Abstract

A variety of psychological disorders may develop following stroke, namely depression. Post-stroke depression has been reported to affect approximately one-third of individuals. These rates may also be influenced by a combination of factors such as age, sex, socioeconomic status, functional independence, cognitive impairment, and stroke severity. The presence of post-stroke depression can significantly impact a wide range of outcomes and overall stroke recovery. Several studies have investigated pharmacological and non-pharmacological treatment options for post-stroke depression. However, no consensus has been reached regarding the most effective and viable treatment. This chapter explores the evidence regarding interventions for the prevention and treatment of post-stroke depression, as well as its prevalence, predictors, and consequences. A brief overview of another mood disorder, post-stroke emotionalism, is also provided.
Key Points

Prevalence of Post-Stroke Depression

- Depression is a common complication post stroke affecting approximately a third of individuals; rates of incidence and recovery vary over time from stroke onset.

Assessment of Post-Stroke Depression

- Post-stroke depression is formally diagnosed based on the DSM-V criteria, as conducted by a mental healthcare professional.
- Post-stroke depression can be screened for using a variety of assessment tools, most notably the Patient Health Questionnaire 9.

Risk Factors for Post-Stroke Depression

- Common risk factors for stroke include prior depression, functional impairment, cognitive deficit, and stroke severity. However, further research is required to establish their relative impact, as well as to determine other potential risk factors.
- Despite extensive research, it is unclear whether lesion location is a risk factor for post-stroke depression.

Consequences of Post-Stroke Depression

- Post-stroke depression may have a negative impact on functional outcomes.
- Post-stroke depression may have a negative impact on physical function.
- Post-stroke depression may have a negative impact on cognitive function.
- Further research is required to determine the impact of post-stroke depression on mortality.

Prevention of Post-Stroke Depression

- Early initiation of antidepressant therapy in non-depressed individuals may be effective in preventing post-stroke depression.
- Fluoxetine, escitalopram, nortriptyline, milnacipran, mirtazapine, and duloxetine have been reported to be effective in preventing depression. There are mixed results regarding the efficacy of sertraline, while mianserin does not appear to be effective.
- It is unclear as to whether coordinated/integrated care programs that provide ongoing, individualized contact and support are effective in improving mood and attenuating depressive symptoms post stroke; further high-quality research is required.
- Home visits from healthcare professionals may not be effective in attenuating depressive symptoms post stroke.
- Community outreach via mail or telephone may not be effective in attenuating depressive symptoms post stroke.
- Motivational interviewing may be effective in improving mood and attenuating depressive symptoms post stroke.
- Dietary supplementation with omega-3 fatty acids is not effective in improving mood post stroke.
- Long-term Vitamin B therapy may be effective in reducing risk of depression following stroke.
Pharmacologic Treatment of Post-Stroke Depression

- Heterocyclic antidepressants, namely nortriptyline, may be an effective treatment for post-stroke depression.
- While some selective serotonin reuptake inhibitors may be effective in the treatment of post-stroke depression (e.g. citalopram), the effectiveness of others is unestablished (e.g. sertraline) or unclear (e.g. fluoxetine).
- Further research is required to determine the effectiveness of adjunctive light therapy in treating post-stroke depression.
- Reboxetine, a noradrenaline reuptake inhibitor, may be an effective treatment for post-stroke depression.
- Further research is required to determine the effectiveness of venlafaxine, a serotonin and noradrenaline reuptake inhibitor, in treating post-stroke depression.
- Methylphenidate, a psychostimulant, may be an effective treatment for post-stroke depression.
- Nefiracetam, a GABA receptor modulator, may not be an effective treatment for post-stroke depression.
- Selegiline, a monoamine oxidase inhibitor, may not be an effective treatment for post-stroke depression.
- Further research is required to determine the effectiveness of valdoxan, a melatonin agonist, in treating post-stroke depression.
- Further research is required to determine the effect of statins on post-stroke depression.
- Pioglitazone may be an effective treatment for post-stroke depression in individuals with type II diabetes.
- Free and Easy Wanderer Plus, an herbal medicine, may be effective in the treatment of post-stroke depression.
- Active care management of antidepressant therapy may improve response to treatment.
- Pharmacological treatment of post-stroke depression may also be effective in improving functional and neurological recovery. However, only some antidepressants have demonstrated efficacy.
- Early treatment with antidepressants may improve long-term survival post stroke, although further research is required.

Non-Pharmacologic Treatment of Post-Stroke Depression

- There are conflicting findings regarding the effectiveness of cognitive-behavioural interventions in treating post-stroke depression.
- Psychosocial-behavioural therapy may be an effective adjunct to treatment of post-stroke depression with antidepressants, although further research is required.
- There are conflicting findings regarding the effectiveness of supportive interventions (e.g. transitional, integrated, or customized care) in treating post-stroke depression.
- There are conflicting findings regarding the effectiveness of music therapy in treating post-stroke depression.
Further research is required to determine the effectiveness of art therapy in treating post-stroke depression.

Further research is required to determine the effectiveness of relaxation therapies in treating post-stroke depression.

There are conflicting findings regarding the impact of physical activity on post-stroke depression.

Speech therapy may not have a significant impact on post-stroke depression, although further research is required.

Hyperbaric oxygen therapy may be an effective adjunctive treatment for post-stroke depression, although further research is required.

Further research is required to determine the effectiveness of electroconvulsive therapy (ECT) in treating post-stroke depression.

Repetitive transcranial magnetic stimulation (rTMS) may be an effective treatment for post-stroke depression.

Further research is required to determine the effectiveness of transcranial direct current stimulation (tDCS) in treating post-stroke depression.

Acupuncture may not be an effective treatment or adjunct for post-stroke depression.

Further research is required to determine the effectiveness of meridian acupressure in treating post-stroke depression.

Reiki may not be an effective treatment for post-stroke depression.

Post-Stroke Emotionalism

Emotionalism affects approximately a fifth of individuals post stroke; rates of incidence and recovery vary over time from stroke onset.

Common risk factors for post-stroke emotionalism include cognitive deficit and anterior lesions. However, further research is required to establish their relative impact, as well as to determine other potential risk factors.

Antidepressants may be an effective treatment for post-stroke emotionalism.

Guidelines for Post-Stroke Mood

Guidelines for post-stroke depression recommend screening, assessment, and treatment with an antidepressant for 6-12 months; adjunctive psychotherapy is a reasonable treatment consideration.
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18.1 Introduction and Prevalence of Post-Stroke Depression

Following stroke, a variety of psychological disorders may develop, namely depression. There are a few possible explanations for the association between the two conditions. First, and least likely, is a coincidental relationship. The second explanation is a neurotransmitter imbalance as a result of cerebral damage caused by the stroke. The third explanation is a negative mood reaction to the physical consequences of the stroke. The impact of the physical illness may wield its effect through the losses it causes to the individual as a major negative life event (e.g., independence, quality of life).

Post-stroke depression (PSD) has been shown to impact a considerable portion of individuals across numerous studies. Based on pooled data from such studies, Robinson and Spalletta (2010) reported a prevalence of 22% for PSD among inpatients in acute or rehabilitation settings, 24% among individuals in outpatient settings, and 14% among individuals in community settings. Similarly, a meta-analysis by Ayerbe et al. (2013b) reported a prevalence of 30% for hospital studies, 30% for rehabilitation studies, and 22% for community studies. Another reported an overall prevalence of 31%, but also examined rates at specific time-points: 28% at 0-1 months, 36% at 2-5 months, 31% at 6-9 months, 33% at 1 year, 25% at 2-4 years, and 23% at 5 years (Hackett & Pickles, 2014). The review by Ayerbe et al. (2013b) had similar findings: an overall prevalence of 29%, with rates of 28% at 0-1 months, 31% at 1-6 months, 33% at 6-12 months, and 25% at >1 year.

As noted in the aforementioned reviews, estimates of PSD prevalence may be affected by the time from stroke onset until assessment. The highest rates of incident depression have been reported in the first few months following stroke, with a decrease in incident depression over the course of the first year (Bour et al., 2010; Bour et al., 2011). While there may be a general trend toward recovery over time, PSD may be persistent for a proportion of individuals (Ayerbe et al., 2013a; Ayerbe et al., 2011). In the review by Ayerbe et al. (2013b), rates of cumulative incidence over five years ranged from 39% to 52% across studies. Rates of recovery from early PSD by one year ranged from 15% to 57%, while rates of persistent PSD over five years ranged from 6% to 36%.

Conclusions Regarding the Prevalence of Post-Stroke Depression

Approximately a third of individuals experience depression post stroke. Generally, incidence decreases and recovery increases over time, although some individuals may experience persistent depression and others may develop late-onset depression.

Depression is a common complication post stroke affecting approximately a third of individuals; rates of incidence and recovery vary over time from stroke onset.

18.2 Assessment of Post-Stroke Depression

Diagnosis

Diagnosis of PSD should be conducted by a mental healthcare professional in a Structure Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (DSM) (Eskes et al., 2015). The DSM-V defines PSD as a “depressive disorder due to another medical condition”. It details the following diagnostic criteria for PSD:

A. Prominent and persistent period of depressed mood or markedly diminished interest or pleasure in all or almost all activities.
B. Evidence from the history, physical examination, or laboratory findings that the disturbance is the direct pathophysiological consequence of another medical condition.
C. Disturbance is not better explained by another mental disorder.
D. Disturbance does not occur exclusively during the course of a delirium.
E. Disturbance causes clinically significant distress or impairment in important areas of functioning.

As well, it includes the following three specifiers:
   a. With depressive features: full criteria not met for major depressive episode.
   b. With major depressive-like episode: full criteria met for major depressive episode, except for C.
   c. With mixed features: symptoms of mania are present but do not predominate.

At present, the criteria provided by the DSM-V are the gold standard for diagnosis of PSD and form the basis for the evaluation of assessment tools (Eskes et al., 2015).

**Screening**

Several tools are available to screen for depression, and some are specific to individuals following stroke. Many of these tools are self-report questionnaires, although some rely on ratings by an observer. Table 18.2.1 presents a comprehensive but non-exhaustive list of screening tools for PSD. (For detailed evaluations of individual outcome measures, see Chapter 20).

<table>
<thead>
<tr>
<th>Table 18.2.1 Screening Tools for Post-Stroke Depression</th>
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<tbody>
<tr>
<td><strong>Self-Reported</strong></td>
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<tr>
<td>Beck Depression Inventory</td>
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<td>CES Depression Scale</td>
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<tr>
<td>Clinical Global Impression</td>
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<tr>
<td>General Health Questionnaire</td>
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<tr>
<td>Geriatric Depression Scale</td>
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<tr>
<td>Hamilton Depression Rating Scale</td>
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<tr>
<td>Hospital Anxiety &amp; Depression Scale</td>
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<tr>
<td>Montgomery Asberg Depression Rating Scale</td>
</tr>
<tr>
<td>Patient Health Questionnaire</td>
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<tr>
<td>Stroke Inpatient Depression Inventory</td>
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<tr>
<td>Wakefield Depression Inventory</td>
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<tr>
<td>Yale Single Question</td>
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<tr>
<td>Zung Self-Rating Depression Scale</td>
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<tr>
<td><strong>Visual-Aided</strong></td>
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<tr>
<td>BAS Depression Cards</td>
</tr>
<tr>
<td>Depression Intensity Scale Circles</td>
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<tr>
<td>Distress Thermometer</td>
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<tr>
<td>Numeric Graphic Rating Scale</td>
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<tr>
<td>Visual Analogue Scale</td>
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</table>

A systematic review by Burton and Tyson (2015) identified 27 screening tools across 30 studies. The authors found that the following tools satisfied all criteria in terms of sensitivity (≥80%), specificity (≥60%), and clinical utility: Patient Health Questionnaire (PHQ), Geriatric Depression Scale, Stroke Aphasic Depression Questionnaire, Signs of Depression Scale, and Yale Single Question. In another review, Meader et al. (2014) identified 18 screening tools across 24 studies. A meta-analysis revealed favourable verification of the PHQ, Hamilton Depression Rating Scale, and Centre of Epidemiological Studies Depression Scale. Recently, Van Ginkel et al. (2013) developed a screening tool known as the Post-Stroke Depression Prediction Scale (DePreS). The authors reported a good predictive performance (sensitivity of 73% and specificity of 75%), although further research is required to fully determine its efficacy.

In terms of screening or classifying patients on the basis of depressive symptomatology, research has demonstrated poor agreement between screening tools and psychiatric diagnoses (Salter et al., 2013). Many of these tools have proven to be quite sensitive but lack specificity (Aben et al., 2002; Lincoln et
al., 2003b; Schramke et al., 1998; Schubert et al., 1992), perhaps due to the inclusion of somatic symptoms. Self-report measures rely on the assumption that the individuals being evaluated are sufficiently self-aware to provide an accurate report, which is not necessarily true of individuals who have experienced a stroke (Kang et al., 2013; Lincoln et al., 2003b). It has been suggested that discrepancies could be explained by an indifference to symptoms typical in patients with right-hemisphere stroke, which would be more pronounced when relying on self-report to assess depression (Dam et al., 1989). As such, it is recommended that patients complete a self-report assessment, with those scoring highly completing a set of observer-rating scales (Salter et al., 2013).

Compliance

Formal screening for PSD is superior to simple observation and is included among the recommendations in current guidelines, although reported compliance is low. For example, the UK National Clinical Guidelines for Stroke recommended screening for depression within the first month after a stroke, but the National Sentinel Audit for the years 2001/2002 revealed a compliance rate of only 50% (Bowen et al., 2005). A survey of healthcare professionals across stroke units in the UK found attitudes toward depression screening were positive despite low compliance (Hart & Morris, 2008). Barriers to screening included lack of time and concerns about tests, while facilitators of screening included being knowledgeable about screening, having screening in the job role, and believing in the value of screening. The particular profession of the individual performing the screening had no impact on compliance.

Conclusions Regarding Assessment of Post-Stroke Depression

Diagnosis of post-stroke depression should be conducted by a mental healthcare professional in Structured Clinical Interview as per the criteria outlined in the DSM-V.

Screening for post-stroke depression can be conducted using a variety of validated assessment tools. However, the Patient Health Questionnaire 9 has shown relatively high sensitivity, specificity, and clinical utility.

Detection of post-stroke depression is often inconsistent, which may be due to the heterogeneity of screening tools.

Compliance with guidelines for screening is generally poor, which may be due to lack of time and knowledge.

Post-stroke depression can be screened for using a variety of assessment tools, most notably the Patient Health Questionnaire 9.

Post-stroke depression is formally diagnosed based on the DSM-V criteria, as conducted by a mental healthcare professional.

18.3 Risk Factors for Post-Stroke Depression

While PSD is a common consequence of stroke, the risk factors for its development have not been clearly delineated. Research has examined demographic factors (e.g. age, sex, socioeconomic status), comorbid conditions (e.g. hypertension, hyperlipidemia, diabetes), clinical outcomes (e.g. functional dependence, cognitive deficit, physical impairment), and psychological issues (e.g. pre-stroke
depression) as potential risk factors for PSD. Studies have also investigated the potential impact of stroke-related features such as size, location, and lateralization. Information regarding risk factors could be useful in developing a predictive tool for identifying those individuals at most risk for developing PSD, which would enable clinicians to provide earlier screening and treatment.

Several studies have attempted to determine risk factors for PSD, but there is a relatively small selection of large multicentre studies. The DESTRO Study from Italy (N=1064) found that female sex, previous stroke, prior depression, and disability were significant predictors of PSD; the risk increased exponentially in individuals with more than one risk factor (Paolucci et al., 2006). These same variables, as well as older age and cardiovascular comorbidities, were found to be risk factors in the Auckland Regional Community Stroke Study (N=1172) (Hackett & Anderson, 2006). However, the full model successfully predicted PSD in half of patients, and only prior depression and disability were independent predictors. Unlike the previous studies, the smaller Bergen Stroke Study from Norway (N=771) reported that PSD was not associated with age, sex, comorbidities, or previous stroke (Naess et al., 2010). In fact, only prior depression was found to a significant risk factor for PSD.

Local stroke registers have been useful in determining risk factors for PSD within large cohorts of patients. The South London Stroke Register (N=3689) identified multiple predictors including stroke severity, cognitive impairment, functional disability, and lack of social support (Ayerbe et al., 2011). The primary predictors for PSD in the Glasgow Local Enhance Service for Stroke (N=4079) were female sex, younger age, lower socioeconomic status, and smoking (Broomfield et al., 2014). In the largest cohort, Jorgensen et al. (2016) examined a register of patients from across Denmark (N=157,243). The authors reported that female sex, older age, prior depression, stroke severity, and cardiovascular comorbidities were among risk factors for PSD.

Considering the wealth of studies regarding PSD and its potential risk factors, systematic reviews and meta-analyses have attempted to aggregate and synthesize the research evidence into a more definitive model. These reviews consistently identified prior depression, stroke severity, and functional disability as risk factors for PSD (Ayerbe et al., 2013b; De Ryck et al., 2014; Hackett & Anderson, 2005; Johnson et al., 2006; Kutlubaev & Hackett, 2014; Ouimet et al., 2001). Other notable risk factors included female sex cognitive impairment (Ayerbe et al., 2013b; Hackett & Anderson, 2005; Johnson et al., 2006; Kutlubaev & Hackett, 2014), social isolation (De Ryck et al., 2014; Ouimet et al., 2001), and female sex (De Ryck et al., 2014).

However, the authors of these reviews reported significant differences in methodology between studies, namely sample size, stroke onset, and outcome measures. The reviews also noted major methodological limitations within each study including the use of screening instruments for diagnosis, exclusion of patients with physical/cognitive impairments, and failure to control for confounding variables. Thus De Ryck et al. (2014) recommended that researchers conduct targeted, prospective, longitudinal studies with sufficient sample size, adequate follow-up, simple repeatable methods, and wide range of variables. Moreover, the authors recommended that clinicians consider the dynamic and multifactorial nature of PSD, which can affect a variety of patients with different experiences, capabilities, and personalities.

**Lesion Location**

The complex association between brain lesion location and PSD has been the topic of much research, and has yielded several conflicting results among studies and reviews. The role of lesion location in the development of PSD is believed to be mediated by the depletion of catecholamines, which may play a
major role in the etiology of depression (Robinson et al., 1986). It has been posited that injured cerebral catecholaminergic neurons markedly reduce neurotransmitter production during the regenerative process, causing a decline in neurotransmitter availability throughout the cerebrum (Robinson et al., 1986). As well, the region close to the frontal lobe has been reported to have the greatest concentration of catecholaminergic fibres (Robinson et al., 1986).

In the 1980s, the Johns Hopkins Group carried out a series of studies exploring the relationship between PSD and lesion location. PSD was found to be more frequent and severe in patients with left hemisphere lesions (Lipsey et al., 1983; Robinson et al., 1987; Robinson & Price, 1982; Robinson et al., 1983; Robinson & Szetela, 1981). Among these patients, the severity of depression correlated inversely with the distance of the lesion from the frontal poles. Patients with subcortical, cerebellar, or brainstem lesions were found to have shorter-lasting depression than patients with cortical lesions (Starkstein et al., 1987; Starkstein et al., 1988). The authors suggested that lesion location may account for up to 50% of the variance in the development of PSD. While some subsequent studies found interhemispheric differences for PSD, many more failed to replicate these findings.

Given the conflicting results among observational studies, systematic reviews have been conducted to better elucidate the impact of lesion location on PSD. In an earlier review, Singh et al. (1998) reported that nearly half of the 13 studies found no significant association between PSD and lesion location. However, the studies were fairly heterogeneous and methodologically poor, and so the authors were unable to make definitive conclusions. A review by Carson et al. (2000) reported that 38 of the 48 included studies failed to find a significant association. Their meta-analysis of all the studies found that lesion location had a small, non-significant relative risk for PSD. As well, many of the studies were not comparable with respect to sample, timing, and evaluation of outcomes.

Stroke onset has been implicated as a potential modifier for the impact of lesion location on PSD (Carson et al., 2000). A review of 26 studies by Bhogal et al. (2004) suggested that left hemisphere lesions were associated with PSD in the acute phase of stroke, while right hemisphere lesions were a risk factor in the chronic phase. However, these results were not supported in a more recent review of 43 studies by Wei et al. (2015). The authors reported a significant association between right hemisphere lesions and PSD in subacute stroke, but failed to find an association between left regardless of stroke onset. In more comprehensive reviews, it has been proposed that other risk factors are greater contributors to the development of PSD than lesion location (Ayerbe et al., 2013b; De Ryck et al., 2014; Kutlubaev & Hackett, 2014).

Conclusions Regarding Risk Factors for Post-Stroke Depression

There is Level 4 and Level 5 evidence that risk factors for post-stroke depression include prior depression, functional impairment, cognitive deficit, and stroke severity.

There is conflicting Level 4 and Level 5 evidence as to whether variables such as age, sex, socioeconomic status, cardiovascular comorbidities, and stroke severity are risk factors for post-stroke depression.

There is conflicting Level 4 and Level 5 evidence as to whether lesion location is a risk factor for post-stroke depression.
Common risk factors for post-stroke depression include prior depression, functional impairment, cognitive deficit, and stroke severity. However, further research is required to establish their relative impact, as well as to determine other potential risk factors.

Despite extensive research, it is unclear whether lesion location is a risk factor for post-stroke depression.

18.4 Consequences Associated with Post-Stroke Depression

18.4.1 Functional Outcome and Post-Stroke Depression

The relationship between functional outcomes and depression is an ongoing topic for debate. The degree to which functional independence influences depression or depression impacts functional independence is uncertain. However, research has suggested that PSD may be associated with rate of recovery and success of rehabilitation. In a systematic review of 14 studies, Kutlubaev and Hackett (2014) concluded that depression had a consistent negative effect on later functional outcomes following stroke. Studies examining the impact of PSD on functional impairment are listed in Table 18.4.1.1.

**Table 18.4.1.1 Studies Evaluating Impact of Post-Stroke Depression on Functional Outcome**

<table>
<thead>
<tr>
<th>Positive Studies</th>
<th>Negative Studies</th>
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<tbody>
<tr>
<td>Bacher et al. (1990)</td>
<td>Sinyor et al. (1986)</td>
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<td>Parikh et al. (1990)</td>
<td>Van de Weg et al. (1999)</td>
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<td>Morris et al. (1992)</td>
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<td>Schmid et al. (2011)</td>
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<td>Brown et al. (2012)</td>
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<td>Ayerbe et al. (2014a)</td>
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<td>Zikic et al. (2014)</td>
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<td>Amaricai &amp; Poenaru (2016)</td>
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<td>Jiao et al. (2016)</td>
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<td>Park et al. (2016)</td>
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<td>Tsuchiya et al. (2016)</td>
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**Discussion**

Several longitudinal studies, both prospective and retrospective in design, have examined the relationship between initial depression status and subsequent functional outcomes. The overwhelming majority of these studies found that individuals with depression at baseline had significantly greater impairment at follow-ups when compared to non-depressed individuals. While patients with PSD may still experience significant functional recovery, it appears as though their functional outcomes remain at a significantly lower level than non-depressed patients over time, despite similar interventions. The relationship between depression and recovery may be reciprocal, such that depression contributes to a progressive deterioration or attenuated recovery of functional outcomes, which in turn contributes to increased depression.

**Conclusions Regarding Functional Outcome and Post-Stroke Depression**
There is Level 2 and Level 3 evidence that depression has a significant, negative impact on functional outcomes post stroke.

Post-stroke depression may have a negative impact on functional outcomes.

18.4.2 Physical Function and Post-Stroke Depression
Physical impairments are a common consequence of stroke. It has also been suggested that PSD may contribute to poor physical functioning. However, there is limited evidence regarding the relationship between initial PSD and subsequent physical outcomes.

Discussion
Overall, there appears to be a significant association between PSD and physical function. Four studies reported that individuals with PSD at baseline had significantly poorer physical outcomes at follow-up than those without PSD (Gainotti et al., 2001; Goodwin & Devanand, 2008; Nannetti et al., 2005; van de Port et al., 2006). Three studies examined the impact on mobility (Gainotti et al., 2001; Goodwin & Devanand, 2008; van de Port et al., 2006), while one study utilized the Fugl-Meyer Assessment (Nannetti et al., 2005). As well, two studies included subjects in the acute/subacute phase of stroke (Gainotti et al., 2001; Nannetti et al., 2005), while two studies included subjects in the chronic phase (Goodwin & Devanand, 2008; van de Port et al., 2006). None of the studies identified failed to find an association between PSD and physical function.

Conclusions Regarding Physical Function and Post-Stroke Depression
There is Level 2 and Level 3 evidence that that depression has a significant, negative impact on physical functional post stroke.

Post-stroke depression may have a negative impact on physical function.

18.4.3 Cognitive Function and Post-Stroke Depression
Cognitive impairments are a common consequence of stroke, and some believe that they contribute to PSD. However, the reciprocal relationship may apply, such that PSD contributes to poor cognitive outcomes. In a systematic review, Zulkifly et al. (2016) included eight studies examining the relationship between PSD and cognitive function. The authors reported that four studies found a positive correlation, while the remaining four studies had inconclusive findings.

Discussion
Overall, there appears to be a relationship between PSD and cognitive impairment, although the relationship appears to be complex. Early longitudinal studies reported that individuals with baseline PSD had greater subsequent cognitive impairment, as per the Mini Mental State Examination, than those without it (Bacher et al., 1990; Morris et al., 1992; Robinson et al., 1986). Later studies replicated these findings in considerably larger cohorts using a variety of outcome measures (Bour et al., 2011; Narushima et al., 2003; Saxena et al., 2008; Spalletta et al., 2002; Tene et al., 2016). However, many of the studies noted that it was difficult to determine whether cognitive impairment was a result of PSD, a risk factor for PSD, or both.

Conclusions Regarding Cognitive Function and Post-Stroke Depression
There is Level 2 evidence that that depression has a significant, negative impact on cognitive function post stroke.

Post-stroke depression may have a negative impact on cognitive function.

18.4.4 Mortality and Post-Stroke Depression
The presence of depressive symptomatology has been reported to be associated with an increase in stroke mortality. While studies have demonstrated that pre-stroke depressive symptoms are associated significantly greater odds of post-stroke mortality (Everson et al., 1998; Kamphuis et al., 2006), they did not examine the impact of PSD on mortality. In a systematic review of 13 studies, Bartoli et al. (2013) reported that presence of PSD was associated with significantly greater odds of mortality. Studies examining the impact of PSD on mortality are listed in Table 18.4.1.

Table 18.4.1.1 Studies Evaluating Impact of Post-Stroke Depression on Mortality

<table>
<thead>
<tr>
<th>Positive Studies</th>
<th>Negative Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>Lewis et al.</em> (2001)</td>
</tr>
<tr>
<td></td>
<td><em>Paolucci et al.</em> (2006)</td>
</tr>
<tr>
<td></td>
<td><em>Almeida &amp; Xiao</em> (2007)</td>
</tr>
<tr>
<td></td>
<td><em>Reynolds et al.</em> (2008)</td>
</tr>
<tr>
<td></td>
<td><em>Willey et al.</em> (2010)</td>
</tr>
<tr>
<td></td>
<td><em>Kemper et al.</em> (2011)</td>
</tr>
<tr>
<td></td>
<td><em>Jiao et al.</em> (2016)</td>
</tr>
</tbody>
</table>

Discussion
While more studies reported that PSD was associated with significantly greater odds of mortality, the remaining studies failed to find an association between the two variables. The reason for the discrepancy between studies is not immediately clear, as the two groups included of a wide range of follow-up periods (1-12 years) and a mix of prospective and retrospective studies; the pooled samples of the two groups was comparable. As such, despite the positive findings of the aforementioned meta-analysis, it is difficult to make a definitive conclusion regarding the impact of PSD on mortality in the short or long term.

Conclusions Regarding Mortality and Post-Stroke Depression

There is conflicting Level 2 and Level 3 evidence as to whether depression post stroke is associated with an increased risk of mortality.

Further research is required to determine the impact of post-stroke depression on mortality.

18.5 Prevention of Post-Stroke Depression

18.5.1 Pharmacotherapy and the Prevention of Post-Stroke Depression
Given the negative impact of PSD on stroke recovery, several studies have investigated various interventions to prevent its development. In a systematic review of 14 RCTs, Hackett et al. (2008) evaluated the efficacy of prophylactic interventions for PSD when compared to standard care. While pharmacotherapy did not demonstrate a consistent treatment effect across 10 trials, 4 trials of
psychotherapy revealed a small but significant effect. Trials evaluating the effectiveness of early initiation of antidepressant therapy are summarized in Table 18.5.1.

### 18.5.1 Summary of Studies Evaluating Prophylactic Pharmacotherapy for Post-Stroke Depression

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design (PEDro Score)</th>
<th>Sample Size</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Almeida et al.</strong> (2006)</td>
<td>RCT (9)</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=111, N&lt;sub&gt;End&lt;/sub&gt;=94</td>
<td>E: Sertraline (50mg/d) C: Placebo</td>
<td>Hospital Anxiety &amp; Depression Scale (-)</td>
</tr>
<tr>
<td><strong>Chollet et al.</strong> (2011)</td>
<td>RCT (9)</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=118, N&lt;sub&gt;End&lt;/sub&gt;=113</td>
<td>E: Fluoxetine (20mg/d) C: Placebo</td>
<td>Montgomery-Asberg Depression Rating Scale (+)</td>
</tr>
<tr>
<td><strong>Palomäki et al.</strong> (1999)</td>
<td>RCT (8)</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=100, N&lt;sub&gt;End&lt;/sub&gt;=81</td>
<td>E: Mianserin (10-60mg/d) C: Placebo</td>
<td>Major Depressive Disorder (-) Hamilton Depression Rating Scale (-) Beck Depression Inventory (-)</td>
</tr>
<tr>
<td><strong>Narushima et al.</strong> (2002)</td>
<td>RCT (8)</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=48, N&lt;sub&gt;End&lt;/sub&gt;=32</td>
<td>E1: Fluoxetine (10-40mg/d) E2: Nortriptyline (25-100mg/d) C: Placebo</td>
<td>Depressive Disorder: E1, E2 vs C (+) Hamilton Depression Rating Scale: E1, E2 vs C (+)</td>
</tr>
<tr>
<td><strong>Tsai et al.</strong> (2011)</td>
<td>RCT (8)</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=92, N&lt;sub&gt;End&lt;/sub&gt;=56</td>
<td>E: Milnacipran (50-100mg/d) C: Placebo</td>
<td>Hamilton Depression Rating Scale (+)</td>
</tr>
<tr>
<td><strong>Robinson et al.</strong> (2008b)</td>
<td>RCT (7)</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=176, N&lt;sub&gt;End&lt;/sub&gt;=134</td>
<td>E1: Escitalopram (5-10mg/d) E2: Problem-solving therapy C: Placebo</td>
<td>Depressive Disorder: E1, E2 vs C (+)</td>
</tr>
<tr>
<td><strong>Rasmussen et al.</strong> (2003)</td>
<td>RCT (7)</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=137, N&lt;sub&gt;End&lt;/sub&gt;=67</td>
<td>E: Sertraline (50mg/d) C: Placebo</td>
<td>Hamilton Depression Rating Scale (+) Geriatric Depression Scale (-)</td>
</tr>
<tr>
<td><strong>Zhang et al.</strong> (2013)</td>
<td>RCT (7)</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=118, N&lt;sub&gt;End&lt;/sub&gt;=95</td>
<td>E: Duloxetine (30-90mg/d) C: No medication</td>
<td>Hamilton Depression Rating Scale (+)</td>
</tr>
<tr>
<td><strong>Dam et al.</strong> (1996)</td>
<td>RCT (7)</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=52, N&lt;sub&gt;End&lt;/sub&gt;=46</td>
<td>E1: Maprotiline (150mg/d) E2: Fluoxetine (20mg/d) C: Placebo</td>
<td>Hamilton Depression Rating Scale: E1, E2 vs C (-)</td>
</tr>
<tr>
<td><strong>Niedermaier et al.</strong> (2004)</td>
<td>RCT (5)</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=70, N&lt;sub&gt;End&lt;/sub&gt;=62</td>
<td>E: Mirtazapine (30-45mg/d) C: No medication</td>
<td>Hamilton Depression Rating Scale (+)</td>
</tr>
</tbody>
</table>

- Indicates non-statistically significant differences between treatment groups
+ Indicates statistically significant differences between treatment groups
E indicates experimental group; C indicates control group
Discussion
Individual studies offer conflicting evidence with regard to prevention of PSD through pharmacological intervention. However, there appears to be a positive trend toward protection against depression associated with prophylactic treatment. Duration of treatment ranged from three months to one year. Two of the studies that did not demonstrate a significant treatment effect reported a shorter duration of intervention; three months (Narushima et al., 2002; Starkstein et al., 2016) and six months (Almeida et al., 2006).

Fluoxetine was found to be a successful prophylactic for PSD in three high-quality trials (Chollet et al., 2011; Dam et al., 1996; Narushima et al., 2002). In individual trials, escitalopram (Robinson et al., 2008b) and nortriptyline (Narushima et al., 2002) also demonstrated efficacy in preventing PSD. However, sertraline revealed mixed results; Rasmussen et al. (2003) found a significant effect in preventing PSD while Almeida et al. (2006) did not find such an effect. Less typical anti-depressants such as mirtazapine (Niedermaier et al., 2004), milnacipran (Tsai et al., 2011), and duloxetine (Zhang et al., 2013) demonstrated a significant preventative effect for PSD. Mianserin exhibited only a short-term effect in preventing PSD, as assessed by multiple measures of depression (Palomaki et al., 1999).

Sudden cessation of preventative pharmacotherapy may be associated with an increased risk for PSD. In a follow-up to Robinson et al. (2008b), Mikami et al. (2011) reported that participants were at a significantly increased risk for developing depression six months following discontinuation of escitalopram when compared to placebo or problem-solving therapy. Similarly, Narushima et al. (2002) (2004) found that participants who discontinued fluoxetine or nortriptyline had a greater risk of depression after six months than those who had received placebo. The authors also reported that only nortriptyline was associated with a greater severity of depressive symptoms when compared to placebo.

<table>
<thead>
<tr>
<th>Study name</th>
<th>Odds ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palomaki et al. (1999)</td>
<td>0.957</td>
<td>0.259</td>
<td>3.333</td>
<td>0.947</td>
</tr>
<tr>
<td>Narushima et al. (2002)</td>
<td>0.314</td>
<td>0.071</td>
<td>1.392</td>
<td>0.127</td>
</tr>
<tr>
<td>Rasmussen et al. (2003)</td>
<td>0.325</td>
<td>0.118</td>
<td>0.897</td>
<td>0.030</td>
</tr>
<tr>
<td>Niedermaier et al. (2004)</td>
<td>0.091</td>
<td>0.019</td>
<td>0.441</td>
<td>0.003</td>
</tr>
<tr>
<td>Almeida et al. (2006)</td>
<td>0.727</td>
<td>0.265</td>
<td>1.998</td>
<td>0.537</td>
</tr>
<tr>
<td>Robinson et al. (2008)</td>
<td>0.321</td>
<td>0.106</td>
<td>0.967</td>
<td>0.044</td>
</tr>
<tr>
<td>Tsai et al. (2011)</td>
<td>0.143</td>
<td>0.016</td>
<td>1.252</td>
<td>0.079</td>
</tr>
<tr>
<td>Chollet et al. (2011)</td>
<td>0.173</td>
<td>0.054</td>
<td>0.555</td>
<td>0.003</td>
</tr>
<tr>
<td>Chollet et al. (2011)</td>
<td>0.341</td>
<td>0.219</td>
<td>0.529</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Figure 18.5.1. Effectiveness of Prophylactic Pharmacotherapy for Post-Stroke Depression

Given that the aforementioned studies included only patients without baseline depression and utilized depression as a primary outcome, a pooled analysis was conducted to evaluate the effectiveness of pharmacological intervention in the prevention of PSD (Figure 18.5.1). Pooled analysis demonstrated a significantly reduced risk for PSD associated with pharmacological treatment (OR=0.38, 95%CI 0.24-0.61). Although there was no significant heterogeneity between studies, there were some notable differences such as the pharmacologic agents used and length of treatment.

Conclusions Regarding Prophylactic Pharmacotherapy for Post-Stroke Depression
There is Level 1a evidence that early initiation of fluoxetine is associated with reduced risk of post-stroke depression when compared to placebo.

There is Level 1b evidence that early initiation of escitalopram is associated with reduced risk of post-stroke depression when compared to placebo.

There is Level 1b evidence that early initiation of nortriptyline is associated with reduced risk of post-stroke depression when compared to placebo.

There is Level 1b evidence that early initiation of milnacipran is associated with reduced risk of post-stroke depression when compared to placebo.

There is Level 1b evidence that early initiation of duloxetine is associated with reduced risk of post-stroke depression when compared to no antidepressant medication.

There is Level 1b evidence that early initiation of mianserin is not associated with reduced risk of post-stroke depression when compared to placebo.

There is conflicting Level 1b evidence regarding the efficacy of sertraline in reducing the risk of post-stroke depression when compared to placebo.

There is Level 2 evidence that early initiation of mirtazapine is associated with reduced risk of post-stroke depression when compared to no antidepressant medication.

**Early initiation of antidepressant therapy in non-depressed individuals may be effective in preventing post-stroke depression.**

Fluoxetine, escitalopram, nortriptyline, milnacipran, mirtazapine, and duloxetine have been reported to be effective in preventing depression. There are mixed results regarding the efficacy of sertraline, while mianserin does not appear to be effective.

### 18.5.2 Care Provision and the Prevention of Post-Stroke Depression

The development of depression post stroke may also be influenced by the provision of regular contact, counselling, and support within various models of care. Studies that have assessed the impact of care provision on the mental health and/or mood of individuals post stroke are summarized in Table 18.5.2.1.

#### 18.5.2.1 Summary of Studies Evaluating the Impact of Care Provision on Post-Stroke Depression

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design (PEDro Score)</th>
<th>Sample Size</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Burton &amp; Gibbon</strong> (2005)</td>
<td>RCT (7)</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=176, N&lt;sub&gt;End&lt;/sub&gt;=128</td>
<td>E: Home visits, C: No follow-up</td>
<td>• Beck Depression Inventory (-)</td>
</tr>
<tr>
<td><strong>Watkins et al.</strong> (2007)</td>
<td>RCT (7)</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=411</td>
<td>E: Motivational interviewing, C: Usual care</td>
<td>• General Health Questionnaire 28: 3mo (+), 12mo (+) • Yale Self-Report Screening Tool: 3mo (+), 12mo (-)</td>
</tr>
</tbody>
</table>

[www.ebrsr.com](http://www.ebrsr.com)
Based on the summarized studies, there is conflicting evidence as to whether ongoing contact and support attenuates the deterioration of mental health and/or mood state following stroke. In an earlier trial, patients received a family support initiative that began care coordination in the hospital and delivered multiple home visits for up to nine months after discharge. Patients who were part of the initiative did not demonstrate any benefit in mood compared to those who received standard care (Lincoln et al., 2003b). Conversely, another trial found that care coordination from a specialized social worker was associated with reduced depression and improved mental health after only three months (Claiborne, 2006). In two trials, Joubert et al. (2008; 2006) evaluated the efficacy of an integrated care program in reducing PSD. The program coordinated care between the hospital physicians and the patient’s general practitioner before discharge, and continued to monitor progress with the patient and practitioner for up to a year. While the earlier trial did not find a significant difference between the
program and standard care, the later trial found fewer depressive symptoms in those who received integrated care and a lower prevalence of PSD.

Ensuring patients are suitably homed after discharge may be a potential factor in averting the development of PSD. Burton and Gibbon (2005) examined the effect of regular home visits from a stroke nurse on independence and mood. The authors found that the intervention was better than standard care in improving independence and aspects of mood, but had no significant impact on depression (Burton & Gibbon, 2005). In a later trial, Drummond et al. (2013) compared patients who received a pre-discharge home visit assessment with an occupational therapist to patients who received only a pre-discharge interview. The home visit assessment was found to be successful in the short-term, with patients reporting significantly lower depression scores at one week but not one month (Drummond et al., 2013). It is worth noting that the intervention group had significantly more hospital readmissions and falls at home, which may have contributed to depression. Greater planning, provisions, and assistance within the home may help maintain a safe and supportive environment, but further research is required to determine its impact on psychosocial outcomes.

Community outreach using postal mail was investigated in two trials, providing either educational resources (Ostwald et al., 2014) or contact information for support (Hackett et al., 2013). The latter trial found that the personalized postcards had no impact on depression when compared to no contact (Hackett et al., 2013). However, the former trial reported that the resource information alone was as effective in reducing depression when provided in addition to home visits (Ostwald et al., 2014). A similar method was utilized by Rochette et al. (2013) in a multicentre trial, which contacted patients via telephone calls as opposed to postal mail. The intervention group received weekly calls, while the control group was encouraged to contact healthcare professionals when needed. Despite the lack of significant between-group differences in depression levels post intervention, the authors noted improvements among both groups of patients. These collective findings suggest that community outreach programs may hold some value for reducing the incidence of PSD.

A single study evaluated the use of a specific intervention, motivational interviewing, and reported positive results (Watkins et al., 2007; Watkins et al., 2011). Compared to usual care, patients who received the intervention showed significant reductions in depressive symptoms up to three months and improvements in mood up to one year. However, it was not clear whether the benefit associated with motivational interviewing was due to the talk therapy technique itself or to the ongoing, individualized attention and support. Further study using an attentional control group may serve to clarify the true efficacy of motivational interviewing.

Conclusions Regarding Care Provision and the Prevention of Post-Stroke Depression

There is Level 1a evidence that community outreach, using post mail or telephone calls, does not reduce depressive symptoms when compared to standard care.

There is Level 1b evidence that a pre-discharge home visit by an occupational therapist reduces short-term depressive symptoms when compared to a pre-discharge hospital interview.

There is Level 1b evidence that motivational interviewing improves mood and reduces depressive symptoms when compared to standard care.
There is Level 1b and Level 2 evidence that home visits from nurses and therapists do not reduce depressive symptoms when compared to information provision or standard care.

There is conflicting Level 2 evidence regarding the effectiveness of coordinated or integrated care programs on reducing depressive symptoms when compared to standard care.

It is unclear as to whether coordinated/integrated care programs that provide ongoing, individualized contact and support are effective in improving mood and attenuating depressive symptoms post stroke; further high-quality research is required.

Home visits from healthcare professionals may not be effective in attenuating depressive symptoms post stroke.

Community outreach via mail or telephone may not be effective in attenuating depressive symptoms post stroke.

Motivational interviewing may be effective in improving mood and attenuating depressive symptoms post stroke.

18.5.3 Dietary Supplementation

18.5.3.1 Omega-3 Fish Oil
There has been considerable debate regarding the possible association between omega-3 polyunsaturated fatty acids (PUFAs) and depressive disorders. Hibbeln (1998) proposed a simple, correlational model demonstrating an inverse association between fish consumption and prevalence of major depression based on the results of a multinational study. While some subsequent trials provided support for such an association, other studies have shown no association between omega-3 PUFAs and depression. In a recent meta-analysis, Appleton et al. (2010) identified 35 RCTs evaluating the impact of omega-3 PUFAs on depressive symptomatology. A pooled analysis of 29 trials demonstrated a significant treatment effect in favour of the supplement, but appeared to be limited to trials enrolling individuals with a diagnosed depressive disorder; the analysis also demonstrated significant heterogeneity. None of the trials in the aforementioned meta-analysis were conducted in the stroke population. A single trial examining the impact of fish oil supplementation on mood following stroke is summarized Table 18.5.3.1.1.

Table 18.5.3.1.1 Summary of Studies Evaluating Omega-3 Supplementation and Mood

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design (PEDro Score)</th>
<th>Sample Size</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poppit et al. (2009)</td>
<td>RCT (9)</td>
<td>NStart=102 NEnd=95</td>
<td>E: Fish oil capsules C: Placebo</td>
<td>• GHQ-28 (-)</td>
</tr>
</tbody>
</table>

- Indicates non-statistically significant differences between treatment groups
+ Indicates statistically significant differences between treatment groups
E indicates experimental group; C indicates control group

Discussion
Poppitt et al. (2009) reported no significant impact on mood associated with a 12-week course of fish oil supplementation following stroke. It should be noted, however, that the study did not focus on prevention or treatment of PSD.

**Conclusions Regarding Omega-3 Fish Oil and the Prevention of Post-Stroke Depression**

*There is level 1b evidence that fish oil supplementation does not impact mood post stroke.*

**Dietary supplementation with omega-3 fatty acids is not effective in improving mood post stroke.**

**18.5.3.2 B-Vitamins**

Depression and stroke share common cardiovascular risk factors. It has been suggested that elevated homocysteine and reduced folate may be some of these shared factors (Almeida et al., 2010; Kim et al., 2008; Tiemeier et al., 2002). Previous studies have demonstrated that vitamin B₁₂ deficiency may be associated with increased risk for depression in elderly community-dwelling individuals (Kim et al., 2008; Tiemeier et al., 2002). Similarly, Huijts et al. (2012) reported a significant association between vitamin B₁₂ deficiency and symptoms of depression in individuals with first-ever lacunar stroke. A single trial has examined the impact of B-vitamins on the risk for PSD, which is summarized in Table 18.5.3.2.1.

### 18.5.3.2.1 Summary of Studies Evaluating B-Vitamin Supplementation and Mood

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design (PEDro Score)</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almeida et al. (2010)</td>
<td>RCT (10)</td>
<td>E: B-Vitamins tablet (1x/d) C: Placebo</td>
<td>Mini-International Neuropsychiatric Interview (+)</td>
</tr>
<tr>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=563 N&lt;sub&gt;End&lt;/sub&gt;=273</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Indicates non-statistically significant differences between treatment groups
+ Indicates statistically significant differences between treatment groups
E indicates experimental group; C indicates control group

**Discussion**

The results of a single high-quality RCT suggest that B-vitamin therapy may be protective against the development of depressive disorders following stroke. It should be noted, however, that this study was part of a larger effort to examine the impact of B-vitamin therapy on the recurrence of cardiovascular events. The optimal timing of for initiating such therapy remains unclear. The average onset from stroke event to enrolment was seven months, and the effectiveness was not apparent until treatment had been administered for approximately six years. Given that the incidence of PSD is highest in the first months following stroke, earlier initiation of preventive strategies might be more effective.

**Conclusions Regarding B-Vitamins and the Prevention of Post-Stroke Depression**

*There is level 1b evidence that Vitamin B therapy, administered over a long period, is associated with reduced risk of post-stroke depression.*

**Long-term Vitamin B therapy may be effective in reducing risk of depression following stroke.**

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18.6 Pharmacologic Treatment of Post-Stroke Depression

Treatment of post-stroke depression may involve the use of medications, psychosocial therapies, or a combination of both modalities. Drug therapy for depression is based on the notion that depression is associated with an imbalance and underactivity of the cerebral noradrenergic and serotonergic systems.

In a meta-analysis of 16 RCTs, Chen et al. (2006) evaluated the efficacy of antidepressants in treating PSD. Treatment was associated with a significant reduction in depressive symptomatology on all scales used to assess outcome, regardless of the treatment response defined by individual studies. The authors also identified a positive relationship between duration and benefit of treatment, suggesting an increasing effect with duration of three weeks onward. More recently, Xu et al. (2016) conducted a similar meta-analysis of 11 RCTs examining antidepressants for PSD. The analysis demonstrated a significant, large treatment effect of antidepressants in attenuating PSD, which remained significant across sample sizes, age groups, gender distributions, and depression severities.

A Cochrane review by Hackett et al. (2008) included 12 RCTs examining the use of pharmacological interventions for the treatment of PSD. Like the aforementioned reviews, the authors included trials examining a variety of agents initiated at a variety of times post stroke and for varying intervals. Pooled analysis demonstrated that use of pharmacotherapy was associated with a small but significant treatment effect. However, the authors noted adverse events associated with the use of pharmacological interventions, namely neurological and gastrointestinal effects.

18.6.1 Heterocyclic Antidepressants

Heterocyclic antidepressants may block the reuptake of both serotonin and norepinephrine to different degrees within the cerebrum, thereby increasing the levels of these neurotransmitters in the brain. Despite the risk profile associated with this class of medications, heterocyclic antidepressants have been reported to be used commonly for the treatment of depression in the elderly (Brown et al., 1995).

Finklestein et al. (1987) conducted a retrospective review of 60 patients with PSD who received no pharmacotherapy or were treated with one of several cyclic antidepressant drugs (e.g. doxepine, maprotiline, trazadone, desipramine, amitriptyline, imipramine). It was found that only 17% of the untreated patients attained an improvement in depression scores compared to 40% of the drug responders. As well, drug responders showed a greater improvement in depression scores than non-drug responders or untreated patients. Despite being a retrospective study, Finklestein et al. (1987) demonstrated the potential value of cyclic antidepressants post stroke.

In the aforementioned review by Xu et al. (2016), subgroup analysis of tricyclic antidepressants demonstrated a significant, large treatment effect in attenuating PSD. Trials investigating the efficacy of heterocyclic drugs in the treatment of PSD are summarized in Table 18.6.1.1.

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design (PEDro Score)</th>
<th>Sample Size</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipsey et al. (1984)</td>
<td>RCT (8)</td>
<td>N_{Start}=39</td>
<td>E: Nortriptyline (20-100mg/d) C: Placebo</td>
<td>• Hamilton Depression Rating Scale (+) • Zung Self-Rating Depression Scale (+) • Present State Examination (-)</td>
</tr>
<tr>
<td>N&lt;sub&gt;End&lt;/sub&gt;=34</td>
<td>Combined scores (HAMD, ZDS, PSE) (+)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------</td>
<td>----------------------------------</td>
<td></td>
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</tr>
<tr>
<td><strong>Robinson et al.</strong> (2000) RCT (8) N&lt;sub&gt;Start&lt;/sub&gt;=56 N&lt;sub&gt;End&lt;/sub&gt;=40</td>
<td>E1: Nortriptyline (25-100mg/d) E2: Fluoxetine (10-40mg/d) C: Placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Hamilton Depression Rating Scale: E1 vs E2, C (+)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gonzalez-Torrecillas et al.</strong> (1995) RCT (7) N&lt;sub&gt;Start&lt;/sub&gt;=130 N&lt;sub&gt;End&lt;/sub&gt;=125</td>
<td>E1: Nortriptyline (25-75mg/d) E2: Fluoxetine (20mg/d) C: No medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Beck Depression Inventory: E1, E2 vs C (+) • Hamilton Depression Rating Scale: E1, E2 vs C (+) • Montgomery-Asberg Depression Rating Scale: E1, E2 vs C (+)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lauritzen et al.</strong> (1994) RCT (7) N&lt;sub&gt;Start&lt;/sub&gt;=20 N&lt;sub&gt;End&lt;/sub&gt;=15</td>
<td>E2: Mianserin (10mg/d) + Imipramine (25-75mg/d) E2: Mianserin (10mg/d) + Desipramine (25-75mg/d)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Bech-Rafaelsen Melancholia Scale (+) • Hamilton Depression Rating Scale (-)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Miyai &amp; Reding</strong> (1998) RCT (6) N&lt;sub&gt;Start&lt;/sub&gt;=24 N&lt;sub&gt;End&lt;/sub&gt;=18</td>
<td>E1: Desipramine (50-100mg/d) E2: Trazodone (50-100mg/d) E3: Fluoxetine (10-20mg/d)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Hamilton Depression Rating Scale (-)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Raffaele et al.</strong> (1996) RCT (5) N&lt;sub&gt;Start&lt;/sub&gt;=22 N&lt;sub&gt;End&lt;/sub&gt;=22</td>
<td>E: Trazodone (300mg/d) C: Placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Zung Depression Scale (-)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Indicates non-statistically significant differences between treatment groups
+ Indicates statistically significant differences between treatment groups
E indicates experimental group; C indicates control group

**Discussion**

In two high-quality trials, nortriptyline demonstrated a significant treatment effect for PSD when compared to placebo (Lipsey et al., 1984; Robinson et al., 2000). When compared to fluoxetine, a selective serotonin reuptake inhibitor, nortriptyline was found to be similarly or more effective in treating PSD (Gonzalez-Torrecillas et al., 1995; Robinson et al., 2000). Other heterocyclic antidepressants, desipramine and trazodone, also demonstrated similar efficacy to fluoxetine (Miyai & Reding, 1998). Lauritzen et al. (1994) examined the efficacy of a tetracyclic antidepressant (i.e. mianserin) when paired with a tricyclic antidepressant (i.e. imipramine or desipramine). While both combinations demonstrated significant reductions in depressive symptoms, there were greater improvements when mianserin was paired with imipramine. In fact, desipramine was found to be less effective than placebo in treating PSD (Raffaele et al., 1996).

Amine medications (e.g. nortriptyline, imipramine, desipramine) have been linked to adverse cardiovascular, anticholinergic, and antihistamine events (Kumar, 1999). Lipsey et al. (1984) noted that confusion, drowsiness, and agitation were significant side effects of nortriptyline. Likewise, Lauritzen et al. (1994) found that a considerable number of patients dropped out due to similar side effects from the tricyclic/tetracyclic antidepressants. However, Robinson et al. (2000) reported a significantly greater dropout rate in patients taking fluoxetine than nortriptyline, often due to cardiovascular and gastrointestinal symptoms. The relatively high incidence of side effects associated with heterocyclic antidepressants must be taken into account when prescribing them, especially in patients of older age and/or with cardiovascular issues.

**Conclusions Regarding Heterocyclic Antidepressants**
There is Level 1a evidence that heterocyclic antidepressants are as effective as fluoxetine in reducing depressive symptoms post stroke.

There is Level 1a evidence that nortriptyline reduces depressive symptoms post stroke when compared to placebo.

There is Level 1b evidence that mianserin reduces depressive symptoms post stroke when paired with imipramine or desipramine, but is more effective with imipramine.

There is Level 2 evidence that desipramine does not reduce depressive symptoms post stroke when compared to placebo.

Heterocyclic antidepressants, namely nortriptyline, may be an effective treatment for post-stroke depression.

18.6.2 Selective Serotonin Reuptake Inhibitors (SSRIs)
Selective serotonin reuptake inhibitors (SSRIs) selectively block the reuptake of serotonin, but have weak affinity for transporters of norepinephrine and dopamine. They are commonly used to treat depressive disorders, especially those characterized by anxiety, insomnia, restlessness, hostility, and trepidation. The use of SSRIs for PSD has been thoroughly investigated, with Mead et al. (2013) identifying 52 studies in a systematic review. Their meta-analysis found that SSRIs were effective in treating symptoms of depression and anxiety, although there was significant heterogeneity between the studies. As well, the authors determined that SSRIs were associated with increased risk of adverse events and associated trial dropout. Studies examining the use of SSRIs in the treatment of PSD are summarized in Table 18.6.2.1.

Table 18.6.2.1 Studies Evaluating Selective Serotonin Reuptake Inhibitors for Post-Stroke Depression

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design (PEDro Score)</th>
<th>Sample Size</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murray et al. (2005)</td>
<td>RCT (9)</td>
<td>N_Start=123 N_End=69</td>
<td>E: Sertraline (50-100mg/d, 26wk) C: Placebo</td>
<td>Montgomery-Asberg Depression Rating Scale: 6wk (-), 26wk (-)</td>
</tr>
<tr>
<td>Fruehwald et al. (2003)</td>
<td>RCT (9)</td>
<td>N_Start=54 N_End=40</td>
<td>E: Fluoxetine (20mg/d, 3mo) C: Placebo</td>
<td>Hamilton Depression Rating Scale: 1mo (-), 3mo (-), 18mo (+) • Beck Depression Inventory: 1mo (-), 3mo (-), 18mo (+)</td>
</tr>
<tr>
<td>Choi-Kwon et al. (2006)</td>
<td>RCT (8)</td>
<td>N_Start=152 N_End=125</td>
<td>E: Fluoxetine (20mg/d, 3mo) C: Placebo</td>
<td>Beck Depression Inventory: 1mo (-), 3mo (-), 6mo (-)</td>
</tr>
<tr>
<td>Andersen et al. (1994)</td>
<td>RCT (8)</td>
<td>N_Start=66 N_End=59</td>
<td>E: Citalopram (10-20mg/d, 6wk) C: Placebo</td>
<td>Hamilton Depression Rating Scale: 3wk (+), 6wk (+) • Bech-Rafaelsen Melancholia Scale: 3wk (+), 6wk (+)</td>
</tr>
</tbody>
</table>
Discussion

Fluoxetine was investigated as a treatment for PSD in six RCTs of moderate to high quality. (2000) The SSRI was reportedly more effective than placebo in reducing depressive symptoms (Fruehwald et al., 2003; Wiart et al., 2000), although one of the trials did not find an effect until a year after completion (Fruehwald et al., 2003). Conversely, two other trials found that three months of fluoxetine was no more effective than placebo in treating depression (Choi-Kwon et al., 2006; Robinson et al., 2000). Fluoxetine also demonstrated similar efficacy to heterocyclic antidepressants in two trials (Gonzalez-Torrecillas et al., 1995; Miyai & Reding, 1998), and lesser efficacy in a later trial (Robinson et al., 2000). Given that these RCT provided a similar dose of fluoxetine (i.e. 20mg), these conflicting results may be due to differences in stroke onset, trial length, and timing of assessment.

Two other SSRIs were investigated as potential interventions for PSD. Citalopram was found to significantly attenuate depression scores on multiple scales when compared to placebo (Andersen et al., 1994). Citalopram was also found to significantly reduce depressive symptoms in depressed patients to those of non-depressed patients after six months of treatment (Bilge et al., 2008). Sertraline, on the other hand, was not an effective treatment for PSD (Murray et al., 2005). While citalopram demonstrated benefit over placebo within three weeks (Andersen et al., 1994), sertraline did not demonstrate efficacy over the course of six months (Murray et al., 2005).

Conclusions Regarding Selective Serotonin Reuptake Inhibitors

There is Level 1a evidence that fluoxetine is no more effective than heterocyclic antidepressants in treating depressive symptoms post stroke.
There is Level 1b evidence that citalopram reduces depressive symptoms post stroke when compared to placebo.

There is Level 1b evidence that sertraline does not reduce depressive symptoms post stroke when compared to placebo.

There is conflicting Level 1b evidence regarding the effectiveness of fluoxetine in treating depressive symptoms post stroke when compared to placebo.

While some selective serotonin reuptake inhibitors may be effective in the treatment of post-stroke depression (e.g. citalopram), the effectiveness of others is unestablished (e.g. sertraline) or unclear (e.g. fluoxetine).

18.6.2.1 Adjunctive Light Therapy

Administration of bright light has demonstrated effectiveness not only for the treatment of seasonal affective disorder but also for non-seasonal depression. In a Cochrane review, Tuunainen et al. (2004) identified 20 studies examining the use of bright light therapy for depression, mostly in combination with drug treatment. Evaluation of these studies revealed a significant effect in favour of treatment over control with minimal adverse effects. A recent meta-analysis by Perera et al. (2016) supported the findings of the Cochrane review, confirming the benefit of adjunctive light therapy for depression. However, similar to the previous review, the authors noted poor quality of evidence due to high risk of bias and inconsistency. A study examining the use of adjunctive light therapy for PSD is summarized in Table 18.6.2.1.1.

Table 18.6.2.1.1 Study Evaluating Adjunctive Light Therapy for Post-Stroke Depression

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design (PEDro Score)</th>
<th>Sample Size</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sondergaard et al. (2006)</td>
<td>RCT (5)</td>
<td>NStart=73, NEnd=63</td>
<td>E: High-Intensity Light Therapy (10,000 lux) + Citalopram (20mg/d)</td>
<td>Hamilton Depression Rating Scale 6 (+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C: Moderate-Intensity Light Therapy (4,000 lux) + Citalopram (20mg/d)</td>
<td>Hamilton Depression Rating Scale 17 (-)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bech-Rafaelsen Melancholia Scale (-)</td>
</tr>
</tbody>
</table>

- Indicates non-statistically significant differences between treatment groups
+ Indicates statistically significant differences between treatment groups
E indicates experimental group; C indicates control group

Discussion

A single RCT examined light therapy, provided as an adjunct to citalopram, for non-seasonal depression in individuals following stroke (Sondergaard et al., 2006). Light therapy was found to be more effective in reducing depressive symptoms when provided at a high rather than moderate intensity. It should be noted, however, that a significant difference between groups was found on only one of the three scales assessing depression. Moreover, the trial did not compare adjunctive light therapy to citalopram therapy alone, and so the full extent of its benefit is unclear.

Conclusions Regarding Adjunctive Light Therapy

There is Level 1b evidence that adjunctive high-intensity light therapy is more effective than moderate-intensity light therapy in treating depressive symptoms post stroke.
Further research is required to determine the effectiveness of adjunctive light therapy in treating post-stroke depression.

18.6.3 Noradrenaline Reuptake Inhibitors (NRI)
Patients suffering from depression characterized by lethargy, anergia, hypokinesis, and hypomimia are said to be suffering from a retarded depression (Rampello et al. 2005). Selective noradrenaline reuptake inhibitors (NRIs) are proposed as an alternative to SSRIs for individuals experiencing such depression. A trial examining the effectiveness of an NRI in the treatment of PSD is summarized in Table 18.6.3.1.

Table 18.6.3.1 Study Evaluating Reboxetine in the Treatment of Post-Stroke Depression

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design (PEDro Score)</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rampello et al. (2005)</td>
<td>RCT (8) NStart=31 NEnd=31</td>
<td>E: Reboxetine (4mg, 2x/d) C: Placebo</td>
<td>• Hamilton Depression Rating Scale (+) • Beck Depression Inventory (+)</td>
</tr>
</tbody>
</table>

- Indicates non-statistically significant differences between treatment groups
+ Indicates statistically significant differences between treatment groups
E indicates experimental group; C indicates control group

Discussion
Over a 16-week course of treatment, reboxetine was associated with significant improvement in retarded PSD when compared to placebo (Rampello et al. 2005). Patients receiving reboxetine experienced only minor side effects and none withdrew from the study. However, further research is required to assess the safety and efficacy of long-term treatment.

Conclusions Regarding Reboxetine

*There is Level 1b evidence that reboxetine reduces depressive symptoms post stroke when compared to placebo.*

*Reboxetine, a noradrenaline reuptake inhibitor, may be an effective treatment for post-stroke depression.*

18.6.4 Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs)
The use of serotonin and noradrenaline reuptake inhibitors (SNRIs) in the treatment of geriatric depression has been examined in several open label studies and RCTs. The findings of these trials have supported the safety and efficacy of SNRIs within this population (Staab & Evans, 2000), although there have been no trials examining their use for treating PSD.

Discussion
Venlafaxine is an antidepressant characterized by the inhibition of the reuptake of serotonin and norepinephrine, as well as dopamine (Staab & Evans, 2000). Two pre-post studies demonstrated its effectiveness in reducing depressive symptoms post stroke, with minimal or no side effects (Dahmen et al., 1999; Kucukalic et al., 2007).
Conclusions Regarding Venlafaxin

There is limited Level 4 evidence that venlafaxine reduces depressive symptoms post stroke.

Further research is required to determine the effectiveness of venlafaxine, a serotonin and noradrenaline reuptake inhibitor, in treating post-stroke depression.

18.6.5 Psychostimulants

Methylphenidate, a psychostimulant approved for treating attention-deficit disorders, has also been used in the treatment of depression in the elderly as an alternative to other antidepressants. Depression in the elderly has been described as a “lack of interest and emotional involvement in one’s surroundings”, and psychostimulants have shown to be effective in treating such symptoms (Johnson et al., 1992). Methylphenidate has its effects in the cortical and subcortical areas of the brain. It is believed to heighten mood by affecting several neurotransmitter systems, particularly the noradrenergic system. Thus methylphenidate may affect PSD by ‘correcting’ the depletion of biogenic amines caused by stroke (Johnson et al., 1992). Studies examining methylphenidate treatment for PSD are summarized in Table 18.6.5.1.

Table 18.6.5.1 Studies Evaluating Methylphenidate in the Treatment of Post-Stroke Depression

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design (PEDro Score)</th>
<th>Sample Size</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade et al. (1998)</td>
<td>RCT (7)</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=21 N&lt;sub&gt;End&lt;/sub&gt;=19</td>
<td>E: Methylphenidate (30mg/d) C: Placebo</td>
<td>• Hamilton Depression Rating Scale (+) • Zung Self-Rating Depression Scale (-)</td>
</tr>
<tr>
<td>Lazarus et al. (1994)</td>
<td>Case Control</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=58 N&lt;sub&gt;End&lt;/sub&gt;=58</td>
<td>E: Methylphenidate (10mg/d) C: Nortriptyline (25-125mg/d)</td>
<td>• Depressive Disorder (-)</td>
</tr>
</tbody>
</table>

- Indicates non-statistically significant differences between treatment groups
+ Indicates statistically significant differences between treatment groups
E indicates experimental group; C indicates control group

Discussion

Six studies examining the efficacy of psychostimulants for PSD were identified, with most providing a maximum dosage of 30 mg per day. In three retrospective studies, methylphenidate was effective in treating depressive symptoms post stroke, with near or complete remission in approximately half of the patients (Johnson et al., 1992; Lingam et al., 1988; Masand et al., 1991). One of these studies found similar results with another psychostimulant, dextroamphetamine (Masand et al., 1991). In a prospective study, the majority of patients demonstrated a clinically significant reduction after a three-week course of methylphenidate (Lazarus et al., 1992). However, it should be noted that all of these studies had small sample sizes.

A larger case control study compared a psychostimulant to a tricyclic antidepressant for the treatment of PSD (Lazarus et al., 1994). Methylphenidate was shown to be as effective as nortriptyline, and had a quicker response time (2-10 days versus 2-4 weeks). In a single RCT, Grade et al. (1998) examined patients in a community-based stroke rehabilitation unit. The authors found methylphenidate significantly more effective than placebo in reducing depressive symptoms.
Conclusions Regarding Methylphenidate

There is Level 1b evidence that methylphenidate reduces depressive symptoms post stroke when compared to placebo.

There is Level 3 evidence that methylphenidate is as effective as nortriptyline in reducing depressive symptoms post stroke.

Methylphenidate, a psychostimulant, may be an effective treatment for post-stroke depression.

18.6.6 GABA Receptor Modulators

Nefiracetam is a novel cyclic gamma aminobutyric acid (GABA) compound with documented effects on neurotransmission, regional blood flow, and glucose utilization. Studies examining nefiracetam for the treatment of PSD are summarized in Table 18.6.6.1.

18.6.6.1 Studies Evaluating Nefiracetam in the Treatment of Post-Stroke Depression

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design (PEDro Score)</th>
<th>Sample Size</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robinson et al. (2008a)</td>
<td>RCT (8)</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=159, N&lt;sub&gt;End&lt;/sub&gt;=139</td>
<td>E1: Nefiracetam (600mg, 2x/d)</td>
<td>• Hamilton Depression Rating Scale (-)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>E2: Nefiracetam (900mg, 2x/d)</td>
<td>• Beck Depression Inventory (-)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C: Placebo</td>
<td></td>
</tr>
<tr>
<td>Starkstein et al. (2016)</td>
<td>RCT (8)</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=13, N&lt;sub&gt;End&lt;/sub&gt;=8</td>
<td>E: Nefiracetam (450mg/d)</td>
<td>• Patient Health Questionnaire 9 (-)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C: Placebo</td>
<td>• Apathy Scale (-)</td>
</tr>
</tbody>
</table>

- Indicates non-statistically significant differences between treatment groups
+ Indicates statistically significant differences between treatment groups
E indicates experimental group; C indicates control group

Discussion

Two high-quality RCTs have compared the efficacy of nefiracetam and placebo in improving mood. In the smaller trial, nefiracetam was not effective in reducing symptoms of depression or apathy (Starkstein et al., 2016). The larger trial utilized two different doses of nefiracetam, which were considerably greater than the dose provided in the smaller trial (Robinson et al., 2008a). However, neither dosage was more effective than placebo in treating PSD.

Conclusions Regarding Nefiracetam

There is level 1a evidence that nefiracetam does not reduce depressive symptoms post stroke when compared to placebo.

Nefiracetam, a GABA receptor modulator, may not be an effective treatment for post-stroke depression.
18.6.7 Monoamine Oxidase Inhibitors

Monoamine oxidase (MAO) is an enzyme that catalyzes the metabolism of monoamine neurotransmitters in its two isoforms, MAO-A and MAO-B. MAO-A preferentially deaminates serotonin, epinephrine, norepinephrine, dopamine, and tyramine, while MAO-B primarily deaminates dopamine. MAO inhibitors have been proposed as a treatment for atypical depression, when more traditional classes of antidepressants have failed. A study examining a MAO inhibitor for the treatment of PSD is summarized in Table 18.6.7.1.

18.6.7.1 Study Evaluating Selegiline in the Treatment of Post-Stroke Depression

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design (PEDro Score)</th>
<th>Sample Size</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bartolo et al. (2015)</td>
<td>RCT (5)</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=47, N&lt;sub&gt;End&lt;/sub&gt;=44</td>
<td>E: Selegiline (10mg/d) C: Placebo</td>
<td>Hamilton Depression Rating Scale (-)</td>
</tr>
</tbody>
</table>

- Indicates non-statistically significant differences between treatment groups
+ Indicates statistically significant differences between treatment groups
E indicates experimental group; C indicates control group

Discussion

One low-quality RCT has examined the use of selegiline, a MAO-B inhibitor, for treating depressive symptoms in patients following stroke (Bartolo et al., 2015). When compared to placebo, six weeks of selegiline therapy did not have a significant treatment effect.

Conclusions Regarding Selegiline

There is Level 2 evidence that selegiline does not reduce depressive symptoms post stroke when compared to placebo.

Selegiline, a monoamine oxidase inhibitor, may not be an effective treatment for post-stroke depression.

18.6.8 Melatonin Agonist

Valdoxan is a melatonin receptor agonist and a 5-HT<sub>2c</sub> serotonin receptor antagonist. This synergistic effect results in increased release of dopamine and noradrenaline, although no effect on monoamines has been observed. As well, valdoxan does not exhibit the same side effects of more typical antidepressants, such as weight gain, sexual dysfunction, and withdrawal. In a meta-analysis, valdoxan at a dose of 25-50 mg was found to decrease depression symptomatology by two weeks in individuals with major depression (Montgomery & Kasper, 2007).

Discussion

In one small pre-post study, valdoxan was found to be effective in the treatment of PSD (Bogolepova et al., 2011). The study found significant improvements in depressive symptoms on the Hamilton Depression Rating Scale and Hospital & Anxiety Depression Scale after treatment and at follow up.

Conclusions Regarding Valdoxan
There is limited Level 4 evidence that valdoxan reduces depressive symptoms post stroke.

Further research is required to determine the effectiveness of valdoxan, a melatonin agonist, in treating post-stroke depression.

18.6.9 Statins
Cholesterol levels are often identified as risk factors for heart and arterial disease. While some studies have suggested that cholesterol concentrations may be associated with a risk of developing depressive symptoms (Aijanseppa et al., 2002; Kim et al., 2006; Kim & Myint, 2004; Morgan et al., 1993), other studies have found this association to be non-significant (Blazer et al., 2002). A study examining the effect of statins on PSD is summarized in Table 18.6.9.1.

Table 18.6.9.1 Study Evaluating Statins in the Treatment of Post-Stroke Depression

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design (PEDro Score)</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim et al. (2014)</td>
<td>Cohort, No Score, NStart=423, NEnd=288</td>
<td>E: Statins, C: No medication</td>
<td>• Hospital Anxiety &amp; Depression Scale (+) • Hamilton Depression Rating Scale (+)</td>
</tr>
</tbody>
</table>

Discussion
In a prospective study, Kim et al. (2014) investigated the effect of various statins on depression in individuals following stroke. The results demonstrated a significant decrease in depressive symptoms in individuals taking statins when compared to those who did not receive them. However, the authors acknowledged that the follow-up evaluation was only conducted once in the year after stroke, and so compliance during the intervention period was unclear. As well, other non-pharmacological treatments were not recorded or considered in the analysis. Therefore RCTs are necessary to determine the effect of statins on mood and depression post stroke.

Conclusions Regarding Statins

There is limited Level 2 evidence that statins may reduce depressive symptoms post stroke when compared to no medications.

Further research is required to determine the effect of statins on post-stroke depression.

18.6.10 Antidiabetics
Antidiabetic medications, such as metformin and pioglitazone, are used to lower blood glucose levels in individuals with type II diabetes mellitus (T2DM). Recent trials have found that pioglitazone was also associated with reduced depression in these individuals, perhaps through insulin sensitization (Kashani et al., 2013; Kemp et al., 2012; Sepanjnia et al., 2012). A trial examining the effect of these medications on depression in individuals post stroke is summarized in Table 18.6.10.1.
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Table 18.6.10.1 Study Evaluating Antidiabetics in the Treatment of Post-Stroke Depression

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design (PEDro Score)</th>
<th>Sample Size</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hu et al. (2015)</td>
<td>RCT (5)</td>
<td>NStart=118 NEnd=102</td>
<td>E: Pioglitazone + Fluoxetine C: Metformin + Fluoxetine</td>
<td>• Hamilton Depression Rating Scale (+)</td>
</tr>
</tbody>
</table>

- Indicates non-statistically significant differences between treatment groups

+ Indicates statistically significant differences between treatment groups

E indicates experimental group; C indicates control group

Discussion

In a single trial, Hu et al. (2015) randomized patients diagnosed with PSD and T2DM to receive fluoxetine with metformin or pioglitazone for three months. The authors found that patients taking pioglitazone had significantly lower depression scores at the end of the trial, regardless of PSD severity.

Conclusions Regarding Antidiabetics

There is limited Level 2 evidence that pioglitazone with fluoxetine reduces depressive symptoms post stroke when compared to metformin with fluoxetine.

Pioglitazone may be an effective treatment for post-stroke depression in individuals with type II diabetes.

18.6.11 Alternative Medicine

Given concerns regarding potential side effects of antidepressants, individuals with depression may choose to self-medicate with alternative medicines, namely herbal products (Davidson & Zhang, 2008). The Chinese preparation Free and Easy Wanderer Plus (FEWP) is a combination of 11 herbal drugs that is used for the treatment of mood disorders. A recent RCT demonstrated that treatment with a standardized preparation of FEWP in individuals with depression was associated with greater reduction of depressive symptoms and higher clinical response rates when compared to placebo (Zhang et al., 2007). A study examining the effect of FEWP on PSD is summarized in Table 18.6.11.1.

Table 18.6.11.1 Study Evaluating Herbal Medicine in the Treatment of Post-Stroke Depression

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design (PEDro Score)</th>
<th>Sample Size</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li et al. (2008)</td>
<td>RCT (8)</td>
<td>NStart=150 NEnd=146</td>
<td>E1: Free and Easy Wanderer Plus (36mg/d) E2: Fluoxetine (20-40mg/d) C: Placebo</td>
<td>• Hamilton Depression Rating Scale: E1, E2 vs C (+); E1 vs E2 (-)</td>
</tr>
</tbody>
</table>

- Indicates non-statistically significant differences between treatment groups

+ Indicates statistically significant differences between treatment groups

E indicates experimental group; C indicates control group

Discussion

In the sole study identified, FEWP was found to be as effective as fluoxetine in reducing depressive symptoms when initiated within the first six weeks of stroke onset; both treatments were more
effective than placebo. In addition, FEWP appeared to have a more rapid effect on depression than fluoxetine, with a response as early as two weeks into the eight-week trial. However, it should be noted that relatively little is known about the specific effects of each component in FEWP and how they might interact with other medications commonly prescribed to individuals post stroke (Davidson & Zhang, 2008).

Conclusions Regarding Herbal Medicine

There is Level 1b evidence that treatment with the herbal preparation, Free and Easy Wanderer Plus, is as effective as fluoxetine and more effective than placebo in reducing depressive symptoms post stroke.

Free and Easy Wanderer Plus, an herbal medicine, may be effective in the treatment of post-stroke depression.

18.6.12 Care Management
Care management programs have been developed to enhance outcomes of pharmacotherapy. In addition to the prescribed medications, these programs provide the patients with education, monitoring, and support. A study examining the impact of a care management intervention on the effectiveness of treatment for PSD is summarized in Table 18.6.12.1.

Table 18.6.12.1 Study Evaluating Care Management for Post-Stroke Depression

<table>
<thead>
<tr>
<th>Author, Year</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Williams et al.</em> (2007)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Design (PEDro Score)</th>
<th>Sample Size</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT (8)</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=188  N&lt;sub&gt;End&lt;/sub&gt;=182</td>
<td>E: Activate-Initiate-Monitor intervention C: Usual care</td>
<td>• Hamilton Depression Rating Scale (+)</td>
</tr>
</tbody>
</table>

- Indicates non-statistically significant differences between treatment groups
+ Indicates statistically significant differences between treatment groups
_E_ indicates experimental group; _C_ indicates control group

Discussion
The care management intervention implemented by Williams et al. (2007) was associated with significant improvement in depressive symptoms over the course of 12 weeks. This improvement was particularly notable in that the control group received antidepressants and an equal number of follow-ups as the intervention group.

Conclusions Regarding Care Management

There is Level 1b evidence that an active care management program enhances the effectiveness of pharmacologic treatment for post stroke depression.

Active care management of antidepressant therapy may improve response to treatment.
18.7 Pharmacologic Treatment of Post-Stroke Depression and Stroke Recovery

18.7.1 Stroke Recovery and Pharmacologic Treatment of Post-Stroke Depression

Given the negative impact that PSD may have on the rate of recovery and rehabilitation, there has been considerable interest in the effects of antidepressants and other psychoactive medications on functional outcomes following stroke. Several trials have examined these effects in individuals, with or without depression, using a variety of outcome measures. In a systematic review, Mead et al. (2013) analyzed the impact of SSRIs on recovery and disability. The authors found that SSRIs had a significant, large effect on reducing disability and improving neurological function. Studies examining the impact of pharmacotherapy for PSD on functional recovery are summarized in Table 18.7.1.1.

### Table 18.7.1.1 Studies Evaluating Stroke Recovery and Pharmacotherapy of Post-Stroke Depression

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design (PEDro Score)</th>
<th>Sample Size</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chollet et al. (2011)</td>
<td>RCT (9)</td>
<td>N_{Start}=118, N_{End}=113</td>
<td>E: Fluoxetine (20mg/d) C: Placebo</td>
<td>Fugl-Meyer Assessment (+) Modified Rankin Scale (+) NIH Stroke Scale (+)</td>
</tr>
<tr>
<td>Robinson et al. (2000)</td>
<td>RCT (8)</td>
<td>N_{Start}=104, N_{End}=83</td>
<td>E1: Nortriptyline (25-100mg/d) E2: Fluoxetine (10-40mg/d) C: Placebo</td>
<td>Functional Independence Measure: E1 vs E2, C (+) John Hopkins Functional Inventory (-) Mini Mental State Exam (-) Social Function Exam (-)</td>
</tr>
<tr>
<td>Wiart et al. (2000)</td>
<td>RCT (8)</td>
<td>N_{Start}=31, N_{End}=29</td>
<td>E: Fluoxetine (20mg/d) C: Placebo</td>
<td>Functional Independence Measure (-) Motricity Index (-) Mini Mental State Exam (-)</td>
</tr>
<tr>
<td>Gonzalez-Torrescillas et al. (1995)</td>
<td>RCT (7)</td>
<td>N_{Start}=130, N_{End}=125</td>
<td>E1: Nortriptyline (25-75mg/d) E2: Fluoxetine (20mg/d) C: No medication</td>
<td>Barthel Index: E1, E2 vs C (+) Karnofsky Performance Status: E1, E2 vs C (+) Orgogozo Scale: E1, E2 vs C (+) Mini Mental State Exam: E1, E2 vs C (+)</td>
</tr>
<tr>
<td>Dam et al. (1996)</td>
<td>RCT (7)</td>
<td>N_{Start}=52, N_{End}=46</td>
<td>E1: Fluoxetine (20mg/d) E2: Maprotiline (150mg/d) C: Placebo</td>
<td>Hemispheric Stroke Scale (-) Barthel Index: E1 vs E2 (+) Good outcome: E1 vs E2, C (+)</td>
</tr>
<tr>
<td>Grade et al. (1998)</td>
<td>RCT (7)</td>
<td>N_{Start}=21, N_{End}=19</td>
<td>E: Methylphenidate (30mg/d) C: Placebo</td>
<td>Functional Independence Measure (+) Fugl-Meyer Assessment (-)</td>
</tr>
<tr>
<td>Reding et al. (1986)</td>
<td>RCT (6)</td>
<td>N_{Start}=27, N_{End}=27</td>
<td>E: Trazodone (50-200mg/d) C: Placebo</td>
<td>Barthel Index (-)</td>
</tr>
<tr>
<td>Miyai &amp; Reding (1998)</td>
<td>RCT (6)</td>
<td>N_{Start}=24, N_{End}=18</td>
<td>E1: Desipramine (50-100mg/d) E2: Trazodone (50-100mg/d) E3: Fluoxetine (10-20mg/d)</td>
<td>Functional Independence Measure: E2, E3 vs E1 (+) Fugl-Meyer Assessment (-)</td>
</tr>
<tr>
<td>Study</td>
<td>Study Type</td>
<td>Start N</td>
<td>End N</td>
<td>E: Intervention</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------------</td>
<td>---------</td>
<td>-------</td>
<td>----------------</td>
</tr>
</tbody>
</table>
| Mikami et al. (2011)          | RCT (6)    | 104     | 61    | Nortriptyline (25-100mg/d) | Placebo         | Modified Rankin Scale: E1 vs C (+)  
Functional Independence Measure (-) |
| Raffaele et al. (1996)        | RCT (5)    | 22      | 22    | Trazodone (300mg/d) | Placebo         | Barthel Index (-)                                      |
| Bilge et al. (2008)           | PCT        | 59      | 59    | Depressed + Citalopram (20mg/d) | Non-Depressed + No medication | Barthel Index: Diagnosis (+), 3mo (+), 6mo (-)  
Rankin Scale: Diagnosis (+), 3mo (+), 6mo (-)  
Scandinavian Stroke Scale: Diagnosis (+), 3mo (+), 6mo (-) |
| Narushima et al. (2003)       | Cohort     | 251     | 251   | Depressed + Antidepressant | Non-Depressed + No medication | Mini Mental State Exam (+): Diagnosis (+), 3mo (-) |
| Siepmann et al. (2015)        | Cohort     | 239     | 239   | SSRIs pre stroke | SSRIs post stroke | Modified Rankin Scale (+)  
NIH Stroke Scale (+)  
Length of stay (+) |
| Gainotti et al. (2001)        | Cohort     | 64      | 64    | Depressed + Antidepressant | Depressed + No medication | Barthel Index (+)  
Rivermead Mobility Index (+)  
Canadian Neurological Scale (-) |

- Indicates non-statistically significant differences between treatment groups  
+ Indicates statistically significant differences between treatment groups  
E indicates experimental group; C indicates control group

**Discussion**

When compared to those without depression, depressed patients often demonstrate significantly poorer functional recovery post stroke (Bilge et al., 2008; Narushima et al., 2003). However, this disparity can be narrowed with antidepressants, such that patients with PSD achieved comparable recovery to non-depressed patients after three to six months of treatment (Bilge et al., 2008; Narushima et al., 2003). The timing of antidepressant treatment may also have an impact on post-stroke recovery. Siepmann et al. (2015) reported that patients whose treatment with SSRIs was initiated pre stroke demonstrated significantly greater functional and neurological recovery than those who received SSRIs only after stroke.

Upon examining only individuals with PSD, Gainotti (2001) found that patients taking antidepressants had significantly greater functional and neurological recovery over time than untreated patients. These findings were supported by several RCTs comparing various antidepressants to controls. Fluoxetine was found to be more effective than control conditions for improving functional and neurological recovery in four trials (Chollet et al., 2011; Dam et al., 1996; Gonzalez-Torrecillas et al., 1995; Mikami et al., 2011), and similarly effective in two trials (Robinson et al., 2000; Wiart et al., 2000). Nortriptyline, on the other hand, yielded significantly greater recovery than controls (e.g. fluoxetine, placebo, no medication) in all relevant trials (Gonzalez-Torrecillas et al., 1995; Mikami et al., 2011; Robinson et al., 2000). Overall, the RCTs provided antidepressants for one to three months, and initiated treatment within the first few months after stroke.
Trazodone, a heterocyclic antidepressant, was examined for its impact on recovery in two trials. The serotonin antagonist and reuptake inhibitor did not demonstrate an advantage over placebo in improvement on the Barthel Index (Raffaele et al., 1996; Reding et al., 1986). Two tricyclic antidepressants, maprotiline and desipramine, also failed to demonstrate significantly greater functional recovery than placebo and other antidepressants (Dam et al., 1996; Miyai & Reding, 1998). Methylphenidate, a psychostimulant, was also studied for its effects on depressive symptoms and functional outcomes. The authors reported that the drug showed significantly greater functional recovery, but not motor recovery, than placebo (Grade et al., 1998).

**Conclusions Regarding Stroke Recovery and Pharmacologic Treatment of Post-Stroke Depression**

*There is Level 1a evidence that antidepressants improve post-stroke functional recovery when compared to no medication.*

*There is Level 1a evidence that fluoxetine improves post-stroke functional recovery, but not cognitive or motor function, when compared to placebo.*

*There is Level 1a evidence that nortriptyline improves post-stroke functional recovery when compared to placebo.*

*There is Level 1a evidence that trazodone does not improve post-stroke functional recovery when compared to placebo.*

*There is Level 1b evidence that methylphenidate improves post-stroke functional recovery when compared to placebo.*

*There is Level 1b evidence that maprotiline does not improve post-stroke functional recovery when compared to placebo.*

*There is Level 1b evidence that desipramine does not improve post-stroke functional recovery when compared to fluoxetine or trazodone.*

*There is limited Level 2 evidence that selective serotonin reuptake inhibitors yield greater improvement in functional recovery when initiated pre stroke than post stroke.*

**Pharmacological treatment of post-stroke depression may also be effective in improving functional and neurological recovery. However, only some antidepressants have demonstrated efficacy.**

### 18.7.2 Mortality and Pharmacologic Treatment of Post-Stroke Depression

Depression is associated with an increased risk of mortality post stroke, especially within the first few years of onset (Bartoli et al., 2013; Morris et al., 1993a). As such, several studies have evaluated pharmacologic treatments for PSD in terms of their impact on mortality. A systematic review by Mead et al. (2013) found that SSRIs were associated with a 25% reduction in risk of mortality when compared to no such medications. Studies examining the impact of antidepressants on post-stroke mortality are summarized in Table 18.7.2.1.
Table 18.7.2.1 Studies Evaluating Mortality and Pharmacotherapy of Post-Stroke Depression

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design (PEDro Score)</th>
<th>Sample Size</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jorge et al. (2003)</td>
<td>RCT (7)</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=104 N&lt;sub&gt;End&lt;/sub&gt;=81</td>
<td>E1: Nortriptyline (25-100mg/d) E2: Fluoxetine (10-40mg/d) C: Placebo</td>
<td>• Mortality (+)</td>
</tr>
<tr>
<td>Mortensen et al. (2014)</td>
<td>Cohort</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=10208 N&lt;sub&gt;End&lt;/sub&gt;=10208</td>
<td>E: SSRI's pre stroke C: No SSRI's</td>
<td>• Mortality: Hemorrhagic (+), Ischemic (-)</td>
</tr>
<tr>
<td>Mortensen et al. (2015)</td>
<td>Cohort</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=5070 N&lt;sub&gt;End&lt;/sub&gt;=5070</td>
<td>E: Antidepressants post stroke C: No antidepressants</td>
<td>• Mortality (+)</td>
</tr>
<tr>
<td>Ayerbe et al. (2014b)</td>
<td>Cohort</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=1354 N&lt;sub&gt;End&lt;/sub&gt;=1354</td>
<td>E1: SSRI's pre stroke E2: SSRI's post stroke C: No SSRI's</td>
<td>• Mortality: E1 vs C (-), E2 vs C (+)</td>
</tr>
<tr>
<td>Ried et al. (2011)</td>
<td>Case Control</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=870 N&lt;sub&gt;End&lt;/sub&gt;=870</td>
<td>E1: SSRI's pre stroke E2: SSRI's post stroke C: No SSRI's</td>
<td>• Mortality: E1 vs C (+), E2 vs C (+)</td>
</tr>
</tbody>
</table>

- Indicates non-statistically significant differences between treatment groups
+ Indicates statistically significant differences between treatment groups
E indicates experimental group; C indicates control group

Discussion

A retrospective study by Ried et al. (2011) demonstrated that treatment with an SSRI prior to stroke was associated with an increased risk for mortality following stroke, when compared to no pre-stroke treatment. However, SSRI treatment initiated after stroke was found to be protective against mortality during the first year, when compared to no post-stroke treatment. After seven years following stroke, SSRIs were again associated with an increased risk of mortality.

Larger prospective studies have reported findings that both support and contradict those of the previous study. Based on data from the South London Stroke Register, Ayerbe et al. (2014b) found that pre-stroke SSRI treatment did not impact post-stroke mortality, but SSRIs were associated with a significantly higher mortality rate when initiated post stroke. Using the Danish Stroke Registry, Mortensen et al. (2014) reported that pre-stroke SSRI treatment was associated with higher mortality rate in only hemorrhagic strokes, perhaps due to increased risk of intracranial bleeding with SSRIs. As well, pre-stroke SSRIs were found to reduce risk of myocardial infarction and recurrent ischemic stroke.

Antidepressants, in general, have been associated with significantly lower short-term mortality when initiated early after stroke, which remained significant across stroke severities (Mortensen et al., 2015). An RCT by Jorge et al. (2003) examined the effects of nortriptyline or fluoxetine on mortality in comparison to placebo. The trial found that antidepressants may have a prolonged, protective effect on post-stroke mortality, even when delivered over shorter treatment periods (Jorge et al., 2003). The association between antidepressant treatment and improved survival was demonstrated in all patients, regardless of depression diagnosis.
Conclusions Regarding Mortality and Pharmacologic Treatment of Post-Stroke Depression

There is Level 1b evidence that early treatment with nortriptyline or fluoxetine is associated with improved long-term survival post stroke when compared to placebo.

There is Level 2 evidence that antidepressants are associated with improved short-term survival post stroke when compared to no medications.

There is conflicting Level 2 evidence regarding the effect of selective serotonin reuptake inhibitors, initiated before or after stroke, on post-stroke mortality.

Early treatment with antidepressants may improve long-term survival post stroke, although further research is required.

18.8 Non-Pharmacologic Treatment of Post-Stroke Depression

18.8.1 Cognitive-Behavioural Interventions
Cognitive behavioural therapy (CBT) is an active, directive, structured intervention for numerous psychological disorders. The approach is based on the notion that emotion and behaviour are determined by experience. Accordingly, CBT concentrates on altering and restructuring the individual’s interaction with their environment and their interpretation of their experiences. Therapy tools include behavioural tests, graded task assignments, and scheduling of activities (Lincoln et al., 1997). Other cognitive-behavioural interventions are rooted in the same theory and utilize a similar approach as CBT. Individual studies examining the use of these interventions in the treatment of PSD are summarized in Table 18.8.1.1.

Table 18.8.1.1 Studies Evaluating Cognitive-Behavioural Interventions for Post-Stroke Depression

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design (PEDro Score)</th>
<th>Sample Size</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Visser et al. (2016) | RCT (7) | N\textsubscript{Start}=166 N\textsubscript{End}=151 | E: Problem-solving therapy  
C: Usual care | • CES Depression Scale (-) |
| Lincoln et al. (2003) | RCT (7) | N\textsubscript{Start}=123 N\textsubscript{End}=111 | E: Cognitive behavioural therapy  
C1: Attention placebo  
C2: Usual care | • Beck Depression Inventory (-)  
• Wakefield Depression Inventory (-) |
| Thomas et al. (2013) | RCT (7) | N\textsubscript{Start}=105 N\textsubscript{End}=89 | E: Behavioural therapy (aphasic)  
C: Usual care | • Stroke Aphasic Depression Questionnaire (+) |
| Chang et al. (2011) | RCT (7) | N\textsubscript{Start}=77 N\textsubscript{End}=66 | E: Knowledge & behaviour therapy  
C: Usual care | • Hamilton Depression Rating Scale (+) |
| Hadidi et al. (2015) | | | E: Problem-solving therapy | • CES Depression Scale (-) |
RCT (7)
N\textsubscript{Start}=22
N\textsubscript{End}=22

<table>
<thead>
<tr>
<th>Hoffmann et al., (2015)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E1: Coping skills therapy</td>
</tr>
<tr>
<td>E2: Self-management</td>
</tr>
<tr>
<td>C: Usual care</td>
</tr>
</tbody>
</table>

- Hospital Anxiety Depression Scale (-)
- Montgomery-Asberg Depression Rating Scale (-)

Discussion

Conventional CBT for PSD was evaluated in an early pre-post test. Lincoln et al. (1997) reported that CBT was associated with a significant reduction in depression scores. However, a subsequent RCT by the authors found that CBT was no more effective than attention placebo or usual care in treating depression (Lincoln & Flannaghan, 2003).

Later trials of CBT-based interventions provided conflicting results. Knowledge and behaviour therapy was found to significantly reduce depressive symptoms (Chang et al., 2011), while coping skills therapy was no more effective than self-management training or usual care (Hoffmann et al., 2015). The former trial also found significant improvements in anger, independence, and QOL with CBT when compared to usual care (Chang et al., 2011). Problem-solving therapy (PST) was evaluated in two trials, although neither targeted depression as a primary outcome. Both trials found that PST was no more effective than placebo in reducing depressive symptoms (Hadidi et al., 2015; Visser et al., 2016). However, PST was associated with significant improvements in coping and quality of life in the latter trial (Visser et al., 2016).

Modified forms of CBT have been developed to address practical challenges and provide potential improvements. The Communication and Low Mood (CALM) program was developed for individuals with post-stroke aphasia, who may have difficulty with some aspects of traditional CBT. In an RCT, CALM was reportedly more effective than usual care in reducing depressive symptoms and improving self-esteem long term (Thomas et al., 2013); it was also found to be more cost effective (Humphreys et al., 2015). The Brainstorm program was developed to provide CBT to individuals with PSD, as well as their caregivers, in a group setting. A pre-post test found the intervention to be effective in reducing symptoms of depression and anxiety, although neither improvement was maintained at long-term follow-up (Ward et al., 2016).

Conclusions Regarding Cognitive Behavioural Interventions

**There is conflicting Level 1a evidence as to whether cognitive behavioral therapy reduces depressive symptoms post stroke when compared to attention placebo or usual care.**

**There is Level 1a evidence that problem-solving therapy is does not reduce depressive symptoms post stroke when compared to usual care.**

**There is Level 1b evidence that aphasic behavioural therapy reduces depressive symptoms post stroke when compared to usual care.**
There is Level 4 evidence that group-based cognitive behavioural therapy reduces depressive symptoms post stroke in the short term.

There are conflicting findings regarding the effectiveness of cognitive-behavioural interventions in treating post-stroke depression.

18.8.1.1 Combined Therapy
While psychotherapeutic interventions have been successful in the treatment of other forms of depression, there is less robust evidence to support their use in the treatment of PSD (Hackett et al. 2008). Supplementation of antidepressants with therapy intended to change the behaviours associated with depression may result in a more effective intervention (Joubert et al., 2008). A study examining the use of antidepressants in combination with a psychotherapeutic intervention is summarized in Table 18.9.1.1.1.

Table 18.9.1.1.1 Studies Evaluating Combined Therapy for Post-Stroke Depression

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design (PEDro Score)</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitchell et al. (2009) RCT (7)</td>
<td>NStart=101 NEnd=92</td>
<td>E: Psychosocial-behavioural intervention + Antidepressants C: Usual care + Antidepressants</td>
<td>• Hamilton Depression Rating Scale (+)</td>
</tr>
</tbody>
</table>

- Indicates non-statistically significant differences between treatment groups
+ Indicates statistically significant differences between treatment groups
E indicates experimental group; C indicates control group

Discussion
In a single trial, Mitchell et al. (2009) found that combining psychosocial-behavioral therapy with antidepressants significantly reduced depressive symptoms relative to the pharmacological treatment alone. This effect was found immediately after 8 weeks of treatment, and was also maintained up to 12 months after the intervention period ended.

Conclusions Regarding Combined Therapy

There is Level 1b evidence that psychosocial-behavioural therapy in combination with antidepressants is more effective than antidepressants alone in reducing depressive symptoms post stroke.

Psychosocial-behavioural therapy may be an effective adjunct to treatment of post-stroke depression with antidepressants, although further research is required.

18.8.2 Supportive Interventions
Much of stroke rehabilitation is focused on facilitating reintegration into the community and supporting adaptation to a new lifestyle. Interventions that provide such facilitation and support often involve multiple components such as care planning, goal setting, self-management training, environmental adaptations, and caregiver/family education. These interventions may also have a positive impact on mood and other psychosocial outcomes. Studies examining the effectiveness of supportive interventions in the treatment of PSD are summarized in Table 18.8.2.1.
Table 18.8.2.1 Studies Evaluating Supportive Interventions for Post-Stroke Depression

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design (PEDro Score)</th>
<th>Sample Size</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graven et al. (2016)</td>
<td>RCT (10)</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=110, N&lt;sub&gt;End&lt;/sub&gt;=94</td>
<td>E: Goal setting program&lt;br&gt;C: Standard care</td>
<td>• Geriatric Depression Scale (+)</td>
</tr>
<tr>
<td>Sackley et al. (2015)</td>
<td>RCT (9)</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=1042, N&lt;sub&gt;End&lt;/sub&gt;=1003</td>
<td>E: Customized care program&lt;br&gt;C: Standard care</td>
<td>• Geriatric Depression Scale (-)</td>
</tr>
<tr>
<td>Wong et al. (2015)</td>
<td>RCT (8)</td>
<td>N=108, N&lt;sub&gt;Start&lt;/sub&gt;=108, N&lt;sub&gt;End&lt;/sub&gt;=99</td>
<td>E: Transitional care program&lt;br&gt;C: Standard care</td>
<td>• CES Depression Scale (+)</td>
</tr>
<tr>
<td>Jones et al. (2016)</td>
<td>RCT (6)</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=78, N&lt;sub&gt;End&lt;/sub&gt;=66</td>
<td>E: Self-management program&lt;br&gt;C: Standard care</td>
<td>• Hospital &amp; Anxiety Depression Scale (-)</td>
</tr>
<tr>
<td>Alexopoulos et al. (2012)</td>
<td>RCT (6)</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=24, N&lt;sub&gt;End&lt;/sub&gt;=24</td>
<td>E: Ecosystem focused therapy&lt;br&gt;C: Education program</td>
<td>• Hamilton Depression Rating Scale (-)</td>
</tr>
</tbody>
</table>

- Indicates non-statistically significant differences between treatment groups
+ Indicates statistically significant differences between treatment groups
E indicates experimental group; C indicates control group

Discussion

Ecosystem focused therapy (EFT) was developed for the treatment of PSD in a community setting. It was based on the concept of stroke as a “catastrophic” event separating an individual from their usual competencies (Alexopoulos et al., 2012). EFT focused on assisting the patient with treatment adherence, problem solving, goal setting, and care coordination. In an RCT, EFT was compared to an educational program, both provided in weekly sessions over three months. Although the patients receiving EFT had lower depression scores than the control intervention, and a greater proportion of them were in remission, these differences were not statistically significant (Alexopoulos et al., 2012).

Other psychosocial interventions for individuals living the community post stroke have been investigated for their impact on PSD. Jones et al. (2016) developed a self-management program that integrated self-efficacy training into scheduled rehabilitation sessions. Sackley et al. (2015) provided customized occupational therapy involving task training, goal setting, environmental adaptations, and caregiver education. Both trials reported the intervention was no more effective than standard care in reduce depressive symptoms. However, it should be noted that neither intervention was developed to target mood.

Programs provided to patients upon discharge from rehabilitation in order to assist them with their transition may also be beneficial in terms of psychosocial outcomes. Wong et al. (2015) investigated the effectiveness of a four-week transitional care program in improving mood, independence, and quality of
life; the program provided care planning with regular follow-ups. When compared to standard care, the program resulted in significantly greater improvement on all outcomes. Graven et al. (2016) developed a specialized program for PSD, which utilized an integrated, multimodal approach to collaborative goal setting (e.g. meetings, referrals, education). The authors reported that the program effectively reduced depressive symptoms for up to 12 months relative to standard care.

Conclusions Regarding Supportive Interventions

There is Level 1b evidence that a goal achievement program reduces depressive symptoms post stroke when compared to standard care.

There is Level 1b evidence that a transitional care program reduces depressive symptoms post stroke when compared to standard care.

There is Level 1b evidence that a self-management program does not reduce depressive symptoms post stroke when compared to standard care.

There is Level 1b evidence that customized occupational therapy does not reduce depressive symptoms post stroke when compared to standard care.

There is Level 1b evidence that ecosystem focused therapy does not reduce depressive symptoms post stroke when compared to an education program.

There are conflicting findings regarding the effectiveness of supportive interventions (e.g. transitional, integrated, or customized care) in treating post-stroke depression.

18.8.3 Music Therapy

The use of music therapy in the treatment of physical, cognitive, communicative, social, and emotional rehabilitation has gained attention in recent years. Music therapy builds a relationship between the therapist and patients through the use of music, instruments, and voice. Marwick (1996) reported that the use of music therapy in stroke rehabilitation might improve behaviour, communication, and psychological state based on limited observations. Studies examining the effectiveness of music therapy in the treatment of PSD are summarized in Table 18.8.3.1.

Table 18.8.3.1 Studies Evaluating Music Therapy for Post-Stroke Depression

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design (PEDro Score)</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarkamo et al. (2008) RCT (6) NStart=60 NEnd=55</td>
<td>E1: Music-listening therapy E2: Language-listening therapy C: Usual care</td>
<td>• Profile of Mood States – Depression: E1 vs E2, C (+)</td>
<td></td>
</tr>
<tr>
<td>Jun et al. (2013) RCT (4) NStart=40 NEnd=30</td>
<td>E: Music-movement therapy C: Usual care</td>
<td>• CES Depression Scale (-)</td>
<td></td>
</tr>
<tr>
<td>Purdie et al. (1997)</td>
<td>E: Music therapy (12 sessions)</td>
<td>• Hospital Anxiety &amp; Depression Scale (*)</td>
<td></td>
</tr>
</tbody>
</table>
Discussion

Three non-randomized controlled trials provided music therapy in weekly sessions (i.e. 30-60 minutes) over an extended period of time (i.e. 4-12 weeks). Therapy was delivered in a treatment setting by specialized therapists with an explicit treatment plan. In two trials, music therapy demonstrated greater reductions in depressive symptoms than usual care, but neither trial reported between-group statistical comparisons (Kim et al., 2011; Purdie et al., 1997). Another trial found no significant differences between music therapy and usual care in improvements to mood (Nayak et al., 2000).

Given the specificity of traditional music therapy, other methods have been developed for different applications. Music-movement therapy, as per an RCT by Jun et al. (2013), involved a combination of musical listening and complementary physical activity. While the intervention yielded a significant improvement in mood when compared to standard care, there was no significant reduction in depressive symptoms. In a higher quality RCT, Sarkamo et al. (2008) examined the effects of daily listening to self-selected music. Individuals who received music-listening therapy had significantly greater improvement in mood and reduction in depressive symptoms than those listening to audio books or receiving usual care. Unlike the intensive music-movement therapy, passive music listening demonstrated a beneficial effect for PSD.

Conclusions Regarding Music Therapy

There is Level 2 evidence that music therapy does not reduce depressive symptoms post stroke when compared to usual care.

There is limited Level 2 evidence that music-listening therapy improves mood post stroke when compared to language-listening therapy and usual care.

There is limited Level 2 evidence that music-movement therapy does not reduce depressive symptoms post stroke when compared to usual care.

There are conflicting findings regarding the effectiveness of music therapy in treating post-stroke depression.
18.8.4 Art Therapy

Art therapy emerged from the combination of visual arts and psychotherapy. Creative expression is believed to help individuals with various psychosocial outcomes such as achieving goals, solving problems, and addressing trauma. Systematic reviews have art therapy for dementia (Beard, 2011), schizophrenia (Ruddy & Milnes, 2005), post-traumatic stress (Schouten et al., 2015), and various mental health disorders (Maujean et al., 2014; Uttley et al., 2015). While these reviews generally supported the clinical effectiveness of art therapy, these findings were often based on few low-quality studies. A single study examining the effectiveness of art therapy in the treatment of PSD is summarized in Table 18.8.4.1.

Table 18.8.4.1 Studies Evaluating Art Therapy for Post-Stroke Depression

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design (PEDro Score)</th>
<th>Sample Size</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kongkasuwan et al. (2016)</td>
<td>RCT (7)</td>
<td>N Start=118 N End=113</td>
<td>E: Art therapy C: Standard care</td>
<td>Hospital Anxiety &amp; Depression Scale (+)</td>
</tr>
</tbody>
</table>

- Indicates non-statistically significant differences between treatment groups
+ Indicates statistically significant differences between treatment groups
E indicates experimental group; C indicates control group

Discussion

There is limited evidence regarding art therapy for post-stroke mood disturbances. In a pilot pre-post test, Ali et al. (2014) demonstrated that both depression and anxiety scores were reduced following six weeks of biweekly art therapy. More recently, an RCT by Kongkasuwan et al. (2016) compared standard care to four weeks of biweekly art therapy, with the goal of enhancing rehabilitation outcomes. Art therapy was associated with significant reductions in symptoms of depression and anxiety, as well as improved quality of life.

Conclusions Regarding Art Therapy

There is Level 1b evidence that art therapy reduces depressive symptoms post stroke when compared to standard care.

Further research is required to determine the effectiveness of art therapy in treating post-stroke depression.

18.8.5 Relaxation Therapy

Relaxation therapy promotes a physical and psychological state that relieves stress and promotes tranquility. Techniques for relaxation include mindfulness, visualization, deep breathing, transcendental meditation, autogenic training, and yoga. In a systematic review and meta-analysis, Manzoni et al. (2008) found that relaxation therapies were effective in reducing levels of anxiety.

Discussion

The evidence for relaxation therapies in individuals post stroke is fairly limited. Kneebone et al. (2014) investigated the effects of autogenic relaxation, where participants silently repeated statements regarding their hemiplegic limb (e.g. “my right arm is very heavy”). Results revealed a significant
reduction in self-reported tension, but its effects on depressive symptoms were not studied. In another pre-post test, Marshall et al. (2014) delivered deep unilateral nostril breathing, where participants breathed through only one nostril at a time. While the intervention demonstrated short-term reductions in anxiety, it did not have a significant impact on depressive symptoms.

**Conclusions Regarding Relaxation Therapy**

*There is limited Level 4 evidence that deep unilateral nostril breathing does not reduce depressive symptoms post stroke.*

*There is limited Level 4 evidence that autogenic training reduces psychological tension post stroke.*

**Further research is required to determine the effectiveness of relaxation therapies in treating post-stroke depression.**

### 18.8.6 Physical Activity

The neurophysiological impact of physical activity on mood states has long been established in the general population (Byrne & Byrne, 1993). In a systematic review, Eng and Reime (2014) examined 13 trials comparing exercise (e.g. resistance, aerobic, Bobath) and control conditions (e.g. passive activity, usual care) in terms of their effectiveness in reducing depressive symptoms post stroke. Exercise programs in these trials provided training by a therapist twice a week for four to twelve weeks. The authors reported that exercise was associated with a small, significant treatment effect upon program completion, but the effect was not maintained at long-term follow-up. Studies examining the impact of exercise programs on PSD are summarized in Table 18.8.6.1.

**Table 18.8.6.1 Studies Evaluating the Impact of Physical Activity on Post-Stroke Depression**

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design (PEDro Score)</th>
<th>Sample Size</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Van de Port et al.</strong> (2012) RCT (8)</td>
<td>N_{Start}=250 N_{End}=242</td>
<td>E: Circuit training (24wk) C: Usual care</td>
<td>• Hospital Anxiety &amp; Depression Scale (-)</td>
<td></td>
</tr>
<tr>
<td><strong>Lai et al.</strong> (2006) RCT (8)</td>
<td>N_{Start}=100 N_{End}=80</td>
<td>E: Specialized exercise program (12wk) C: Usual care</td>
<td>• Geriatric Depression Scale (+)</td>
<td></td>
</tr>
<tr>
<td><strong>Mead et al.</strong> (2007) RCT (8)</td>
<td>N_{Start}=66 N_{End}=62</td>
<td>E: Resistance training (12wk) C: Relaxation training</td>
<td>• Hospital Anxiety &amp; Depression Scale (-)</td>
<td></td>
</tr>
<tr>
<td><strong>Linder et al.</strong> (2015) RCT (8)</td>
<td>N_{Start}=99 N_{End}=91</td>
<td>E: Exercise program + Robotic device (8wk) C: Exercise program</td>
<td>• CES Depression Scale (-)</td>
<td></td>
</tr>
<tr>
<td><strong>Harrington et al.</strong> (2010) RCT (7)</td>
<td>N_{Start}=243 N_{End}=228</td>
<td>E: Group exercise program (8wk) C: Usual care</td>
<td>• Hospital Anxiety &amp; Depression Scale (-)</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Study Design</td>
<td>N Start</td>
<td>N End</td>
<td>Intervention</td>
</tr>
<tr>
<td>------------------------</td>
<td>--------------</td>
<td>---------</td>
<td>-------</td>
<td>--------------</td>
</tr>
<tr>
<td>Lennon et al. (2008)</td>
<td>RCT (7)</td>
<td>48</td>
<td>46</td>
<td>E: Aerobic training (10wk)</td>
</tr>
<tr>
<td>Sims et al. (2009)</td>
<td>RCT (7)</td>
<td>45</td>
<td>43</td>
<td>E: Resistance training (10wk)</td>
</tr>
<tr>
<td>Immink et al. (2014)</td>
<td>RCT (7)</td>
<td>25</td>
<td>22</td>
<td>E: Yoga (10wk)</td>
</tr>
<tr>
<td>Topcuoglu et al. (2015)</td>
<td>RCT (6)</td>
<td>52</td>
<td>40</td>
<td>E: Aerobic training (4wk)</td>
</tr>
<tr>
<td>Brittle et al. (2009)</td>
<td>RCT (5)</td>
<td>56</td>
<td>46</td>
<td>E: Group exercise program (5wk)</td>
</tr>
<tr>
<td>Song &amp; Park (2015)</td>
<td>RCT (5)</td>
<td>40</td>
<td>40</td>
<td>E: Aerobic training + Virtual reality (8wk)</td>
</tr>
<tr>
<td>Park et al. (2015)</td>
<td>RCT (4)</td>
<td>30</td>
<td>23</td>
<td>E: Group task-oriented circuit training (6wk)</td>
</tr>
<tr>
<td>Taricco et al. (2014)</td>
<td>PCT</td>
<td>229</td>
<td>199</td>
<td>E: Adaptive physical activity program (8wk)</td>
</tr>
<tr>
<td>Stuart et al. (2009)</td>
<td>PCT</td>
<td>93</td>
<td>78</td>
<td>E: Adaptive physical activity program (12wk)</td>
</tr>
<tr>
<td>Baek et al. (2014)</td>
<td>PCT</td>
<td>40</td>
<td>40</td>
<td>E: Circuit training (8wk)</td>
</tr>
<tr>
<td>Calabro et al. (2015)</td>
<td>PCT</td>
<td>30</td>
<td>29</td>
<td>E: Gait training + Robotic device (8wk)</td>
</tr>
<tr>
<td>Smith &amp; Thompson (2008)</td>
<td>PCT</td>
<td>20</td>
<td>20</td>
<td>E: Aerobic training (4wk)</td>
</tr>
<tr>
<td>McDonnell et al. (2014)</td>
<td>Cohort</td>
<td>40</td>
<td></td>
<td>E: Group exercise program (12wk)</td>
</tr>
</tbody>
</table>
Discussion

Aerobic exercise depends on the aerobic energy-generating process and is utilized to improve cardiovascular fitness. Two trials found that four weeks of aerobic training was associated with a significant reduction in depressive symptoms compared to standard care (Lennon et al., 2008; Smith & Thompson, 2008; Topcuoglu et al., 2015). However, a higher quality trial reported that a ten-week aerobic training program was no more effective in treating PSD than standard care (Lennon et al., 2008). Exercises of lower intensity and impact, such as yoga, have also been investigated for their effect on mood. After a ten-week yoga program, participants’ symptoms of depression and anxiety no different than those on a waitlist (Immink et al., 2014).

Resistance training causes muscles to contract against external force and is utilized to increase strength, tone, mass, and/or endurance. Two trials found that resistance training had no impact on depressive symptoms (Mead et al., 2007; Sims et al., 2009). Circuit training is a combination of high-intensity aerobic and resistance exercises in order to build endurance. While one non-randomized trial reported eight weeks of circuit training as superior to conventional exercise in treating depressive symptoms (Baek et al., 2014), a high-quality RCT found long-term circuit training no more effective than standard care (van de Port et al., 2012). Circuit training may be more effective in targeting depression when delivered in a communal setting (Y. Park et al., 2015).

Exercise programs can be delivered one-on-one or in a group setting. Some trials have found group programs to be effective in reducing depressive symptoms (Macko et al., 2008), even more so than individual exercise (Y. Park et al., 2015) or usual care (McDonnell et al., 2014; Stuart et al., 2009), while other similar trials did not find them to be beneficial (Batcho et al., 2013; Brittle et al., 2009; Calugi et al., 2016; Harrington et al., 2010; Taricco et al., 2014). Exercise programs can also be enhanced or augmented with technological devices. In a home exercise program, the addition of a robotic device demonstrated no impact on PSD (Linder et al., 2015). However, in an aerobic exercise program, participants using virtual reality showed greater reductions in depressive symptoms that those using a conventional ergometer (Song & Park, 2015).

In a specialized exercise program for individuals living at home after stroke, Lai et al. (2006) targeted strength, endurance, flexibility, balance, and motor function. After 3 months, participants in the program had significantly lower depressive symptoms than those who received standard care. An adaptive physical activity program developed by Stuart et al. (2009) was similar to the previous program but was delivered in a group setting within the community. Compared to individuals receiving only standard care, program participants demonstrated significant reductions in depressive symptoms after three months. However, an eight-week adaptive physical activity program by Taricco et al. (2014) was not associated with improved depression after treatment or at one-year follow-up (Calugi et al., 2016).

Conclusions Regarding Physical Activity

There is Level 1a evidence that resistance training does not reduce depressive symptoms post stroke when compared to relaxation training or usual care.
There is Level 1b evidence that a specialized, therapeutic exercise program reduces depressive symptoms post stroke when compared to usual care.

There is Level 1b evidence that yoga does not reduce depressive symptoms post stroke when compared to usual care.

There is conflicting Level 1b and Level 2 evidence as to whether aerobic exercise reduces depressive symptoms post stroke when compared to usual care.

There is conflicting Level 1b and Level 2 evidence as to whether circuit training reduces depressive symptoms post stroke when compared to basic exercise or usual care.

There is conflicting Level 1b and Level 2 evidence as to whether exercise with technological enhancements reduce depressive symptoms post stroke when compared to standard exercise.

There is conflicting Level 1b, Level 2, and Level 4 evidence as to whether group exercise programs reduce depressive symptoms post stroke when compared to individual exercise or usual care.

There is conflicting Level 2 evidence as to whether an adaptive physical activity program reduces depressive symptoms post stroke when compared to usual care.

There are conflicting findings regarding the impact of physical activity on post-stroke depression.

18.8.7 Speech Therapy

The counselling role of speech therapists is thought to help patients adapt to their communication disturbances and better express their needs, which in return may alleviate emotional problems (Lincoln et al. 1985). In fact, participants in a community-based speech therapy program demonstrated improved psychological wellbeing (Hoen et al., 1997). Studies examining the impact of speech therapy on PSD are summarized in Table 18.8.7.1.

Table 18.8.7.1 Studies Evaluating the Impact of Speech Therapy on Post-Stroke Depression

<table>
<thead>
<tr>
<th>Author, Year Study Design (PEDro Score) Sample Size</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lincoln et al. (1985) RCT (5) N_{Start}=168 N_{End}=149</td>
<td>E: Speech therapy C: Usual care</td>
<td>• MAACL Depression (-)</td>
</tr>
<tr>
<td>Konecny et al. (2014) RCT (4) N_{Start}=99 N_{End}=99</td>
<td>E: Speech therapy + Orofacial therapy C: Speech therapy</td>
<td>• Beck Depression Inventory (+)</td>
</tr>
</tbody>
</table>

- Indicates non-statistically significant differences between treatment groups
+ Indicates statistically significant differences between treatment groups
E indicates experimental group; C indicates control group

Discussion
Two RCTs that provided speech therapy and evaluated depression outcomes were identified. In an early trial, Lincoln et al. (1985) found no psychosocial benefits (i.e. depression, anxiety, hostility) from speech therapy in aphasic patients. More recently, Konecny et al. (2014) investigated orofacial therapy targeting oral spasticity to improve communication in addition to traditional speech therapy. The authors reported that the combined intervention significantly reduced depression symptoms compared to those receiving only speech therapy.

**Conclusions Regarding Speech Therapy**

*There is Level 1b evidence that speech therapy does not reduce depressive symptoms post stroke when compared to standard care.*

*There is Level 1b evidence that combined speech and orofacial therapies are more effective in reducing depressive symptoms post stroke than speech therapy alone.*

**Speech therapy may not have a significant impact on post-stroke depression, although further research is required.**

### 18.8.8 Hyperbaric Oxygen Therapy

Hyperbaric oxygen therapy (HBOT) administers patients with 100% oxygen at high atmospheric pressure in an isolated treatment chamber. While it is an established treatment for medical conditions, such as decompression illness and carbon monoxide poisoning, it has been suggested that HBOT may treat certain mental health issues. Studies examining the effectiveness of HBOT in the treatment of PSD are summarized in Table 18.8.8.1.

#### Table 18.8.8.1 Studies Evaluating Hyperbaric Oxygen Therapy for Post-Stroke Depression

<table>
<thead>
<tr>
<th>Author, Year Study Design (PEDro Score) Sample Size</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Yan et al. (2015)</strong>&lt;br&gt;China RCT (6)&lt;br&gt;N&lt;sub&gt;Start&lt;/sub&gt;=90&lt;br&gt;N&lt;sub&gt;End&lt;/sub&gt;=90</td>
<td>E1: HBOT + Fluoxetine (20mg/d)&lt;br&gt;E2: Fluoxetine (20mg/d)&lt;br&gt;E3: HBOT</td>
<td>• Hamilton Depression Rating Scale:&lt;br&gt; E1 vs E2, E3 (+)</td>
</tr>
<tr>
<td><strong>Cao et al. (2013)</strong>&lt;br&gt;RCT (6)&lt;br&gt;N&lt;sub&gt;Start&lt;/sub&gt;=60&lt;br&gt;N&lt;sub&gt;End&lt;/sub&gt;=60</td>
<td>E: HBOT (45min/d) + Dexamethasone (5mg/d)&lt;br&gt;C: Deanxit (10mg/d)</td>
<td>• Hamilton Depression Rating Scale (+)</td>
</tr>
</tbody>
</table>

- Indicates non-statistically significant differences between treatment groups
+ Indicates statistically significant differences between treatment groups
E indicates experimental group; C indicates control group

**Discussion**

In an RCT, Cao et al. (2013) compared HBOT to an antidepressant-antipsychotic medication over the course of a month. The authors reported that HBOT was more effective in reducing depressive symptoms than the pharmacologic treatment. An RCT by Yan et al. (2015) compared a regimen of HBOT and fluoxetine to treatment with only HBOT or fluoxetine. The combined treatment was more effective in treating PSD than the individual treatments. However, direct comparisons between HBOT and fluoxetine were not reported.
Conclusions Regarding Adjunctive Hyperbaric Oxygen Therapy

There is Level 1b evidence that hyperbaric oxygen therapy with fluoxetine reduces depressive symptoms post stroke when compared to either intervention alone.

There is Level 1b evidence that hyperbaric oxygen therapy reduces depressive symptoms post stroke when compared to the psychoactive medication Deanxit.

Hyperbaric oxygen therapy may be an effective adjunctive treatment for post-stroke depression, although further research is required.

18.8.9 Electroconvulsive Therapy
Electroconvulsive therapy (ECT) is a psychiatric treatment that delivers electrically-induced seizures. It is an older intervention used to treat major depressive disorder, schizophrenia, and mania. It has traditionally been considered effective (Janicak et al., 2002), although notable cognitive side effects have been reported (Kellner et al., 2010).

Discussion
Currently, there are no prospective studies evaluating the use of ECT in individuals post stroke. Two retrospective studies (Currier et al., 1992; Murray et al., 1986) suggested that ECT was a relatively safe and effective treatment for PSD. However, one of the studies reported that patients were at risk for relapse following ECT, despite good initial responses and maintenance therapy with antidepressant medications (Currier et al., 1992).

Conclusions Regarding Electroconvulsive Therapy

There is limited Level 4 evidence that electroconvulsive therapy (ECT) reduces depressive symptoms post stroke.

Further research is required to determine the effectiveness of electroconvulsive therapy (ECT) in treating post-stroke depression.

18.8.10 Repetitive Transcranial Magnetic Stimulation
Repetitive transcranial magnetic stimulation (rTMS) applies a magnetic field to the head, inducing an electric current at the brain and delivering a series of magnetic pulses. Initially developed as an alternative non-invasive stimulation treatment for disorders of the CNS, it has since been shown effectiveness as a treatment for major depressive disorder (Grunhaus et al., 2003; Janicak et al., 2002) and treatment-resistant depression (George & Post, 2011; Loo et al., 2003).

In a recent systematic review, McIntyre et al. (2016) evaluated rTMS for the treatment of depression due to cerebrovascular disease (i.e. vascular depression and PSD). The authors reported that active rTMS demonstrated a greater decrease in depressive symptoms than sham stimulation. rTMS was also associated with greater rates of response and remission, without any significant side effects or adverse events. Studies examining the effectiveness of rTMS in treating PSD are summarized in Table 18.8.10.1.

Table 18.8.10.1 Summary of Studies Evaluating rTMS in the Treatment of Post-Stroke Depression
### Discussion

Two high-quality RCTs found that higher-frequency rTMS (10Hz) was associated with significant reductions in depressive symptoms when compared to sham stimulation (Jorge et al., 2004; Kim et al., 2010) or lower-frequency rTMS (Kim et al., 2010). One trial included individuals with PSD resistant to antidepressants (Jorge et al., 2004), while the other trial included individuals without a formal diagnosis of depression (Kim et al., 2010). Neither study reported severe side effects or adverse events associated with rTMS. Given the small sample sizes, future research of rTMS for PSD should focus on large, multicentre RCTs.

### Conclusions Regarding Repetitive Transcranial Magnetic Stimulation

There is Level 1a evidence that repetitive transcranial magnetic stimulation (rTMS) reduces depressive symptoms post stroke.

**Repetitive transcranial magnetic stimulation (rTMS) may be an effective treatment for post-stroke depression.**

### 18.8.11 Transcranial Direct Current Stimulation

Transcranial direct current stimulation (tDCS) delivers a constant, low electrical current to the scalp, which can either excite (anodal tDCS) or attenuate (cathodal tDCS) neuronal activity. It is a relatively newer form of non-invasive stimulation that has demonstrated efficacy and tolerability in treating major depressive episodes (Meron et al., 2015; Shiozawa et al., 2014).

Discussion

A single study examining the effect of tDCS on PSD was identified. Valiengo et al. (2016) delivered daily tDCS (2mA) for ten days, with an additional session at four and six weeks. The authors reported that depression scores significantly decreased over time on two different scales.

### Conclusions Regarding Transcranial Direct Current Stimulation

There is limited Level 4 evidence that transcranial direct current stimulation (tDCS) reduces depressive symptoms post stroke.
Further research is required to determine the effectiveness of transcranial direct current stimulation (tDCS) in treating post-stroke depression.

### 18.8.12 Acupuncture

Acupuncture is a form of traditional Chinese medicine that has been used to treat musculoskeletal issues and relieve various types of pain. It is based upon a theoretical network of channels (“meridians”) that are connected to different body parts and through which life-energy (“chi”) is believed to flow. Practitioners insert needles into specific places in the body (“acupoints”) in order to manipulate the meridian system. While it is often considered part of complementary and alternative medicine, acupuncture has more recently become integrated into mainstream biomedicine.

A systematic review by Chan et al. (2015) found that acupuncture in combination with antidepressant medications was an effective and safe treatment for depression. In a stroke-specific review, Yang et al. (2016) reported that acupuncture was associated with a large, significant effect in reducing depressive symptoms. Studies examining the effectiveness of acupuncture in treating PSD are summarized in Table 18.8.12.1.

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design (PEDro Score)</th>
<th>Sample Size</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fang et al.</strong> (2016)</td>
<td>RCT (9)</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=360 N&lt;sub&gt;End&lt;/sub&gt;=348</td>
<td>E: Acupuncture + Herbal medicine  C: Standard care</td>
<td>• Hamilton Depression Rating Scale (+)  • Self-Rating Depression Scale (+)</td>
</tr>
<tr>
<td><strong>Wayne et al.</strong> (2005)</td>
<td>RCT (9)</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=33 N&lt;sub&gt;End&lt;/sub&gt;=24</td>
<td>E: Acupuncture  C: Sham acupuncture</td>
<td>• CES Depression Scale (-)</td>
</tr>
<tr>
<td><strong>Qian et al.</strong> (2015)</td>
<td>RCT (8)</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=68 N&lt;sub&gt;End&lt;/sub&gt;=65</td>
<td>E: Acupuncture + Placebo  C: Sham acupuncture + Fluoxetine (20mg/d)</td>
<td>• Hamilton Depression Rating Scale: 2wk (+), 6wk (-), 12wk (-)</td>
</tr>
<tr>
<td><strong>Man et al.</strong> (2014)</td>
<td>RCT (8)</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=43 N&lt;sub&gt;End&lt;/sub&gt;=33</td>
<td>E: Dense cranial acupuncture  + Body electroacupuncture  C: Non-invasive cranial acupuncture  + Body electroacupuncture</td>
<td>• Hamilton Depression Rating Scale: 1wk (+), 2wk (-), 4wk (-)</td>
</tr>
<tr>
<td><strong>Zhang et al.</strong> (2016)</td>
<td>RCT (5)</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=70 N&lt;sub&gt;End&lt;/sub&gt;=65</td>
<td>E: Acupuncture  C: Escitalopram (10mg/d)</td>
<td>• Montgomery-Asberg Depression Rating Scale: 4wk (+), 8wk (-)  • Hamilton Depression Rating Scale (-)</td>
</tr>
</tbody>
</table>

- Indicates non-statistically significant differences between treatment groups  
+ Indicates statistically significant differences between treatment groups  
E indicates experimental group; C indicates control group

**Discussion**

A prospective, non-controlled study by Youn et al. (2013) found that electroacupuncture was associated with significant reductions in depressive symptoms, when provided daily for four months. Their findings also suggested that participants with good motor function had greater improvement than those with
poor motor function. In an RCT, Man et al. (2014) provided four weeks of electroacupuncture in combination with dense or non-invasive cranial acupuncture, which were delivered directly to acupoints on the forehead innervated by the trigeminal sensory pathway (Zhang, 2015). Both dense and non-invasive cranial acupuncture yielded significant reductions in depression over time. Participants receiving dense cranial acupuncture showed a significantly greater reduction in depressive symptoms after the first week, but not at subsequent assessments. More recently, Fang et al. (2016) examined the effects of acupuncture and herbal medicine in patients receiving conventional rehabilitation post stroke. Compared to rehabilitation alone, the addition of traditional Chinese medicines effectively treated depressive symptoms.

Given a potential placebo effect, trials have compared the effects of active and sham acupuncture. An early RCT found that traditional acupuncture was no more effective than the sham in treating depression or improving functional independence (Wayne et al., 2005). In a later trial, Qian et al. (2015) compared traditional acupuncture with an antidepressant placebo to sham acupuncture with a true antidepressant (fluoxetine). At an early assessment, the authors reported significantly greater reduction in depressive symptoms with acupuncture-placebo than sham-fluoxetine, but found similar improvement between groups later on. Similarly, Zhang et al. (2015) reported that acupuncture was associated with short-term reductions in depressive symptoms when compared to treatment with an antidepressant (escitalopram). However, this significant difference was not found at subsequent assessments, and both treatments were associated with improvements over time.

Conclusions Regarding Acupuncture

*There is Level 1b evidence that a combination of acupuncture and herbal medicine reduces depressive symptoms post stroke when compared to standard care.*

*There is Level 1b evidence that acupuncture is no more effective than sham acupuncture in reducing depressive symptoms post stroke.*

*There is Level 1b evidence that dense cranial acupuncture reduces post-stroke depressive symptoms in the short term when compared to non-invasive cranial acupuncture.*

*There is Level 1b and Level 2 evidence that acupuncture reduces post-stroke depressive symptoms in the short term when compared to antidepressants.*

*There is Level 2 and Level 4 evidence that electroacupuncture reduces depressive symptoms post stroke.*

**Acupuncture may not be an effective treatment or adjunct for post-stroke depression.**

18.8.12.1 Acupressure

Similar to acupuncture, acupressure is a form of traditional Chinese medicine that is based upon the principles of the meridian system. Practitioners apply pressure to specific acupoints using their hands. A study examining the effectiveness of acupressure in treating PSD is summarized in Table 18.8.12.1.1.

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
</table>

Table 18.8.12.1.1 Studies Evaluating Acupressure in the Treatment of Post-Stroke Depression
### Study Design (PEDro Score)

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Kang et al. (2009) | RCT (5) \(N_{\text{Start}}=56\) \(N_{\text{End}}=56\) | E: Meridian acupressure  
C: Usual care | • Beyer Six-Face Rating Scale (+) |

- Indicates non-statistically significant differences between treatment groups  
+ Indicates statistically significant differences between treatment groups  
E indicates experimental group; C indicates control group

### Discussion

In a low-quality RCT, Kang et al. (2009) compared meridian acupressure to standard care. The authors found significant reductions in depressive symptoms associated with acupressure, as well as improvements in functional outcomes.

**Conclusions Regarding Meridian Acupressure**

There is limited Level 2 evidence that meridian acupressure reduces depressive symptoms post stroke when compared to standard care.

Further research is required to determine the effectiveness of meridian acupressure in treating post-stroke depression.

### 18.8.13 Reiki Treatment

Reiki is a form of alternative medicine that originated in Japan. It is based on the theory that ‘life energy’ is transferred to patients when practitioners place their hands on or directly above the body, which promotes physical or psychological healing (Borang, 2001). A study examining the effectiveness of reiki in treating PSD is summarized in Table 18.8.13.1.

**Table 18.8.13.1 Studies Evaluating Reiki in the Treatment of Post-Stroke Depression**

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Sample Size</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Shiflett et al. (2002) | RCT (7) \(N_{\text{Start}}=50\) \(N_{\text{End}}=44\) | E1: Reiki  
C1: Sham reiki  
C2: No treatment | • CES Depression Scale (-) |

- Indicates non-statistically significant differences between treatment groups  
+ Indicates statistically significant differences between treatment groups  
E indicates experimental group; C indicates control group

**Discussion**

In a single RCT, reiki was compared to sham therapy and no treatment (Shiflett et al., 2002). The authors reported that reiki was no more effective than the control conditions in reducing depressive symptoms or improving functional independence.

**Conclusions Regarding Reiki Treatment**
There is Level 1b evidence that reiki treatment does not reduce depressive symptoms post stroke when compared to sham reiki or no treatment.

Reiki may not be an effective treatment for post-stroke depression.

18.9 Post-Stroke Emotionalism

Pathological crying or laughing has been given many different labels within the literature including emotionalism, emotional incontinence, emotional lability, pathological affect, or pseudobulbar affect (Allman et al., 1990). While there is no consensus regarding the most appropriate label or definition for this condition, many reports refer to the definition provided by the Oxfordshire Community Stroke Project. The authors presented the defining characteristics of emotionalism as “an increase in tearfulness with episodes of crying that were sudden or unheralded and not all under normal social control”; the same criteria can be applied to laughing (House et al., 1989). Emotionalism is often accompanied by changes to facial expression and body posture (Allman et al., 1990).

Considerable variation exists in the severity, frequency, and duration of emotionalism. Patients who are severely affected may have as many as 100 episodes per day, each lasting from one to ten minutes, while those who are the least affected may present with inappropriate facial grimacing (House et al., 1989). There is also variation in the nature of the preceding stimuli, the social context of the behaviour, and the accompanying mood changes (Allman et al., 1990). Individuals experiencing emotionalism may withdraw from participation in normal social roles due to distress and fear of social embarrassment (Andersen, 1995, 1997), which has shown to negatively impact their quality of life (Chen et al., 2011; Choi-Kwon et al., 2008; Choi-Kwon & Kim, 2002).

18.9.1 Prevalence of Post-stroke Emotionalism

The reported prevalence of emotionalism following stroke ranged from 11% (House et al., 1989) to 34% (Kim & Choi-Kwon, 2000) in individual studies. This figure depends on both the criteria used to define emotionalism and the time elapsed since stroke onset. In the earlier criteria, House et al. (1989) suggested that emotionalism represents a loss of ability to control emotional response at a low level of stimulation rather than simple inappropriateness of response. The later criteria by Kim and Choi-Kwon (2000) proposed that the patient and relatives agree on excessive and inappropriate laughing or crying that had occurred on more than two occasions. Most participants in the former study were able to identify provoking stimuli for their episodes (i.e. sadness and sentimentality) (House et al., 1989), but this was not necessarily the case in the latter study (Kim & Choi-Kwon, 2000). In a comparison of the two studies, Tang et al. (2004) found that the Kim and Choi-Kwon (2000) criteria yielded in a much higher frequency than the criteria of House et al. (1989) (17.9% vs 6.3%). As such, there is a need to develop a single set of criteria for the diagnosis of post-stroke emotionalism.

Within the first few months of stroke onset, reported prevalence of emotionalism ranged from 8% (Tang et al., 2009) to 29% (Eccles et al., 1999). The majority of patients identified the onset of emotionalism during the acute phase of stroke (Andersen et al., 1995a; House et al., 1989), although the prevalence may be slightly greater during the subacute phase (Choi-Kwon et al., 2012; House et al., 1989). The frequency and severity of crying/laughing episodes have demonstrated improvement over the first year post stroke and may resolve by the chronic phase (Andersen, 1997; House et al., 1989), such the reported prevalence of emotionalism at one year is approximately 11% (Andersen et al., 1995a; House et al., 1989). In a systematic review of 15 studies with 3391 participants, Gillespie et al. (2016) reported
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the prevalence of post-stroke emotionalism to be 17% within one month, 20% between one and six months, and 12% after six months.

**Conclusion Regarding the Prevalence of Post-Stroke Emotionalism**

*Approximately a fifth of individuals experience emotionalism post stroke. The majority of individuals develop emotionalism in the acute phase of stroke and recover in the chronic phase.*

**Emotionalism affects approximately a fifth of individuals post stroke; rates of incidence and recovery vary over time from stroke onset.**

**18.9.2 Risk Factors for Post-Stroke Emotionalism**

Risk factors for the development of post-stroke emotionalism have not been well defined. Post-stroke emotionalism has been associated with cognitive impairment (Andersen et al., 1995b; House et al., 1989; Tang et al., 2009; Wang et al., 2016), motor impairment (Andersen et al., 1995b; Kim & Choi-Kwon, 2000), and functional disability (Andersen et al., 1995a; Choi-Kwon et al., 2012) in multiple studies. Other reported predictors of emotionalism include female sex (Kim & Choi-Kwon, 2000), younger age (Calvert et al., 1998; Tang et al., 2004), low social support (Choi-Kwon et al., 2012; Wei et al., 2016), and severe stroke (Choi-Kwon et al., 2012; Tang et al., 2004). These findings should be interpreted with caution, however, given the lack of consistent risk factors reported across all available studies.

Individuals experiencing post-stroke emotionalism may exhibit more symptoms of psychological disorders or syndromes than those without it. A significant association has been reported between emotionalism and depressive symptoms post stroke (Andersen et al., 1995a; Calvert et al., 1998; Eccles et al., 1999; House et al., 1989; Kim & Choi-Kwon, 2000; MacHale et al., 1998), although there is less evidence supporting an association with prior depression (Tang et al., 2004). As previously mentioned, emotionalism has demonstrated significant correlations with poor psychological adjustment (Eccles et al., 1999) and coping ability (Wei et al., 2016), as well as considerable emotional distress (Calvert et al., 1998) and anger proneness (Choi-Kwon et al., 2006; Wang et al., 2016). However, as many of these psychological conditions are co-occurring, the exact nature of the relationship between them remains unclear.

Similar to research of post-stroke depression, studies have attempted to determine a relationship between lesion location and the development of emotionalism with varied results. Several studies have reported a significant correlation between emotionalism and lesions in the anterior region of the brain (Choi-Kwon et al., 2012; Choi-Kwon & Kim, 2002; House et al., 1989; Kim & Choi-Kwon, 2000; MacHale et al., 1998; Morris et al., 1993b; Tang et al., 2009; Wei et al., 2016). Lesions in the lenticulocapsular (Choi-Kwon et al., 2012; Kim, 2002; Kim & Choi-Kwon, 2000) and pontine (Andersen et al., 1995b; Wang et al., 2016) regions have also been implicated in post-stroke emotionalism. There is less consensus regarding laterality, as studies have found emotionalism to be associated with lesions in left (House et al., 1989), right (MacHale et al., 1998), and bilateral (Andersen et al., 1995b; Wang et al., 2016) regions. More recently, it has been suggested that the laterality or size of the lesion is less significant than the specific location in terms of its impact on post-stroke emotionalism (Choi-Kwon et al., 2012; Wang et al., 2016).
Due the reported pattern of lesions, earlier studies postulated that post-stroke emotionalism was associated with damage to the serotonergic system (Andersen et al., 1995a; Kim, 2002; Kim & Choi-Kwon, 2000). In fact, Moller et al. (2007) later found that patients with emotionalism post stroke had a lower baseline binding potential of the serotonin receptor than those without it. Moreover, Kim et al. (2012) demonstrated a higher susceptibility to post-stroke emotionalism in patients with a specific allele for the serotonin transporter gene-linked promotor region. Future research should examine the role of the serotonergic system in post-stroke emotionalism.

**Conclusion Regarding Risk Factors for Post-Stroke Emotionalism**

*There is Level 4 and Level 5 evidence that cognitive deficit and anterior lesions are risk factors for emotionalism post stroke.*

*There is conflicting Level 4 and Level 5 evidence as to whether factors such as age, sex, stroke severity, functional impairment, and lesion laterality are risk factors for post-stroke emotionalism.*

*Common risk factors for post-stroke emotionalism include cognitive deficit and anterior lesions. However, further research is required to establish their relative impact, as well as to determine other potential risk factors.*

**18.9.3 Treatment of Post-Stroke Emotionalism**

There are relatively few published studies regarding treatment of post-stroke emotionalism. An updated Cochrane review included seven trials of antidepressant medication in the treatment of post-stroke emotionalism (Hackett et al., 2010). Five trials assessed the effectiveness of selective serotonin reuptake inhibitors (SSRIs) and two trials examined tricyclic antidepressants (TCAs). While the authors did not pool results, due to the heterogeneity of assessment methods used in the included studies, they concluded that both classes of antidepressants were associated with significant reductions in symptoms of emotionalism. Studies examining the effectiveness of pharmacologic treatment of post-stroke emotionalism are summarized in Table 18.9.3.1.

**Table 18.9.3.1 Studies Evaluating Pharmacologic Treatment of Post-Stroke Emotionalism**

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design (PEDro Score)</th>
<th>Intervention</th>
<th>Main Outcome(s) Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choi-Kwon et al. (2006) RCT (8)</td>
<td>NStart=152 NEnd=125</td>
<td>E: Fluoxetine (20mg/d, 3mo) C: Placebo</td>
<td>• Visual Analogue Scale: Crying (+) • Visual Analogue Scale: Anger (+) • Visual Analogue Scale: Laughing (-) • Beck Depression Inventory (-)</td>
</tr>
<tr>
<td>Brown et al. (1998) RCT (8)</td>
<td>NStart=20 NEnd=19</td>
<td>E: Fluoxetine (20mg/d, 10d) C: Placebo</td>
<td>• Crying frequency (+) • Lawson &amp; MacLeod Rating Scale of Emotionalism (+)</td>
</tr>
<tr>
<td>Robinson et al. (1993) RCT (7)</td>
<td>NStart=82 NEnd=81</td>
<td>E: Nortriptyline (20-100mg/d, 6wk) C: Placebo</td>
<td>• Pathological Laughter &amp; Crying Scale (+) • Hamilton Depression Rating Scale (+)</td>
</tr>
<tr>
<td>Burns et al. (1999)</td>
<td></td>
<td>E: Sertraline (50mg/d, 8wk)</td>
<td>• Crying frequency (+)</td>
</tr>
</tbody>
</table>
RCT (7)
N_{Start}=28
N_{End}=24
C: Placebo
• Emotional Lability Questionnaire (+)
• Clinician impression of change (+)

Andersen et al. (1993)
RCT (6)
N_{Start}=16
N_{End}=13
E: Citalopram (10-20mg/d, 3wk)
C: Placebo
• Crying frequency (+)
• Hamilton Depression Rating Scale (+)

- Indicates non-statistically significant differences between treatment groups
+ Indicates statistically significant differences between treatment groups
E indicates experimental group; C indicates control group

Discussion

Five RCTs of good quality demonstrated a significant and positive effect on post-stroke emotionalism associated with antidepressant treatment, whether a TCA or SSRI. Treatment appeared to be well-tolerated and was associated with a reduction in the frequency and severity of crying/laughing episodes. However, it should be noted that cessation of treatment was often associated with a recurrence of outbursts. These findings are in line with the premise that emotionalism develops as a result of damage to serotonergic pathways (Andersen, 1995, 1997; Kim & Choi-Kwon, 2000).

As noted by Hackett et al. (2010), these results should be interpreted with caution. The studies failed to use a consistent definition of post-stroke emotionalism, although there is a lack of consensus as to what constitutes pathological emotional expression. As well, there was considerable variation in the methods used to assess emotionalism. Most studies relied upon a combination of interviews and self-report, and only a single study (Robinson et al., 2000) utilized a scale specific to the evaluation of pathological crying and laughing. Time post stroke and duration of treatment also varied between studies. Further research is required to determine the optimal timing and duration of treatment, as outbursts associated with post-stroke emotionalism tend to become less frequent and less severe over the first year months post stroke.

Despite a known relationship between depression and emotionalism, few studies attempted to control for the possible effects of depression on study outcomes. Some studies did not include individuals with major depressive disorder (Andersen et al., 1993; Brown et al., 1998; Burns et al., 1999), but still included those with depressive symptoms. Choi-Kwon et al. (2006) performed subgroup analyses of individuals with depression, emotional incontinence, and anger proneness, although these conditions are not necessarily mutually exclusive. Only Robinson et al. (1993) examined the impact of depression on the improvement in emotionalism, based on a subgroup analysis of participants matched for depression scores. Within the small subgroup, treatment of emotionalism with nortriptyline was effective independent of depression (Robinson et al., 1993).

Conclusion Regarding the Treatment of Post-Stroke Emotionalism

There is Level 1a evidence that selective serotonin reuptake inhibitors improve symptoms of emotionalism post stroke when compared to placebo.

There is Level 1a evidence that tricyclic antidepressants improve symptoms of emotionalism post stroke when compared to placebo.

Antidepressants may be an effective treatment for post-stroke emotionalism.
18.10 Guidelines for Post-Stroke Mood

There are several sets of rehabilitation guidelines that provide recommendations for the assessment and treatment of mood disorders following stroke. In general, these guidelines acknowledge the importance of identifying and diagnosing depression, and recommend using standardized assessments. Most guidelines indicate that a clinical interview conducted by an appropriate mental healthcare professional is required for diagnosis. Treatment with antidepressant medications are recommended, although the details of treatment are not clearly stated. The role of psychotherapy is acknowledged, but the limited evidence of its effectiveness is noted. The Canadian Stroke Best Practice Recommendations (Eskes et al., 2015) are endorsed by the Canadian Stroke Network and the Heart & Stroke Foundation. The specific recommendations for post-stroke mood are detailed in Table 18.10.1.

Table 18.10.1 Canadian Stroke Best Practice Recommendations

<table>
<thead>
<tr>
<th>Recommendations for Post-Stroke Mood</th>
</tr>
</thead>
</table>

### 1.1 Screening for Depression

1. All patients with stroke should be screened for depressive symptoms, given the high prevalence of depression post-stroke, the need for screening to detect depression, and the strong evidence for treating symptomatic depression post-stroke.
2. Screening should be undertaken using a validated tool to maximize detection of depression.
3. Stroke patient assessments should include evaluation of risk factors for depression, particularly a history of depression.
4. For patients who experience some degree of communication challenge or deficits following stroke, appropriate strategies for screening of possible depression should be implemented to ensure adequate assessment and access to appropriate treatment.

Note: Common risk factors associated with depression include increasing stroke severity, functional dependence, presence of cognitive impairment, and history of previous depression. Increased functional dependence (e.g. requiring help with activities of daily living) and having a history of pre-stroke depression may be the two most salient risk factors for the development of depression. Communication deficits and social isolation may also be considered as possible risk factors for depression.

### 1.2 Timing of Screening for Depression

1. Screening for depression may take place at various stages throughout the continuum of stroke care, particularly at transition points. Repeated screening may be required since the ideal timing for screening for depression is unclear.
2. Screening for depressive symptoms could be considered during acute care stay in patients at high risk for depression, particularly if evidence of depression or mood changes is noted. Stroke patients who are identified as at risk could be screened before discharge from acute care.
3. Screening for depressive symptoms should be considered during transition points in care, such as from an inpatient acute setting to an inpatient rehabilitation setting, and or before return to the community.
4. Screening for depressive symptoms should be considered following discharge to the community, at stroke prevention clinic assessments, during follow-up appointments, and during periodic health assessments with primary care practitioners and consulting specialists.

### 1.3 Assessment of Depression

1. Patients identified with a high probability of clinically significant depression during screening should be assessed in a timely manner by a healthcare professional with expertise in diagnosis, management, and follow-up of depression in patients following stroke.

### 1.4 Non-Pharmacological Management of Depression

1. There is a lack of evidence to support use of psychotherapy as a monotherapy in the treatment of depression. However, it is reasonable to consider these therapies (either cognitive behavioral therapy or interpersonal therapy) as one of the first line treatments for acute major depressive disorders poststroke, given their demonstrated efficacy in primary depressive disorders.
Treatment for depression may include psychotherapy as an adjunct in combination with antidepressants, as appropriate to the patients’ health state and other deficits (e.g. communication and other cognitive deficits).

Treatment should be provided with the goal of preventing relapse.

Other approaches to adjunctive treatment of depression are emerging, but these require more research. These include physical exercise, music, mindfulness, acupuncture, deep breathing, meditation, visualization, and repetitive transcranial magnetic stimulation. These could be considered on an individual basis at the discretion of the treating healthcare professional.

1.5 Pharmacotherapy for Depression

Patients with mild depressive symptoms or those diagnosed with minor depression may initially be managed by ‘watchful waiting’.

Pharmacological treatment should be considered/started if the depression is persistent and interferes with day-to-day functioning and recovery goals, or worsens.

Patients diagnosed with a depressive disorder following formal assessment should be considered for a trial of antidepressant medication.

No one drug or drug class has been found to be superior for depression treatment. Side effect profiles, however, suggest that some selective serotonin reuptake inhibitors may be favored in this patient population.

Choice of an antidepressant medication will depend upon symptoms of depression, potential known side effects of the medication, particularly in the child or older adult, drug interactions with other current medications, and underlying disease conditions.

Response to treatment should be monitored regularly by a health professional. Monitoring should include evaluation of any changes in the severity of depression, review of potential side effects, and update of ongoing management plans.

If a good response is achieved, treatment should be continued for a minimum of 6–12 months.

Examples of a ‘good response’ may be indicated by positive changes in thoughts and self-perceptions (e.g., hopelessness, worthlessness, guilt), emotional symptoms (e.g. sadness, tearfulness), neurovegetative symptoms (e.g. sleep, appetite), and improved motivation to carry out daily activities.

If the patient’s mood has not improved two to four weeks after initiating treatment, check that the patient is taking the medicine as prescribed. If yes, then consider increasing the dose or changing to another antidepressant.

Following the initial course of treatment, maintenance therapy could be considered on an individual basis (consider previous history and risk factors for recurrence of depression).

If a decision is made to discontinue an antidepressant, it should be tapered over one to two-months.

Following initial treatment for depression, patients should continue to be monitored for recurrence of depressive symptoms, as part of ongoing comprehensive stroke management. The involvement and feedback of patients, family, and caregivers can be an important component of ongoing monitoring.

Note: Watchful waiting is defined as a period of time when the patient who displays mild depressive symptoms is monitored closely without additional therapeutic interventions to determine whether the mild depressive symptoms will improve. The timeframe for watchful waiting varies in the literature somewhere between two and four weeks. It is often described as including suggestions to the patient for self-help strategies and participation in physical exercise and other strategies.

1.6 Prophylactic Treatment for Depression

At this time, the routine use of prophylactic antidepressants for all stroke patients is not recommended as the risk – benefit has not been clearly established.

Emerging data on the use of pharmacotherapy to prevent depression suggests that pharmacotherapy may be reasonable for some patients.

Further research is required to define at risk patients, choice of antidepressant agents, optimal timing, and duration of intervention.

1.7 Other Mood States (Anxiety, Apathy, and Emotionalism)

Anxiety frequently co-exists with depression following stroke or may appear in patients not clinically depressed. For patients with marked anxiety with or without clinical depression, it is reasonable to offer psychotherapy.
a. Although evidence is limited in stroke patients, psychotherapy may be considered as an adjunct to pharmacotherapy.

ii. Apathy frequently co-exists with depression following stroke or may appear in patients not clinically depressed. For patients with marked apathy, with or without clinical depression, it is reasonable to offer psychotherapy.

iii. In cases of severe, persistent, or troublesome tearfulness (emotional incontinence or lability), patients may be given a trial of antidepressant medication. Side effect profiles suggest that some selective serotonin reuptake inhibitors may be preferred over others for this patient population. There is no evidence for non-pharmacotherapy for this condition.

1.8 Ongoing Monitoring, Support, and Education

i. Patients and families should be given information and education about the potential impact of stroke on their mood and that of family and caregivers; patients and families should be provided with the opportunity to talk about the impact of stroke on their lives at all stages of care.

ii. Patients and their caregivers should have their psychosocial and support needs assessed as part of ongoing stroke management.

Adapted from Eskes et al. (2015)

Conclusions Regarding Clinical Practice Guidelines

Screening for post-stroke depression should be conducted in all individuals following stroke using a validated tool and throughout the continuum of care.

Assessment of post-stroke depression should be conducted by an experienced health professional in individuals with a high probability of clinically significant depression.

Treatment with an appropriate antidepressant for a period of 6 to 12 months should be considered for individuals diagnosed with a depressive disorder; regular monitoring of response by a health professional is required.

Treatment with psychotherapy as an adjunct to antidepressants is a reasonable consideration, given demonstrated efficacy in primary depressive disorders; other non-pharmacological interventions require more research.

Prophylactic treatment for post-stroke depression using antidepressants is not recommended.

Guidelines for post-stroke depression recommend screening, assessment, and treatment with an antidepressant for 6-12 months; adjunctive psychotherapy is a reasonable treatment consideration.
Summary

1. Approximately a third of individuals experience depression post stroke. Generally, incidence decreases and recovery increases over time, although some individuals may experience persistent depression and others may develop late-onset depression.

2. Diagnosis of post-stroke depression should be conducted by a mental healthcare professional in Structured Clinical Interview as per the criteria outlined in the DSM-V.

3. Screening for post-stroke depression can be conducted using a variety of validated assessment tools. However, the Patient Health Questionnaire 9 has shown relatively high sensitivity, specificity, and clinical utility.

4. Detection of post-stroke depression is often inconsistent, which may be due to the heterogeneity of screening tools.

5. Compliance with guidelines for screening is generally poor, which may be due to lack of time and knowledge.

6. There is Level 4 and Level 5 evidence that risk factors for post-stroke depression include prior depression, functional impairment, cognitive deficit, and stroke severity.

7. There is conflicting Level 4 and Level 5 evidence as to whether variables such as age, sex, socioeconomic status, cardiovascular comorbidities, and stroke severity are risk factors for post-stroke depression.

8. There is conflicting Level 4 and Level 5 evidence as to whether lesion location is a risk factor for post-stroke depression.

9. There is Level 2 and Level 3 evidence that depression has a significant, negative impact on functional outcomes post stroke.

10. There is Level 2 and Level 3 evidence that that depression has a significant, negative impact on physical functional post stroke.

11. There is Level 2 evidence that that depression has a significant, negative impact on cognitive function post stroke.

12. There is conflicting Level 2 and Level 3 evidence as to whether depression post stroke is associated with an increased risk of mortality.

13. There is Level 1a evidence that early initiation of fluoxetine is associated with reduced risk of post-stroke depression when compared to placebo.

14. There is Level 1b evidence that early initiation of escitalopram is associated with reduced risk of post-stroke depression when compared to placebo.

15. There is Level 1b evidence that early initiation of nortriptyline is associated with reduced risk of post-stroke depression when compared to placebo.
16. There is Level 1b evidence that early initiation of milnacipran is associated with reduced risk of post-stroke depression when compared to placebo.

17. There is Level 1b evidence that early initiation of duloxetine is associated with reduced risk of post-stroke depression when compared to no antidepressant medication.

18. There is Level 1b evidence that early initiation of mianserin is not associated with reduced risk of post-stroke depression when compared to placebo.

19. There is conflicting Level 1b evidence regarding the efficacy of sertraline in reducing the risk of post-stroke depression when compared to placebo.

20. There is Level 2 evidence that early initiation of mirtazapine is associated with reduced risk of post-stroke depression when compared to no antidepressant medication.

21. There is Level 1a evidence that community outreach, using post mail or telephone calls, does not reduce depressive symptoms when compared to standard care.

22. There is Level 1b evidence that a pre-discharge home visit by an occupational therapist reduces short-term depressive symptoms when compared to a pre-discharge hospital interview.

23. There is Level 1b evidence that motivational interviewing improves mood and reduces depressive symptoms when compared to standard care.

24. There is Level 1b and Level 2 evidence that home visits from nurses and therapists do not reduce depressive symptoms when compared to information provision or standard care.

25. There is conflicting Level 2 evidence regarding the effectiveness of coordinated or integrated care programs on reducing depressive symptoms when compared to standard care.

26. There is Level 1b evidence that fish oil supplementation does not impact mood post stroke.

27. There is Level 1b evidence that Vitamin B therapy, administered over a long period, is associated with reduced risk of post-stroke depression.

28. There is Level 1a evidence that heterocyclic antidepressants are as effective as fluoxetine in reducing depressive symptoms post stroke.

29. There is Level 1a evidence that nortriptyline reduces depressive symptoms post stroke when compared to placebo.

30. There is Level 1b evidence that mianserin reduces depressive symptoms post stroke when paired with imipramine or desipramine, but is more effective with imipramine.

31. There is Level 2 evidence that desipramine does not reduce depressive symptoms post stroke when compared to placebo.

32. There is Level 1a evidence that fluoxetine is no more effective than heterocyclic antidepressants in treating depressive symptoms post stroke.
33. There is Level 1b evidence that citalopram reduces depressive symptoms post stroke when compared to placebo.

34. There is Level 1b evidence that sertraline does not reduce depressive symptoms post stroke when compared to placebo.

35. There is conflicting Level 1b evidence regarding the effectiveness of fluoxetine in treating depressive symptoms post stroke when compared to placebo.

36. There is Level 1b evidence that adjunctive high-intensity light therapy is more effective than moderate-intensity light therapy in treating depressive symptoms post stroke.

37. There is Level 1b evidence that reboxetine reduces depressive symptoms post stroke when compared to placebo.

38. There is limited Level 4 evidence that venlafaxine reduces depressive symptoms post stroke.

39. There is Level 1b evidence that methylphenidate reduces depressive symptoms post stroke when compared to placebo.

40. There is Level 3 evidence that methylphenidate is as effective as nortriptyline in reducing depressive symptoms post stroke.

41. There is level 1a evidence that nefiracetam does not reduce depressive symptoms post stroke when compared to placebo.

42. There is Level 2 evidence that selegiline does not reduce depressive symptoms post stroke when compared to placebo.

43. There is limited Level 4 evidence that valdoxan reduces depressive symptoms post stroke.

44. There is limited Level 2 evidence that statins may reduce depressive symptoms post stroke when compared to no medications.

45. There is limited Level 2 evidence that pioglitazone with fluoxetine reduces depressive symptoms post stroke when compared to metformin with fluoxetine.

46. There is Level 1b evidence that treatment with the herbal preparation, Free and Easy Wanderer Plus, is as effective as fluoxetine and more effective than placebo in reducing depressive symptoms post stroke.

47. There is Level 1b evidence that an active care management program enhances the effectiveness of pharmacologic treatment for post stroke depression.

48. There is conflicting Level 1a evidence as to whether cognitive behavioral therapy reduces depressive symptoms post stroke when compared to attention placebo or usual care.

49. There is Level 1a evidence that problem-solving therapy is does not reduce depressive symptoms post stroke when compared to usual care.
50. **There is Level 1b evidence that aphasic behavioural therapy reduces depressive symptoms post stroke when compared to usual care.**

51. **There is Level 4 evidence that group-based cognitive behavioural therapy reduces depressive symptoms post stroke in the short term.**

52. **There is Level 1b evidence that psychosocial-behavioural therapy in combination with antidepressants is more effective than antidepressants alone in reducing depressive symptoms post stroke.**

53. **There is Level 1b evidence that a goal achievement program reduces depressive symptoms post stroke when compared to standard care.**

54. **There is Level 1b evidence that a transitional care program reduces depressive symptoms post stroke when compared to standard care.**

55. **There is Level 1b evidence that a self-management program does not reduce depressive symptoms post stroke when compared to standard care.**

56. **There is Level 1b evidence that customized occupational therapy does not reduce depressive symptoms post stroke when compared to standard care.**

57. **There is Level 1b evidence that ecosystem focused therapy does not reduce depressive symptoms post stroke when compared to an education program.**

58. **There is Level 2 evidence that music therapy does not reduce depressive symptoms post stroke when compared to usual care.**

59. **There is limited Level 2 evidence that music-listening therapy improves mood post stroke when compared to language-listening therapy and usual care.**

60. **There is limited Level 2 evidence that music-movement therapy does not reduce depressive symptoms post stroke when compared to usual care.**

61. **There is Level 1b evidence that art therapy reduces depressive symptoms post stroke when compared to standard care.**

62. **There is limited Level 4 evidence that deep unilateral nostril breathing does not reduce depressive symptoms post stroke.**

63. **There is limited Level 4 evidence that autogenic training reduces psychological tension post stroke.**

64. **There is Level 1a evidence that resistance training does not reduce depressive symptoms post stroke when compared to relaxation training or usual care.**

65. **There is Level 1b evidence that a specialized, therapeutic exercise program reduces depressive symptoms post stroke when compared to usual care.**
66. There is Level 1b evidence that yoga does not reduce depressive symptoms post stroke when compared to usual care.

67. There is conflicting Level 1b and Level 2 evidence as to whether aerobic exercise reduces depressive symptoms post stroke when compared to usual care.

68. There is conflicting Level 1b and Level 2 evidence as to whether circuit training reduces depressive symptoms post stroke when compared to basic exercise or usual care.

69. There is conflicting Level 1b and Level 2 evidence as to whether exercise with technological enhancements reduce depressive symptoms post stroke when compared to standard exercise.

70. There is conflicting Level 1b, Level 2, and Level 4 evidence as to whether group exercise programs reduce depressive symptoms post stroke when compared to individual exercise or usual care.

71. There is conflicting Level 2 evidence as to whether an adaptive physical activity program reduces depressive symptoms post stroke when compared to usual care.

72. There is Level 1b evidence that speech therapy does not reduce depressive symptoms post stroke when compared to standard care.

73. There is Level 1b evidence that combined speech and orofacial therapies are more effective in reducing depressive symptoms post stroke than speech therapy alone.

74. There is Level 1b evidence that hyperbaric oxygen therapy with fluoxetine reduces depressive symptoms post stroke when compared to either intervention alone.

75. There is Level 1b evidence that hyperbaric oxygen therapy reduces depressive symptoms post stroke when compared to the psychoactive medication Deanxit.

76. There is limited Level 4 evidence that electroconvulsive therapy (ECT) reduces depressive symptoms post stroke.

77. There is Level 1a evidence that repetitive transcranial magnetic stimulation (rTMS) reduces depressive symptoms post stroke.

78. There is limited Level 4 evidence that transcranial direct current stimulation (tDCS) reduces depressive symptoms post stroke.

79. There is Level 1b evidence that a combination of acupuncture and herbal medicine reduces depressive symptoms post stroke when compared to standard care.

80. There is Level 1b evidence that acupuncture is no more effective than sham acupuncture in reducing depressive symptoms post stroke.

81. There is Level 1b evidence that dense cranial acupuncture reduces post-stroke depressive symptoms in the short term when compared to non-invasive cranial acupuncture.
82. There is Level 1b and Level 2 evidence that acupuncture reduces post-stroke depressive symptoms in the short term when compared to antidepressants.

83. There is Level 2 and Level 4 evidence that electroacupuncture reduces depressive symptoms post stroke.

84. There is limited Level 2 evidence that meridian acupressure reduces depressive symptoms post stroke when compared to standard care.

85. There is Level 1b evidence that reiki treatment does not reduce depressive symptoms post stroke when compared to sham reiki or no treatment.

86. Approximately a fifth of individuals experience emotionalism post stroke. The majority of individuals develop emotionalism in the acute phase of stroke and recover in the chronic phase.

87. There is Level 4 and Level 5 evidence that cognitive deficit and anterior lesions are risk factors for emotionalism post stroke.

88. There is conflicting Level 4 and Level 5 evidence as to whether factors such as age, sex, stroke severity, functional impairment, and lesion laterality are risk factors for post-stroke emotionalism.

89. There is Level 1a evidence that selective serotonin reuptake inhibitors improve symptoms of emotionalism post stroke when compared to placebo.

90. There is Level 1a evidence that tricyclic antidepressants improve symptoms of emotionalism post stroke when compared to placebo.

91. Screening for post-stroke depression should be conducted in all individuals following stroke using a validated tool and throughout the continuum of care.

92. Assessment of post-stroke depression should be conducted by an experienced health professional in individuals with a high probability of clinically significant depression.

93. Treatment with an appropriate antidepressant for a period of 6 to 12 months should be considered for individuals diagnosed with a depressive disorder; regular monitoring of response by a health professional is required.

94. Treatment with psychotherapy as an adjunct to antidepressants is a reasonable consideration, given demonstrated efficacy in primary depressive disorders; other non-pharmacological interventions require more research.

95. Prophylactic treatment for post-stroke depression using antidepressants is not recommended.
References


combination of dense cranial electroacupuncture stimulation and body acupuncture for post-stroke depression. *BMC Complementary and Alternative Medicine, 14*(255).


