive Grip Force Modulation (at post-treatment only) (+)  
• Wisconsin Card Sorting Task (-)  
• Trail-Making Test Parts A & B (-)  
• Stroop Test (-) |
| Fernandez-Gonzalo et al. (2016)           | RCT (4)   | 32      | 29     | E: ECC-overload flywheel leg press, 2 times a week for 12 weeks. C: Daily routine      | • Quadricep femoris volume (+)  
• Cross sectional area (+)  
• Berg Balance Scale (+)  
• Dual-task performance (+)  
• Forward Digit Span (+)  
• Backward Digit Span (+) |

+ Indicates statistically significant differences between treatment groups  
- Indicates no statistically significant differences between treatment groups

Discussion

In two non-randomized studies, exercise was found to improve cognitive outcomes. Both Rand et al. (2010) and Kluding et al. (2009) reported significant improvements on the Rey Auditory Verbal Learning Test, Walking While Talking Test and Stroop Test, and on the Digit Span Backwards Test, Fugl-Meyer Assessment Scale and Stroke Impact Scale respectively. However, both studies were limited due to small sample sizes and single group designs. As well, it is not possible to determine if the demonstrated improvements in Rand et al. (2010) were a result of the exercise program, the leisure and recreation component, or both. A larger non-randomized study conducted by Marzolini et al. (2013) involving exercise classes, nutritional counselling, and cardiac monitoring revealed a significant reduction in the proportion of patients who met the criteria for mild cognitive deficits at six-month follow-up.

Multiple RCTs examined the effectiveness of structured exercise programs on cognition. Moore et al. (2015) and Fernandez-Gonzalo et al. (2016) both saw significant improvements on physical measures as well as cognitive measures. Although neither study used the same outcome measure, both employed a specific exercise regime as opposed to general training. By comparison Tang et al. (2016) examined the effects of aerobic exercise in general on cognition and found no significant differences between groups even though the same outcome measures were used by Fernandez-Gonzalo. This implies that there are
inherent benefits to completing a specific structured exercise regime compared to a more general or free routine.

Calabro (2015) was interested if the method of delivery of table-tilting could influence outcome (robot compared to therapist). In a high quality RCT, Calabro (2015) determined that when table verticalization was delivered using a robotic table patients saw a significant improvement compared to those whose verticalization therapy was delivered by a therapist. There was also a significant improvement in electrophysiological measures such as motor evoked potentials. The standardization of delivered care by a robotic program compared to a therapist may improve the overall rehabilitation of patients.

The meta-analysis presented by Colcombe and Kramer (2003) suggested that 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 conducted by Quaney et al. (2009) that consisted of progressive, resistance aerobics training in 45-minute sessions did not report positive impact on the assessed cognitive functions. It is unclear whether intensity of exercise training has a direct effect on cognitive outcomes, as the majority of studies conducted sessions longer than the 30 minutes highlighted by Colcombe and Kramer (2003). In comparing an exercise program with an emphasis on resistance, balance, and aerobics, without prescribed treatment, Liu-Ambrose & Eng (2015) reported a significant difference in cognitive assessments at three and six months in favour of the intervention. The results suggested that an exercise and recreation program is of benefit to executive functioning in community-dwelling patients with mild cognitive impairment.

Conclusions Regarding Exercise Programs Post Stroke

There is conflicting level 1a evidence regarding the effect of exercise therapy on cognitive rehabilitation post stroke.

There is level 1b evidence that robotic table verticalization can demonstrate greater improvements in both electrophysiological and cognitive measures compared to verticalization delivered by a therapist.

There is level 1a and level 2 evidence that exercise programs with a focus on resistance, balance and aerobics can result in significant cognitive gains.

Structured exercise programs which focus on resistance, balance, and aerobics can improve cognitive function.

Verticalization provided by a robotic table is more effective than verticalization therapy provided by a therapist.

Further evidence is required to examine the value of specific exercise interventions compared to more general exercise interventions.

12.5.8 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 of rTMS on cognitive function. While the majority of studies have been conducted using young, healthy participants, a RCT reported that treatment with 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). Studies examining the effects of rTMS on cognitive function post stroke are summarized in Table 12.5.8.1.

### Table 12.5.8.1 Summary of Studies Evaluating rTMS for Cognitive Function

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Study Design (Pedro Score)</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim et al. (2010)</td>
<td>RCT (8)</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=18 N&lt;sub&gt;End&lt;/sub&gt;=18</td>
<td>E1: High-frequency rTMS (10Hz) E2: Low-frequency rTMS (1Hz) C: Sham rTMS</td>
<td>• Tower of London Test (-)  • Computerized Neuropsychological Test Battery (-)  • Beck Depression Inventory (+)</td>
</tr>
<tr>
<td>Lu et al. (2015)</td>
<td>RCT (6)</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=54 N&lt;sub&gt;End&lt;/sub&gt;=50</td>
<td>E: Repetitive Transcranial Magnetic Stimulation C: Sham therapy</td>
<td>• Montreal Cognitive Assessment (+)  • Loewenstein Occupational Therapy (+)  • Rivermead Behavior Memory Test (+)  • Plasma BDNF (+)</td>
</tr>
<tr>
<td>Rektorova et al. (2005)</td>
<td>RCT crossover (6)</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=7 N&lt;sub&gt;End&lt;/sub&gt;=7</td>
<td>E1: rTMS over left dorsolateral prefrontal cortex E2: rTMS over left motor cortex</td>
<td>• Stroop Test (+)  • Wechsler Adult Intelligence Scale-R (-)</td>
</tr>
</tbody>
</table>

+ Indicates statistically significant differences between treatment groups  
- Indicates no statistically significant differences between treatment groups

### Discussion

Rektorova et al. (2005) reported improvements in executive function following rTMS over the dorsolateral prefrontal cortex (DPC) compared to the left motor cortex. However, Kim et al. (2010) demonstrated that neither high nor low frequency rTMS of the DPC was associated with improvements in overall cognitive function. Both RCTs were very small and assessment heterogeneous, and neither study offered assessment periods extending beyond the end of the treatment period. A more recent RCT by Lu et al. (2015) found significant improvements on cognitive measures like the Montreal Cognitive Assessment and Rivermead Behavior Test. Lu et al. (2015) demonstrates that specific rTMS interventions can be very effective in improving cognition, and therefore further study regarding rTMS as an intervention for cognitive function post stroke is required using a standardized paradigm.

### Conclusions Regarding Repetitive Transcranial Magnetic Stimulation Post Stroke

There is level 1b evidence that high-frequency, low-frequency and sham rTMS are not significantly different at improving cognitive performance.

There is level 1b evidence that rTMS in general compared to sham therapy can significantly improve cognitive functioning.

There is level 4 evidence that rTMS to the left DPC may be associated with improvements in executive function following stroke.

RTMS has a positive effect on executive function following stroke. Further research is required to determine if this effect is a result of a specific placement or frequency of the rTMS therapy.
12.5.9 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 healthy populations (Antal et al., 2004; Fregni et al., 2005; Kincais et al., 2004; Nitsche et al., 2003). Studies examining the effects of rTMS on cognitive function post stroke are summarized in Table 12.5.9.1.

Table 12.5.9.1 Summary of Trials Evaluating tDCS for Cognitive Function

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Study Design (Pedro Score)</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kang et al. (2009)</td>
<td>RCT Crossover (8)</td>
<td>NStart=20 NEnd=20</td>
<td>E: Anodal tDCS C: Sham tDCS</td>
<td>• Go/No Go Test Response Accuracy (-) • Go/No Go Test Correct Responses (-)</td>
</tr>
<tr>
<td>Jo et al. (2009)</td>
<td>RCT crossover (7)</td>
<td>NStart=10 NEnd=10</td>
<td>E: Anodal tDCS C: Sham tDCS</td>
<td>• Working Memory Task accuracy (+) • Working Memory Task response time (-)</td>
</tr>
</tbody>
</table>

+ Indicates statistically significant differences between treatment groups
- Indicates no statistically significant differences between treatment groups

Discussion

Working memory and attention are of particular importance in relearning and recovery post stroke. The results of two crossover studies suggest that anodal tDCS to the left dorsolateral prefrontal cortex may result in some improvement to these areas of cognitive function (Jo et al., 2009; Kang et al., 2009). However, due to limits in sample sizes and methodologies, further research is required.

Conclusions Regarding Transcranial Direct Current Stimulation Post Stroke

There is level 1a evidence that anodal tDCS to the left dorsolateral prefrontal cortex may be associated with improvements in working memory and attention.

Anodal tDCS to the left dorsolateral prefrontal cortex may help to improve working memory and attention. Further research is required.
12.6 Pharmacotherapy for Vascular Cognitive Impairment

Devasenapathy and Hachinski (2000) noted that, “the early manifestations of vascular cognitive impairment [VCI] 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 donepezil (Chui, 2000), memantine (Mobius, 1999), nimodipine, pentoxifylline, hydergine, propentofylline, piracetam, and ginkgo biloba. However, most of these have all shown only modest and/or clinically irrelevant effects. Chui (2000) noted that the therapeutic effects are usually very similar in patients with Alzheimer’s disease and vascular dementia, suggesting that these two types of dementia may share a common pharmacodynamic basis or underlying pathophysiology.

12.6.1 Aspirin

Daily aspirin therapy has been shown to reduce the incidence of transient ischemic attacks, 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 on cognitive outcomes is not well studied. A trial examining aspirin in the treatment of vascular dementia is summarized in Table 12.6.1.1.

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Study Design (Pedro Score)</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meyer et al. (1989)</td>
<td>RCT (6)</td>
<td>NStart=70</td>
<td>E: Aspirin (325mg/d)</td>
<td>• Cognitive Capacity Screening Examination (+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NEnd=62</td>
<td>C: Usual Care</td>
<td>• Cerebral blood flow (+)</td>
</tr>
</tbody>
</table>

+ Indicates statistically significant differences between treatment groups
- Indicates no statistically significant differences between treatment groups

Discussion

The pilot study by Meyer et al. (1989) demonstrated benefits associated with aspirin therapy in vascular dementia post stroke, though the results should be interpreted with caution given the limitations of methodology. No further randomized controlled trials assessing the effects of aspirin on post-stroke dementia could be identified by either the present review or Cochrane Reviews. This could be in part due to difficulties in designing ethical randomized controlled trials within an environment of aspirin use for other purposes such as the primary and secondary prevention of stroke (Devine & Rands, 2003).

In a retrospective case analysis of 78 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 required.

Conclusion Regarding Aspirin for Vascular Dementia

There is level 1b evidence that aspirin is effective in stabilizing and/or improving cognitive outcomes in patients with multi-infarct dementia.
Aspirin is a common antithrombotic therapy used in the treatment of vascular dementia and may be effective in stabilizing cognitive deficit post stroke. Further research is required.

12.6.2 GABA Agonists

12.6.2.1 Phosphodiesterase Inhibitor

GABA agonists such as phosphodiesterase inhibitors have been shown to promote functional recovery in rodent models of artery occlusion as well as upregulated neurogenesis, synaptogenesis and regional blood flow (Bednar, 2008; Menniti et al., 2009). Although the mechanism by which these effects take place is not yet well understood there are clear clinical implications for the use of GABA agonists in the cognitive rehabilitation of post-stroke patients.

Table 12.6.2.1.1 Summary of Trials Evaluating Phosphodiesterase Inhibitors

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Study Design (Pedro Score)</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Di Cesare et al. (2016) RCT (9)</td>
<td>Stark=139</td>
<td>NEnd= 137</td>
<td>E: 6mg of Phosphodiesterase-5 inhibitor once a day for 90 days C: Placebo</td>
<td>CMH test (-) Modified Rankin Scale (-) NIH Stroke Scale (-) Box and Blocks Test (-) Hand Grip Strength (-) Repeatable Battery Assessment of Neuropsychological Status (-) Naming and Coding Subtest (-) Line Cancellation Test (-) Recognition Memory Test (-)</td>
</tr>
</tbody>
</table>

Discussion

Di Cesare et al., (2016) conducted a high level RCT to examine the effects of phosphodiesterase-5 inhibitor, the authors note that the study was terminated prematurely due to a futility rule determined by the investigators where the probably of finding a significant result was less than 20% due to the methodological design and execution of the study. GABA agonists represent a unique area of pharmacological interventions for the remediation or improvement of cognition post-stroke, however more RCTs are required to make reliable conclusions about any potential clinical benefits in treating individuals with GABA agonists.

Conclusion Regarding Phosphodiesterase-5 Inhibitors

There is level 1b evidence that phosphodiesterase-5 inhibitor may not be effective in remediating cognitive deficits.

There is insufficient evidence to make a conclusion about the effectiveness of GABA agonists to remEDIATE cognitive deficits.
12.6.2.2 Cholinesterase Inhibitors

Cholinergic agents – donepezil, rivastigmine and galantamine – have been used in the treatment 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 dementia is less clear (Craig & Birks, 2005). A meta-analysis by Kavirajan and Schneider (2007) found that cholinesterase inhibitors may produce small benefits in cognition of uncertain clinical significance in patients with mild to moderate vascular dementia, but evidence was insufficient to support their widespread use.

12.6.2.2.1 Donepezil

Donepezil is a selective acetylcholinesterase inhibitor used in the treatment of mild to moderate 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). In a Cochrane Review, Malouf & Birks (2004) found two RCTs examining the use of donepezil in patients with VCI and vascular dementia. The authors concluded that evidence supported the benefits of donepezil in improving cognition function, clinical global impression, and activities of daily living in patients with mild to moderate VCI after 6 months treatment. They recommended extending studies in order to establish its efficacy in patients with advanced stages of VCI. Studies examining the use of donepezil in the treatment of vascular dementia are summarized in Table 12.6.2.1.1.

Table 12.6.2.2.1.1 Summary of Trials Evaluating Donepezil

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Study Design (Pedro Score)</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roman et al. (2010)</td>
<td>RCT (7)</td>
<td></td>
<td>E: Donepezil (5mg/d) C: Placebo</td>
<td>• Mini Mental State Exam (+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Alzheimer’s Disease Assessment Scale-Cognitive subscale (+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Clinician’s Interview-Based Impression of Change-Plus (at 18wk) (+)</td>
</tr>
<tr>
<td>Wilkinson et al. (2003)</td>
<td>RCT (7)</td>
<td></td>
<td>E1: Donepezil (5mg/d) E2: Donepezil (5mg/d for 28d, 10mg/d after) C: Placebo</td>
<td>• Alzheimer’s Disease Assessment Scale-Cognitive subscale (+)</td>
</tr>
<tr>
<td>Black et al. (2003)</td>
<td>RCT (7)</td>
<td></td>
<td>E1: Donepezil (5mg/d) E2: Donepezil (5mg/d for 28d, 10mg/d thereafter) C: Placebo</td>
<td>• Clinician’s Interview-Based Impression of Change-Plus (+)</td>
</tr>
<tr>
<td>Whyte et al. (2008)</td>
<td>PCT</td>
<td></td>
<td>E1: Galantamine (4-12mg/d) E2: Donepezil (5-10mg/d) C: Placebo</td>
<td>• Functional Independence Measure-Motor (+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Executive Interview (-)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Digit Span Test (-)</td>
</tr>
</tbody>
</table>

+ Indicates a statistical significant difference between treatment groups
- Indicates no statistical significant difference between treatment groups

Discussion

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). Whyte et al. (2008) demonstrated that patients with recent stroke demonstrated greater functional improvement (Functional Independence Measure-Motor) over a 12-week treatment period when compared to a historical, matched comparator group.

In a more recent and larger RCT by Roman et al. (2010), small but significant improvements were demonstrated in cognitive but not global function outcomes after donepezil treatment. The authors suggest that mild levels of impairment may have resulted in a ceiling effect for the Clinician’s Interview Based Impression of Change-Plus assessments, or that this particular assessment tool is not sufficiently sensitive to detect small but important changes. These results were echoed by Rockwood et al. (2013), who found small but significant improvements on a number of measures, including the Mini Mental State Exam, Neuropsychiatric Inventory, and Clinical Global Impression. The authors recommended the use of more patient-centered and executive function measures in studies of dementia.

Roman et al. (2010) conducted subgroup analyses based on the presence of hippocampal atrophy (HA). Participants with normal-sized hippocampi (NH) on MRI performed significantly better than those with HA on the Alzheimer’s Disease Assessment Scale-Cognitive (ADAS-cog), the Number Cancellation Test, and Disability Assessment for Dementia administered at baseline. In addition, there was a differential treatment effect identified such that NH patients treated receiving donepezil demonstrated greater improvements on the ADAS-cog than those with HA. Patients 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.

Conclusions Regarding Donepezil for Vascular Dementia

There is level 1a evidence that donepezil taken for 24 weeks may improve cognitive function in patients with probable or possible vascular dementia.

There is 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 may improve cognitive and global function in patients with vascular dementia.

12.6.2.2 Rivastigmine

Rivastigmine is an acetylcholine-esterase inhibitor and a butyrylcholine-esterase inhibitor. In patients with mixed dementia, treatment with rivastigmine has been associated with significant benefits over treatment with placebo (Erkinjuntti et al., 2003; Kumar et al., 2000). 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. 2003; Kumar et al. 2000). Studies examining the use of rivastigmine in the treatment of vascular dementia are summarized in Table 12.6.2.2.1.

Table 12.6.2.2.1 Summary of Trials Evaluating Rivastigmine

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Study Design (Pedro Score)</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
</table>

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<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Start N</th>
<th>End N</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ballard et al. (2008)</td>
<td>RCT</td>
<td>719</td>
<td>572</td>
<td>Rivastigmine (3-12 mg/d)</td>
<td>Vascular Dementia Assessment Scale (+)</td>
</tr>
<tr>
<td>Moretti et al. (2003)</td>
<td>RCT</td>
<td>208</td>
<td>208</td>
<td>Rivastigmine (3-6 mg/d) plus Aspirin (100 mg/d)</td>
<td>Behavioural Pathology in Alzheimer’s Disease (+)</td>
</tr>
<tr>
<td>Moretti et al. (2004)</td>
<td>PCT</td>
<td>64</td>
<td>64</td>
<td>Rivastigmine (3-6 mg/d) plus Aspirin (100 mg/d) plus Nimodipine (60mg/d)</td>
<td>Behavioural Pathology in Alzheimer’s Disease (+)</td>
</tr>
<tr>
<td>Moretti et al. (2002)</td>
<td>PCT</td>
<td>16</td>
<td>16</td>
<td>Rivastigmine (3-6 mg/d) plus Aspirin (100 mg/d)</td>
<td>Ten-point Clock Drawing Test (+)</td>
</tr>
<tr>
<td>Moretti et al. (2001)</td>
<td>PCT</td>
<td>16</td>
<td>16</td>
<td>Rivastigmine (3-6 mg/d) plus Aspirin (100 mg/d)</td>
<td>Ten-point Clock Drawing Test (+)</td>
</tr>
</tbody>
</table>

+ Indicates statistically significant differences between treatment groups
- Indicates no statistically significant differences between treatment groups

**Discussion**

In a series of trials by Moretti et al. (2001; 2002, 2003; 2004), the authors found that patients with vascular dementia showed less deterioration in overall cognitive function, and less caregiver burden, when treated with rivastigmine compared to aspirin. However, outcomes were assessed using a variety of measures and the results for each measure were inconsistent across trials. A large-scale review by Ballard et al. (2008) found similarly inconsistent results regarding the efficacy of rivastigmine treatment for vascular dementia, with significant improvements on some outcome measures and none on others. As well, the authors argued that any improved cognitive outcomes were derived from effects in older patients with mixed dementia.

In a Cochrane Review, Birks et al. (2013) found three RCTs examining the use of rivastigmine for patients with VCI and vascular dementia. The authors concluded that there was insufficient evidence to support or refute the use of rivastigmine in the treatment of dementia, given that only one study detected a benefit on cognition. As such, they recommended that further studies be conducted.

**Conclusions Regarding Rivastigmine for Vascular Dementia**

There is conflicting level 1a evidence regarding treatment with rivastigmine and its effect on vascular dementia and cognitive decline.

There is level 2 evidence that treatment with rivastigmine is associated with more stable cognitive performance and improved behavioural outcomes among patients with vascular dementia.
Treatment with rivastigmine may stabilize cognitive performance and improve behaviour in patients with vascular dementia. Further research is required.

12.6.2.3.2 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 (Olin & Schneider, 2001). Studies examining the use of galantamine in the treatment of vascular dementia are summarized in Table 12.6.2.3.1.

Table 12.6.2.3.1 Summary of Trials Evaluating Galantamine

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Study Design (Pedro Score)</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
</table>
| **Auchus et al. (2007)** | RCT (9) | E: Galantamine (24mg/d)  
C: Placebo | • Alzheimer’s Disease Assessment Scale-Cognitive subscale (+)  
• Alzheimer’s Disease Cooperative Study-Activities of Daily Living (-)  
• Clinician’s Interview-Based Impression of Change-Plus (-)  
• Neuropsychiatric Inventory (-)  
• Executive Interview-25 (+) |
| **Erkinjuntti et al. (2002)** | RCT (8) | E: Galantamine (24mg/d)  
C: Placebo | • Alzheimer’s Disease Assessment Scale-Cognitive subscale (+)  
• Clinician’s Interview-Based Impression of Change-Plus (+) |
| **Erkinjuntti et al. (2003)** | RCT (6) | E: Galantamine (24mg/d) (continuation from 2002 study)  
C: Placebo (patients from 2002 study) | • Alzheimer’s Disease Assessment Scale-Cognitive subscale (-)  
• Progressive Deterioration Scale (among hypertensive patients only) (+)  
• Global Deterioration Scale (among hypertensive patients only) (+) |
| **Whyte et al. (2008)** | PCT | E1: Galantamine (4-12mg/d)  
E2: Donepezil (5-10mg/d)  
C: Placebo | • Functional Independence Measure-Motor (+)  
• Executive Interview (-)  
• Digit Span Test (-) |

+ Indicates statistically significant differences between treatment groups  
- Indicates no statistically significant differences between treatment groups

Discussion

Erkinjuntti et al. (2002) found that treatment of galantamine for vascular dementia was associated with benefits in terms of cognitive and functional ability. Subgroup analysis suggested that these effects were seen most clearly in cases of mixed dementia rather than vascular dementia. In a continuation of their trial, Erkinjuntti et al. (2003) noted that benefits derived from galantamine treatment were greater among patients with concurrent vascular risk factors, specifically hypertension.

Auchus et al. (2007) reported that taking up to 24 mg of galantamine over the course of 26 weeks was effective in improving cognitive abilities, including executive function, in patients with vascular dementia. However, improvements in activities of daily living with galantamine were not significantly
different from those achieved with placebo. Whyte et al. (2008) found that improvements in cognitive function in patients treated with galantamine were not significantly different than those treated with donepezil. As well, performance on the Functional independence Measure-Motor Subscale was not different in patients receiving galantamine treatment or control, although donepezil experienced significantly greater improvement than both groups.

In a Cochrane Review, Birks and Craig (2006) found two RCTs examining the use of galantamine in patients with VCI and vascular dementia. The authors concluded that galantamine offered some advantage over placebo in cognitive and global function, though it was associated with gastrointestinal side-effects. As such, they recommended that further studies be conducted.

Conclusions Regarding Galantamine for Vascular Dementia

There is level 1a evidence that treatment with galantamine is associated with improvements in cognitive and global function. However, the benefits associated with treatment are more clearly demonstrated among patients with mixed dementia than vascular dementia.

Treatment with galantamine may improve cognitive and global function in patients with mixed dementia. However, its impact on patients with post-stroke cognitive impairments is less clear. Further research is required.

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 (Pantoni et al., 2000). It has been used most frequently in the treatment of Alzheimer’s dementia and multi-infarct dementia. Studies examining the use of nimodipine in the treatment of vascular dementia are summarized in Table 12.6.2.2.1.

Table 12.6.3.1 Summary of RCTs Evaluating Nimodipine

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Study Design (Pedro Score)</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pantoni et al. (2000)</td>
<td>RCT (8)</td>
<td>N_{Start}=259 N_{End}=209</td>
<td>E: Nimodipine (90mg/d) C: Placebo</td>
<td>• Gottfries-Brâne-Steen Scale (-) • Mini Mental State Exam (-) • Clinical Dementia Rating (-) • Word Fluency Test (-) • Digit Span Test (-)</td>
</tr>
<tr>
<td>Pantoni et al. (2005)</td>
<td>RCT (8)</td>
<td>N_{Start}=242 N_{End}=184</td>
<td>E: Nimodipine (90mg/d) C: Placebo</td>
<td>• Mini Mental State Exam (+) • Global Deterioration Scale (+) • Sandoz Clinical Assessment Geriatric Scale (-)</td>
</tr>
<tr>
<td>Besson et al. (1988)</td>
<td>RCT (7)</td>
<td>N_{Start}=20 N_{End}=17</td>
<td>E: Nimodipine (90mg/d) C: Placebo</td>
<td>• Dementia Checklist (-) • Sandoz Clinical Assessment Geriatric Scale (-) • Katzman Memory-Orientation-Concentration Test (-) • Royal College of Physicians Test (-)</td>
</tr>
<tr>
<td>Sze et al. (1998)</td>
<td>RCT (6)</td>
<td>N_{Start}=100</td>
<td>E: Nimodipine (90mg/d) C: No treatment</td>
<td>• Fuld Object-Memory Evaluation (+) • Mini Mental State Exam (+)</td>
</tr>
</tbody>
</table>
Discussion

In an early study by Besson et al. (1988), nimodipine treatment showed no benefit over placebo in improving cognitive function on any outcome measure after 24 weeks. Similar results were found after a 26 week trial conducted by Pantoni et al. (2000). However, Sze et al. (1998) reported significant improvements in cognition after only 12 weeks of the same nimodipine dosage compared to placebo. As well, a later trial by Pantoni et al. (2005) found significantly greater cognitive improvements and less global deterioration in patients treated with nimodipine rather than placebo, although there was no significant difference on the Sandoz Clinical Assessment Geriatric Scale.

In a Cochrane Review, Birks and Lopez-Arrieta (2002) found fifteen RCTs examining the use of nimodipine in patients with Alzheimer’s, vascular, or mixed dementia. The authors reported short-term improvements in global function and activities of daily living associated with nimodipine treatment. They recommended extending studies in order to better assess long-term outcomes.

Conclusions Regarding Nimodipine for Vascular Dementia

There is level 1a evidence that nimodipine may not be beneficial in the treatment of vascular dementia.

There is level 1b evidence that treatment with nimodipine may slow cognitive deterioration in patients with vascular dementia.

Treatment with nimodipine may not be beneficial in the treatment of memory deficits in patients with vascular dementia. Further research is required.

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 use of memantine in the treatment of vascular dementia are summarized in Table 12.6.4.1.

Table 12.6.4.1 Summary of RCTs Evaluating Memantine

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Study Design (Pedro Score)</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
</table>
| Orgogozo et al. (2002) | RCT (8)                    | N_{Start}=321 N_{End}=288 | E: Memantine (20mg/d) C: Placebo | • Alzheimer’s Disease Assessment Scale-Cognitive subscale (+)  
• Mini Mental State Exam (+)  
• Gottfries-Brâne-Steen Scale (+)  
• Nurses’ Observation Scale for Geriatric Patients (+)  
• Clinician’s Interview-Based Impression of Change-Plus (-) |
| Wilcock et al. (2002)  | RCT (8)                    | N_{Start}=579 N_{End}=548 | E: Memantine (20mg/d) C: Placebo | • Alzheimer’s Disease Assessment Scale-Cognitive subscale (+)  
• Clinician’s Interview-Based Impression of Change-Plus (-) |

+ Indicates statistically significant differences between treatment groups

- Indicates no statistically significant differences between treatment groups
- Indicates no statistically significant differences between treatment groups

Discussion
Both Orgogozo et al. (2002) and Wilcock et al. (2002) found significant stabilization and improvement on the Alzheimer’s Disease Assessment Scale-Cognitive Subscale, but not on the Clinician’s Interview-Based Impression of Change-Plus, after 28 weeks of memantine treatment for vascular dementia relative to placebo. In addition, Wilcock et al. (2002) noted that treatment effects may be larger among patients with greater cognitive impairment (Mini Mental State Exam<15) or with small vessel disease.

In a Cochrane Review, McShane et al. (2006) found twelve RCTs examining the use of memantine in patients with Alzheimer’s, vascular, or mixed dementia. The authors reported a small benefit of memantine in moderate to severe Alzheimer’s dementia, which was not clinically detectable in patients with mild to moderate vascular dementia. As such, they recommended that further studies be conducted regarding vascular dementia.

Conclusions Regarding Memantine for Vascular Dementia

There is level 1a evidence that treatment with memantine is associated with stabilization or improvement of cognitive function in patients with vascular dementia.

Treatment with memantine may be associated with stabilization or improvement of cognitive function in patients with vascular dementia.

12.6.5 Pentoxifylline
Pentoxifylline is a methylxanthine compound that has been associated with a significant increase in cerebral blood flow (Hartmann, 1983). In a review by Sha and Callahan (2003), four RCTs were found examining the use of pentoxifylline in the treatment of vascular dementia. 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 following treatment with pentoxifylline. After secondary analyses of subgroups based upon more restrictive criteria for vascular dementia, they found that trends toward a positive result became more significant. The studies reviewed by Sha and Callahan (2003) are summarized in Table 12.6.5.1.

Table 12.6.5.1 Summary of RCTs Evaluating Pentoxifylline

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Study Design (Pedro Score)</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blume et al. (1992)</td>
<td>RCT (8)</td>
<td>NStart=80</td>
<td>E: Pentoxifylline (400 mg 3/d)</td>
<td>• Sandoz Clinical Assessment Geriatric Scale (+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NEnd=ND</td>
<td>C: Placebo</td>
<td>• Figure Joint Test (+)</td>
</tr>
<tr>
<td>EPMID Study Group</td>
<td>RCT (7)</td>
<td>NStart=289</td>
<td>E: Pentoxifylline (400 mg 3/d)</td>
<td>• Sandoz Clinical Assessment Geriatric Scale (+)</td>
</tr>
<tr>
<td>(&quot;European Pentoxifylline</td>
<td></td>
<td>NEnd=269</td>
<td>C: Placebo</td>
<td>• Sandoz Clinical Assessment Geriatric Scale-Cognitive subscale (+)</td>
</tr>
<tr>
<td>Multi-Infarct Dementia Study,&quot;</td>
<td></td>
<td></td>
<td></td>
<td>• Gottfries-Bråne-Steen Scale (+)</td>
</tr>
<tr>
<td>1996)</td>
<td></td>
<td></td>
<td></td>
<td>• Gottfries-Bråne-Steen Scale (ITT sample) (-)</td>
</tr>
</tbody>
</table>
Discussion

Overall, studies have demonstrated a trend toward positive effects on cognitive function associated with the use of pentoxifylline in vascular dementia. Although Ghose et al. (1987) did not yield any significant differences between pentoxifylline and placebo, patients with multi-infarct dementia demonstrated significant improvements. Black et al. (1992) showed subgroups of patients with stroke that exhibited significantly slower cognitive deterioration after taking pentoxifylline compared to a placebo, but these differences were not statistically significant. Blume et al. (1992) reported significant improvements in favour of pentoxifylline treatment relative to placebo on a number of outcome measures, including the Sandoz Clinical Assessment Geriatric Scale.

In a multi-centre trial conducted by the EPMID Study Group ("European Pentoxifylline Multi-Infarct Dementia Study," 1996), patients treated with pentoxifylline demonstrated significantly greater improvement in overall cognitive function compared to patients treated with a placebo. Adverse events were reported by both groups, but side effects such as nausea and vomiting were experienced mostly by the pentoxifylline group. The study group noted that some centres enrolled only 1 patient, while the largest cohort was 32 patients. Despite this heterogeneity, significant results were consistent within the treatment group.

Conclusion Regarding Pentoxifylline for Vascular Dementia

There is level 1a evidence that treatment with pentoxifylline is associated with cognitive benefits in patients with multi-infarct dementia.

Treatment with pentoxifylline may improve cognitive function in patients with multi-infarct dementia.

12.6.6 Citicoline

Citicoline (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 (Alvarez et al., 1997). Studies examining the use of citicoline in the treatment of cognitive function are summarized in Table 12.6.6.1.

12.6.6.1 Summary of RCTs Evaluating Citicoline

<table>
<thead>
<tr>
<th>Author (Year) Study Design (Pedro Score) Sample Size</th>
<th>Intervention</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Cohen et al. (2003)
RCT (7)
N Start = 39
N End = 30
E: Citicoline (500mg 2/d)
C: Placebo
- Mini Mental State Exam (-)
- Dementia Rating Scale (-)

Alvarez-Sabin et al. (2013)
RCT (7)
N Start = 347
N End = 199
E: Citicoline (1g/d)
C: Placebo
- Attention and Executive Function Battery (+)
- Benton’s Temporal Orientation (+)
- Modified Rankin Scale (-)
- Memory, Language, Motor Speed, and Spatial Perception Battery scores (-)

Alvares-Sabin (2016)
RCT (4)
N Start = 163
N End = 163
E: 1g/day of citicoline
C: Standard care
- Global Cognitive Impairment (+)
- Poorer GCI was associated with negative European Quality of Life scores

+ Indicates statistically significant differences between treatment groups
- Indicates no statistically significant differences between treatment groups

Discussion
Despite the limited literature concerning the use of citicoline in the treatment and prevention of dementia and cognitive decline, there are still mixed results for its effectiveness. Cohen et al. (2003) did not find any significant differences in cognitive function as measured by the Mini Mental State Exam and Dementia Rating Scale. Although citicoline did not protect patients from vascular dementia, the authors noted that the rate of cognitive decline was smaller compared to previous research on Alzheimer’s patients. Conversely, Alvarez-Sabin et al. (2013) and Alvarez-Sabin et al. (2016) reported a significant improvements on measures of cognition and attention. Attention and Executive Function test battery and a Benton’s Temporal Orientation test were used in Alvares-Sabin et al. (2013) between citicoline and placebo, while Global Cognitive Impairment was examined in Alvares-Sabin et al. (2016). Overall, the results from all three studies suggest that citicoline may have some benefit in preserving or improving cognitive function, but it is not an effective treatment in the prevention of dementia. Further research is required in order to make more substantial conclusions.

Conclusions Regarding Citicoline for Cognitive Function

There is conflicting level 1a evidence regarding the effect of citicoline in the long term management of cognitive function post stroke.

More research is required to determine the effect of citicoline on post-stroke cognitive function.

12.6.7 Antidepressants
Tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are used in the treatment of depression following stroke. Given the association between the presence of depression and cognitive dysfunction, studies have investigated the effect of antidepressants on cognition post stroke, as summarized in Table 12.6.6.1.

12.6.7.1 Summary of Trials Evaluating Antidepressants

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Study Design (Pedro Score)</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
12. Post-Stroke Cognitive Disorders

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Design</th>
<th>Start N</th>
<th>End N</th>
<th>Treatment</th>
<th>Controls</th>
<th>Outcome Measures</th>
</tr>
</thead>
</table>
| Kimura et al. (2000) | RCT (8) | 106 | 47 | Nortriptyline (100mg/d) | Placebo | - Mini Mental State Exam (-)  
  - Mini Mental State Exam (among patients who responded to treatment only) (+) |
| Jorge et al. (2010) | RCT (7) | 129 | 110 | Escitalopram (10mg/d) | Placebo | - Repeatable Battery for the Assessment of Neuropsychological Status (+)  
  - Functional Independence Measure-Cognitive (+)  
  - Wechsler Adult Intelligence Scale-Similarities (-)  
  - Trail-Making Tests A & B (-)  
  - Stroop Test (-) |
| Sato et al. (2006) | PCT | 18 | 18 | Milnacipran (30-60mg/d) | Placebo | - Mini Mental State Exam (+)  
  - Hamilton Rating Scale for Depression (-) |

+ Indicates statistically significant differences between treatment groups  
- Indicates no statistically significant differences between treatment groups

**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; Lipsey et al., 1984; Robinson et al., 1986). 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).

In a trial by Sato et al. (2006), treatment of post-stroke depression with milnacipran for 3 months demonstrated significant improvements in cognition, though not in depression symptoms. Kimura et al. (2000) showed significant positive effects associated with treatment of nortriptyline for 1.5-3 months and remission of post-stroke depression, but only for those patients who were diagnosed with major depression. More recently, Jorge et al. (2010) evaluated the effect of escitalopram on cognitive function in a group of patients with stroke but no depression. 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 Antidepressants for Cognitive Function**

*There is level 1a and level 2 evidence that treatment with antidepressants may be associated with and improvement in cognitive functioning in patients without post-stroke depression.*

**Antidepressants may be useful at improving cognitive impairments in patients without post-stroke depression.**

**12.6.8 Selegiline**

The literature regarding selegiline (L-Deprenyl) and cognitive function post stroke is limited. Freedman et al. (1998) tested the efficacy of selegiline on patients with Alzheimer’s disease, but reported no significant differences in measures of cognition compared to a control group. Sivenius et al. (2001) found positive improvements among patients with stroke following a course of selegiline, including stroke severity, motor function, activities of daily living, quality of life, and depression. However, the authors reported a lack of statistically significant findings, and cognitive outcomes were not measured. A
recent trial examining the use of selegiline in the treatment of cognitive function post stroke is summarized in Table 12.6.1.1.

### Table 12.6.8.1 Summary of RCT Evaluating Selegiline

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Study Design (Pedro Score)</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
</table>
| Bartolo et al. (2015) | RCT (8)                   | N<sub>Start</sub>=47 N<sub>End</sub>=44 | E: Selegiline (10mg/d) C: Placebo | • Logical Memory Immediate (+)  
• Trail-Making Test A (+)  
• Raven’s Colored Progressive Matrices 47 (at 2wk only) (+)  
• Attentive Matrices (at 2wk only) (+)  
• Logical Memory Delayed (at 2wk only) (+)  
• Trail-Making Test B (at 6wk only) (+)  
• Stroop Tests T & E (at 6wk only) (+) |

+ Indicates statistically significant differences between treatment groups  
- Indicates no statistically significant differences between treatment groups

### Discussion

Despite the limited findings regarding selegiline and cognition, Bartolo et al. (2015) reported significant differences on multiple assessments of cognitive function in favour of selegiline compared to a placebo at two and six week follow-ups, without any reported adverse effects. The authors noted that selegiline enhances the release of dopamine, which can modulate attentional function. However, further research is required to fully understand the effects of selegiline in improving cognitive impairment and in preventing cognitive decline.

**Conclusions Regarding Selegiline for Cognitive Function**

There is level 1b evidence that selegiline may improve cognitive function post stroke, with benefits lasting as long as six weeks.

**Selegiline may be effective in improving post-stroke cognitive function. Further research is required.**

### 12.6.9 Xueshuan Xinmai

Xueshuan Xinmai tablets (XXMT) are a patented traditional Chinese medicine which is used to promote blood circulation. XXMT tablets incorporate anti-inflammatory, anti-oxidant, and blood lipid regulating ingredients traditionally used in Chinese medicine. Wei et al. (2015) is one of the first RCTs to examine the effectiveness of XXMT with the intention of promoting the testing of traditional Chinese medicines in the same rigorous manner that other interventions are tested. XXMT show promising results in both rodent and preclinical trials.

### Table 12.6.9.1 Summary of Trials Evaluating Xueshuan Xinmai

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Study Design (Pedro Score)</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
</table>
| Wei et al. (2015)   | RCT (9)                    | N<sub>Start</sub>=28 N<sub>End</sub>=27 | E: Xueshuan xinmai tablets were given 3 times a day for 3 months C: Placebo | • Auditory verbal learning test (+)  
• General mental status (-)  
• Complex Figure Task (+)  
• Attention (-) |
Discussion
Wei et al. (2015) demonstrated that XXMT can be an effective treatment for the remediation of memory deficits, however it may not be effective in treating attention or language ability deficits. Wei et al. (2015) add to the growing body of work which is now scientifically evaluating traditional Chinese medicines. Further research is needed specifically on XXMT to determine its effectiveness in a clinical environment.

Conclusion Regarding Xueshuan Xinmai

There is level 1b evidence that XXMT may be an effective treatment for memory remediation but not attention or language deficits.

Although XXMT has been shown to improve memory, further research is needed in order to determine the robustness of XXMT in treating cognitive deficits.

12.6.10 Vinpocetine

The current literature on the use and effectiveness of vinpocetine is limited. Vinpocetine acts as both a vasodilator and a cerebral metabolic enhancer (Szobor & Klein, 1976) and has proven effects as neuroprotectant (Patyar et al., 2011). Vinpocetine is derived from the leaves of the *Vinca minor* plant and ultimately becomes a synthetic ethyl ester (Patyar et al., 2011). Like many other new emerging treatments more research is needed to determine the efficacy of vinpocetine on the rehabilitation of cognition, specifically in post-stroke patients.

Table 12.6.10.1 Summary of Trials Evaluating Vinpocetine

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Study Design (Pedro Score)</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhang et al. (2016)</td>
<td>RCT (4)</td>
<td>NStart=610, NEnd=404</td>
<td>E: 30g of IV vinpocetine daily for 7 days + IV supplements</td>
<td>• Mini Mental State Examination (+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C: IV supplements</td>
<td>• NNIHSS (+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Modified Rankin Scale (+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Barthel Index (+)</td>
</tr>
</tbody>
</table>

Discussion
Zhang et al. (2016) found a significant improvement on all cognitive measures in participants who were treated with IV vinpocetine. To our knowledge this is the first multicenter RCT to examine the effectiveness of this pharmacoological intervention on a stroke population. Participants in the treatment group experienced a significant increase in cognitive abilities, quality of life, and neurological functioning. Further research is needed to elaborate on the potential effectiveness of vinpocetine as a treatment for cognitive deficits in stroke rehabilitation, as strong evidence has only been provided by one RCT.

Conclusion Regarding vinpocetine

There is level 2 evidence that IV vinpocetine is effective in improving cognition and quality of life.
Vinpocetine has demonstrated in one RCT that it can be effective in the rehabilitation of cognitive deficits. Further research is needed to determine the extent of its effectiveness and potential limits on more specific elements of cognition such as attention, memory and executive functioning.

12.7 Cochrane Reviews of Cognitive Rehabilitation Post Stroke

There are currently four Cochrane Reviews that examine the efficacy of treatments for cognitive impairment following stroke. They investigate a range of therapeutic strategies, including pharmacotherapy and occupational therapy, as well as interventions targeted at memory and attention deficits specifically. These reviews are valuable in synthesizing the available evidence surrounding cognitive rehabilitation post stroke, and are summarized in Table 12.7.1.

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Country</th>
<th>Title</th>
<th>Description</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chung et al. (2013)</td>
<td>UK</td>
<td>Cognitive Rehabilitation for Executive Dysfunction in Adults with Stroke or Other Adult Non-Progressive Acquired Brain Damage</td>
<td>Nineteen studies were included in this review (n_total=907). Inclusion Criteria: RCTs investigating restorative, compensative, and adaptive interventions for cognitive rehabilitation. Studies included participants with non-progressive acquired brain injury. Objectives: To determine the effects of cognitive rehabilitation on global executive dysfunction (primary outcome) for adults with stroke or other non-progressive acquired brain injuries.</td>
<td>Three studies compared cognitive rehabilitation with sensorimotor therapy, but none reported on primary outcome. Six studies compared cognitive rehabilitation with no treatment or placebo, but none reported on primary outcome. Ten studies compared two different cognitive rehabilitation approaches, but demonstrated no statistically significant effect on primary outcome. Eight studies demonstrated no statistically significant effect on the secondary outcomes. Ten studies explored restorative interventions and four studies explored compensative interventions, but none explored adaptive interventions. No statistically significant effect was demonstrated compared with other interventions. Authors concluded that there was insufficient evidence to reach any deductions or recommendations about the effect of cognitive rehabilitation on executive function or other secondary outcome measures. Further high-quality trials are required.</td>
</tr>
<tr>
<td>Das Nair &amp; Lincoln (2008)</td>
<td>UK</td>
<td>Cognitive Rehabilitation for Memory Deficits Following Stroke</td>
<td>Two studies were included in this review (n_total=18). Inclusion Criteria: RCTs investigating memory therapy. Studies included participants with memory deficits post stroke. Drug trials were not included. Objectives: - To determine if patients who receive cognitive therapies post stroke experience a better functional outcome than those who do not receive therapy. - To determine if individuals who receive</td>
<td>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 mnemonic programme (30 sessions over 10 weeks) applied in 2 phases (Phase I: rapid generation of images from given verbal information; Phase II: phase I skills applied to problems in daily life). No significant effects of treatment were noted in either study. Authors concluded that there is insufficient evidence to support or refute the use of memory rehabilitation strategies in the treatment of cognitive impairment post stroke. Further high-quality trials are required.</td>
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</table>
cognitive therapy post stroke experience better memory function.

<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion Criteria</th>
<th>Objectives</th>
<th>Results</th>
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<tbody>
<tr>
<td>Hoffman et al. (2010) Australia</td>
<td>One RCT was included in the review (n=33). Inclusion Criteria: RCTs, quasi-randomized trials, and crossover trials investigating therapies carried out or supervised by an occupational therapist. Studies included participants with cognitive deficits post stroke. Drug trials were not included.</td>
<td>To determine if occupational therapy strategies effect improvement in cognitive abilities and functional activities of daily living in individuals with cognitive impairment post stroke.</td>
<td>No significant effects of the treatment were noted in the one included study, which was significantly biased and of low methodological quality. Authors concluded that there is insufficient evidence to support or refute the use of occupational therapy strategies in the treatment of cognitive impairment post stroke. Further high-quality trials are required.</td>
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<tr>
<td>Loetscher &amp; Lincoln (2013) UK</td>
<td>Six studies were included in this review (n_{total} =223). Inclusion Criteria: RCTs investigating attention therapy. Studies included participants with attention deficits post stroke. Drug trials were not included. Objectives: To determine if individuals who receive attention treatment have improved outcomes in attentional functions than those who do not receive therapy. - To determine whether those who receive attention therapies will have better outcomes in quality of life, independence in activities of daily living, and mood.</td>
<td>A significant trend was found in the immediate effects of treatment in global attention functioning (2 studies) when comparing treatment with usual care (X=+0.53, 95%CI 0.03-1.08, p=0.06). There were no significant effects observed in long term improved global attention functioning (2 studies). A significant effect in favour of treatment for divided attention (4 studies) (X=+0.67, 95%CI 0.35-0.98, p&lt;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. Authors concluded that the short term and long term effectiveness of therapies for attention deficits following stroke is largely unconfirmed, though some changes were observed in short term effectiveness. Further high-quality trials are required.</td>
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</table>

Overall, the four Cochrane reviews examining interventions for cognitive impairment post stroke that have been conducted to date are largely inconclusive. Few randomized controlled trials have been conducted, and many are lacking methodological quality. The general consensus 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 their use.

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 (DSM)-V, delirium is characterized by:
1. A disturbance in attention and awareness;
2. The disturbance develops over a short period of time, represents an acute change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day;
3. An additional disturbance in cognition (i.e. memory deficit, disorientation, language, visuospatial ability, or perception);
4. The disturbance in criteria (1) and (2) are not better explained by a pre-existing, established or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal such as a coma;
5. Evidence from history, physical examination or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal, or exposure to a toxin, or is due to multiple etiologies.

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

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

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

Rates for delirium are possibly under-estimated, as delirium 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 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-fac torial and represent an interaction between predisposing risk factors (personal vulnerability) and precipitating factors (noxious events or events related to hospitalization) (Inouye & Charpentier, 1996). In a review, Inouye (2006) presented the following categories of risk factors (see Table 12.8.2.1): demographic, cognitive, functional, sensory, oral intake, drug use, and co-morbidities. Precipitating events were placed into the following categories: primary neurologic diseases (including stroke), inter-current illnesses, environmental stressors, prolonged sleep deprivation, drug use, and surgery. Taking this approach, stroke is considered both a significant risk factor and a precipitating factor (Edlund et al., 2006; Inouye, 2006).

<table>
<thead>
<tr>
<th>Table 12.8.2.1 Categories of Risk Factors (Inouye, 2006)</th>
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<tbody>
<tr>
<td><strong>Demographic</strong></td>
</tr>
<tr>
<td>Age ≥ 65</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Previous delirium</td>
</tr>
<tr>
<td>Depression</td>
</tr>
</tbody>
</table>

Inouye (2006) suggested that dementia is the leading risk factor for delirium. A meta-analysis by Elie et al. (1998) included studies examining delirium in patients over the age of 50 and reported that the presence of dementia increased the risk for delirium 5-fold (OR=5.2). 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 patients with acute stroke, 24.7% with previous cognitive decline (no dementia) developed delirium within 48 hours of admission, compared to 45.5% with dementia and 13.2% without previous cognitive decline. Ferro et al. (2002) cited previous cognitive decline, extensive motor impairment, metabolic and infectious complications, sleep apnea, and older age as significant risk factors for post-stroke delirium. McManus et al. (2009) reported significant risk factors for post-stroke delirium as Barthel Index score <10, elevated C-reactive protein, unsafe swallow,
and poor vision. However, previous cognitive decline did not reach significance as an independent predictor of delirium.

Caeiro et al. (2004) found intracerebral haemorrhages, left hemispatial neglect, medical complications, and older age to be significant risk factors for post-stroke delirium. Sheng et al. (2006) demonstrated that haemorrhagic stroke, pre-stroke dementia, metabolic disorders, Glasgow Coma Scale score <15, inability to raise both arms, and older age were all significant risk factors for post-stroke delirium. Most recently, Oldenbeuving et al. (2011) identified a number of independent risk factors for post-stroke delirium, including: previous cognitive decline, right hemisphere stroke, large artery stroke, carotid artery disease, brain atrophy, and high score on the National Institutes of Health Stroke Scale.

### 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 (e.g. falls, infections, 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 patients with no delirium, the presence of delirium post stroke has been associated with longer hospitalization, a reduced likelihood of discharge home, poorer functional outcome at discharge on the Barthel Index and Rankin Scale, and greater losses of independence in terms of activities of daily living (p<0.001) (Henon et al., 1999; McManus et al., 2009; Sheng et al., 2006). Long-term follow-up at 6 and 12 months following stroke has demonstrated that patients who had experienced delirium were less likely to be living at home, and had poorer functional outcomes and lower Mini Mental State Exam 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, the authors identified stroke as one of the factors associated with decline in function.

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 Miu and Yeung (2013), who observed both a higher inpatient mortality and higher 1-year mortality, and Shi et al. (2012), who found a higher risk of mortality at 12 months (OR=4.91, 95%CI 3.18-7.6). McManus et al. (2009) found post-stroke delirium to be significantly associated with increased inpatient mortality but not with mortality post discharge. 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 patients with stroke. Similarly, in their review, Ferro et al. (2002) stated 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 review, Inouye (2006) stated that as many as 30-40% of cases of delirium may be preventable. 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 (2001). A single study examining the management of risk factors in the prevention of delirium was identified, which is summarized in Table 12.8.4.

### Table 12.8.4.1 Summary of RCT Evaluating Prevention of Delirium

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Study Design (Pedro Score)</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inouye et al. (1999)</td>
<td>PCT</td>
<td>EG: Multicomponent risk factor intervention</td>
<td>• Incidence of Delirium (+)</td>
</tr>
<tr>
<td></td>
<td>NStart=47 NEnd=44</td>
<td>CG: Usual Care</td>
<td>• Total number of days with Delirium (+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Total number of episodes of Delirium (+)</td>
</tr>
</tbody>
</table>

+ Indicates statistically significant differences between treatment groups
- Indicates no statistically significant differences between treatment groups

### Discussion

The study by Inouye et al. (1999) 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, it was not clear that any individuals with stroke were actually part of the study.

### Conclusions Regarding Prevention of Delirium

**There is level 2 evidence that a multi-component approach to the management of known risk factors may be associated with reduced incidence and duration of delirium. However, this has not been demonstrated within the stroke population; further research is required.**

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

### 12.8.5 Treatment of Delirium Post Stroke

There is limited information regarding effective treatment of delirium post stroke. In a small pilot study, Oldenbeuving et al. (2011) 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, and was reportedly successful. All patients were weaned from the drug after one week, with no short-term recurrence of dementia and no major side effects. However, a large RCT is needed to better examine the effectiveness of rivastigmine in the treatment of delirium.

In general, strategies proposed for the management of post-stroke 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). These non-pharmacologic approaches to management can be implemented for all patients. Inouye (2006) recommends creating a calm and comfortable environment for the patient that emphasizes interaction with family, staff, and orienting influences (e.g. calendars, clocks, familiar objects); changes to the environment and routine are limited. As well, the regimen provides quiet time night to promote sleep and wakefulness and encourages mobility during the day. Lundstrom et al. (2005) supported the effectiveness of a program based on heightened awareness of predisposing and precipitating factors, as
well as increased individual care. However, as the authors noted, there were no systematic changes to treatment strategies noted and no significant differences in strategies were recorded between the intervention and control wards.

Ferro et al. (2002) listed the use of pharmacological sedation as appropriate in the management of delirium post stroke. However, the use of drugs in the treatment of post-stroke delirium should be approached with caution. Many of the compounds used to treat post-stroke delirium may worsen symptoms of cognitive impairment, and thus impair a patient’s ability to understand and cooperate with treatment (Meagher, 2001). In particular, drugs with anticholinergic properties may cause symptoms of delirium post stroke. In a study of patients with stroke, Caeiro et al. (2005) demonstrated that the percentage of those taking medication with anticholinergic (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, given that 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.

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

There is limited level 4 evidence regarding the impact of short-term treatment with rivastigmine on post-stroke delirium. Further research is required.

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

1. There is conflicting level 5 evidence regarding the link between post-stroke depression and cognitive and functional impairment.

2. There is level 1a evidence indicating no statistical association between lowering of blood pressure and a reduction in the risk for the development of dementia.

3. There is level 1a evidence that antihypertensive medication may prevent recurrence of stroke, but not reduce cognitive decline or dementia.

4. There is level 1b evidence that reducing risk factors detrimental to brain health such as cholesterol levels, blood pressure, and BMI may have no significant effect on cognitive performance.

5. There is mixed level 1a and level 2 evidence regarding the effect of computerized training for attention tasks on the performance of specific attention tasks.

6. There is mixed level 1a evidence that cognitive rehabilitation may improve divided attention but not global measures of attention and standardised attentional assessments.

7. There is level 1b evidence that Attention Process Training may improve aspects of visual and auditory attention.

8. There is level 1b evidence that an intensive, computerized training program may result in improvements in both working memory and attention.

9. There is level 1b evidence that visual attention retraining using the Useful Field of View may be more effective than conventional computerized visuoperceptual training at improving the on-road driving performance of individuals with right-sided lesions.

10. There is level 1a evidence that compensatory strategies may be effective at improving memory outcomes, including imagery-based, process-oriented, and self-efficacy training.

11. There is level 1b evidence that home visits combined with mailed letters containing resources and information may result in an improvement of self-reported health status for both patients and caregivers after 6 months compared to mailed letters only.

12. There is level 1b and level 2 evidence that mental imagery may improve relearning of activities of daily living in patients with acute stroke and minimal cognitive deficits.

13. There is limited level 2 evidence that patients in group-based interventions may not improve memory abilities any better than patients who did not receive intervention while on a waiting list.

14. There is level 1b evidence that an analogical problem-solving skills approach may increase problem-solving abilities and performance of extended activities of daily living.

15. There is level 1b evidence that self-regulation training may increase executive control over motor but not cognitive function, although these findings may be biased.
16. There is level 2 evidence that goal management training may be beneficial in the rehabilitation of executive function.

17. There is level 1b and level 2 evidence that acupuncture can be an effective intervention in the remediation of cognitive deficits.

18. There is level 1b evidence that problem-solving therapy is not an effective intervention for the improvement of executive functioning.

19. There is level 1b evidence that tailored occupational cognitive interventions do not significantly affect return to work or executive functions.

20. There is level 2 evidence that visual training in combination with other interventions can improve executive functions.

21. There is mixed level 1b evidence that physical therapy in combination with mindful interventions can improve cognition and quality of life post-stroke.

22. There is level 1b evidence that acupuncture combined with nimodipine can improve cognitive functioning short term.

23. There is level 1b evidence that standard care combined with computerized training may improve cognitive performance more than standard care alone.

24. There is limited level 2 evidence that virtual reality training combined with computerized cognitive training may improve cognitive performance more than computerized cognitive training alone.

25. There is level 1b evidence that electroacupuncture may improve attention, praxis, perception and orientation, but not thinking, organization memory and mental health.

26. There is level 1b evidence that high-intensity TENS may not be more effective than low-frequency TENS at improving cognitive functioning.

27. There is level 1b evidence that self-regulated music therapy may have a positive impact on verbal memory and focused attention in individuals with left hemisphere stroke.

28. There is conflicting level 1a evidence regarding the effect of exercise therapy on cognitive rehabilitation post stroke.

29. There is level 1b evidence that robotic table verticalization can demonstrate greater improvements in both electrophysiological and cognitive measures compared to verticalization deliver by a therapist.

30. There is level 1b and level 2 evidence that exercise programs with a focus on resistance, balance and aerobics can result in significant cognitive gains.

31. There is level 1b evidence that high-frequency, low-frequency and sham rTMS are not significantly different at improving cognitive performance.
32. There is level 1b evidence that rTMS in general compared to sham therapy can significantly improve cognitive functioning.

33. There is level 4 evidence that rTMS to the left DPC may be associated with improvements in executive function following stroke.

34. There is level 1a evidence that anodal tDCS to the left dorsolateral prefrontal cortex may be associated with improvements in working memory and attention.

35. There is level 1b evidence that aspirin is effective in stabilizing and/or improving cognitive outcomes in patients with multi-infarct dementia.

36. There is a level 1b evidence that phosphodiesterase-5 inhibitor may not be effective in remediating cognitive deficits.

37. There is level 1a evidence that donepezil taken for 24 weeks may improve cognitive function in patients with probable or possible vascular dementia.

38. There is level 1a evidence that treatment with donepezil is associated with improvement in global function for individuals with probable or possible vascular dementia.

39. There is conflicting level 1a evidence regarding treatment with rivastigmine and its effect on vascular dementia and cognitive decline.

40. There is level 2 evidence that treatment with rivastigmine is associated with more stable cognitive performance and improved behavioural outcomes among patients with vascular dementia.

41. There is level 1a evidence that treatment with galantamine is associated with improvements in cognitive and global function. However, the benefits associated with treatment are more clearly demonstrated among patients with mixed dementia than vascular dementia.

42. There is level 1a evidence that nimodipine may not be beneficial in the treatment of vascular dementia.

43. There is level 1b evidence that treatment with nimodipine may slow cognitive deterioration in patients with vascular dementia.

44. There is level 1a evidence that treatment with memantine is associated with stabilization or improvement of cognitive function in patients with vascular dementia.

45. There is level 1a evidence that treatment with pentoxifylline is associated with cognitive benefits in patients with multi-infarct dementia.

46. There is conflicting level 1a evidence regarding the effect of citicoline in the long term management of cognitive function post stroke.

47. There is level 1a and level 2 evidence that treatment with antidepressants may be associated with and improvement in cognitive functioning in patients without post-stroke depression.
48. There is level 1b evidence that selegiline may improve cognitive function post stroke, with benefits lasting as long as six weeks.

49. There is level 1b evidence that XXMT may be an effective treatment for memory remediation but not attention or language deficits.

50. There is level 2 evidence that IV vinpocetine is effective in improving cognition and quality of life.

51. There is level 2 evidence that a multi-component approach to the management of known risk factors may be associated with reduced incidence and duration of delirium. However, this has not been demonstrated within the stroke population; further research is required.

52. There is limited level 4 evidence regarding the impact of short-term treatment with rivastigmine on post-stroke delirium. Further research is required.
References


12. Post-Stroke Cognitive Disorders


