Abstract

A variety of emotional and behavioural disorders may develop following stroke. In stroke, prevalence rates of depression and anxiety have been reported to be as high as 24% and 29% respectively. These rates may be influenced by a combination of factors such as age, sex, socioeconomic factors, functional independence post-stroke, and the presence of cognitive disorders post-stroke which play a crucial role in an individual’s emotional well-being and can significantly impact recovery. Many studies have investigated pharmacological and non-pharmacological treatment options for post-stroke mood disturbances; however, no consensus has been reached regarding the most effective and viable treatment option available although the most effective treatment option appears to be pharmacological. This chapter explores the evidence of the various interventions on reducing post-stroke depression and other mood disorders, and delves into the possible risk factors that can facilitate the occurrence of post-stroke mood disturbances.
Key Points

Prevalence of Post-Stroke Depression
- Depression is a common complication post-stroke affecting approximately one-third of patients.
- Comorbidity of depression and anxiety could potentially occur in one-third of stroke patients and could still be prevalent in one-fifth of patients after five years.
- The highest rates of incident depression are reported in the first month post stroke and, while incidence may decline over time and there may be a general trend toward improvement, PSD may persist for years in a significant proportion of individuals.

Risk Factors
- The risk factors most commonly associated with increased risk for post-stroke depression (PSD) include female gender, younger age, past history of depression or psychiatric illness, functional limitations, and cognitive impairment.

Stroke Location
- Despite an abundance of research, the influence of stroke location on the risk for developing post-stroke depression has not been determined.
- Stroke involvement of the basal ganglia may be associated with the development of PSD.

Screening and Assessment
- Detection and diagnosis of post-stroke depression is often inconsistent. Compliance with guidelines for screening is poor. Identified barriers to routine screening include time pressures and concerns about screening tools.
- There is evidence to suggest that the PHQ-9 is an effective diagnostic tool, as well for the CES-D and HAM-D, for PSD.

Consequences of Post-Stroke Depression
- Depression post-stroke has a negative impact on functional recovery.
- Functional dependence may be associated with greater levels of depression, cognitive deficit, and illness comorbidity.
- Early identification and treatment of post-stroke depression may serve to enhance functional recovery.

Social Activities Post-Stroke
- There is a significant association between the presence of depression and greater social isolation.
- Returning to work and/or playing sports may be associated with higher levels of depression compared to engaging in passive activities.

Cognitive Impairment and Depression
- Executive dysfunction has been found to be associated with older age.
- Post-stroke depression is associated with cognitive impairment and is likely reciprocal. Further research is required.
Mortality and Depression Post-Stroke

- The presence of mental health disorders post stroke is associated with increased risk for mortality.
- Depression and use of anti-depressants post-stroke have been found to be associated with greater rates of suicide and suicidal ideation.

Prevention of Post-Stroke Depression

- Early initiation of antidepressant therapy in non-depressed individuals is effective in preventing post-stroke depression.
- Fluoxetine, Escitalopram, Milnacipran and Mirtazapine have been reported to be effective in preventing depression but there is mixed results concerning the efficacy of Sertraline.

Prevention of Post-Stroke Depression

- Ongoing, individualized contact and support may reduce the risk for deterioration of psychological health following stroke.
- There is mixed results regarding community outreach programs with evidence suggesting that home visits can reduce depression and functioning but other results suggest support provided by a liaison from a stroke family support service did not provide any greater improvement than usual care.
- Dietary supplementation with omega-3 fatty acids has no impact on mood post stroke.
- Long-term vitamin-B therapy may reduce risk for depression following stroke.

Pharmacological Treatment of Post-Stroke Depression

- Heterocyclic antidepressants may improve post-stroke depression.
- Selective Serotonin Reuptake Inhibitors (SSRIs) may be effective in the treatment of post-stroke depression. Further study is required.
- Light therapy may be an effective adjunct to treatment with SSRI antidepressants.
- Reboxetine may be an effective treatment for “retarded” post-stroke depression characterized by lethargy and slowness to initiate action.
- More evidence is required to determine the efficacy of venlafaxine and duloxetine for post-stroke depression.
- Nefiracetam may not be an effective treatment for post-stroke depression.
- Methylphenidate (a psychostimulant) appears to be effective in treating symptoms of depression and has an earlier onset of action than traditional antidepressants.
- More studies are needed to determine the effect of valdoxan, a melatonin agonist, on post-stroke depression.
- The herbal medicine Free and Easy Wanderer Plus (FEWP) may be effective in the treatment of PSD. Further research is required.
- Active care management in conjunction with antidepressant therapy may improve response to treatment; however, more research is needed.
• Treatments with Nortriptyline may improve post-stroke depression and functional recovery. Limited evidence also suggests that Maprotiline and Citalopram have a similar effect as Nortriptyline.

• Fluoxetine, Trazadone, or Desipramine may not be associated with improved post-stroke depressive symptoms.

• Treatment with antidepressants following stroke may improve long-term survival; however, additional studies are warranted.

Non-Pharmacological Treatment of Post-Stroke Depression

• There is insufficient evidence to evaluate the use of electroconvulsive therapy as a treatment for post-stroke depression.

• Use of repetitive transcranial magnetic stimulation is associated with reduced symptoms of post-stroke depression.

• Cognitive behavioural therapy (CBT) may not be effective in the treatment of post-stroke depression; however, mood-based CBT may offer a promising non-pharmacological avenue for improving general mood. Further research is required to determine if different forms of CBT and mindfulness may be advantageous at improving post-stroke depression.

• Psychosocial behavioural therapy may be used as an effective adjunct to treatment with antidepressants; however, further research is needed.

• Hyperbaric oxygen therapy may improve post-stroke depression when combined with dexamethasone or fluoxetine.

• There is conflicting and limited evidence regarding the effect of music therapy on depressive symptoms.

• Limited evidence suggests that speech therapy does not appear to improve depression post-stroke; however, more studies are needed.

• Exercise training, whether progressive group programs, treadmill training or aerobic training, does not appear to be associated with a reduction in symptoms of depression post stroke. Further research is required.

• Ecosystem focused therapy may not be an effective treatment for post-stroke depression. Further research is required.

• More studies are needed to determine the effect of acupuncture on post-stroke depression.

• Although limited evidence suggests that Reiki Treatments may not improve post-stroke depression, more studies are needed to confirm its lack of effect.

• More studies are needed to determine the effect of meridian acupressure on post-stroke depression.

• More studies are needed to determine the effect of massage therapy on post-stroke anxiety.

• More studies are needed to determine the effect of relaxing therapies on post-stroke anxiety and depression symptomology.
• More studies are needed to determine the effect of art therapy on post-stroke anxiety and depression.

**Non-Pharmacological Treatment of Post-Stroke Depression**

• There is insufficient evidence to evaluate the use of electroconvulsive therapy as a treatment for post-stroke depression.

• Use of repetitive transcranial magnetic stimulation is associated with reduced symptoms of post-stroke depression.

• Cognitive behavioural therapy (CBT) may not be effective in the treatment of post-stroke depression however, mood-based CBT may offer a promising non-pharmacological avenue for improving general mood. Further research is required to determine if different forms of CBT and mindfulness may be advantageous at improving post-stroke depression.

• Psychosocial behavioural therapy may be used as an effective adjunct to treatment with antidepressants however, further research is needed.

• Hyperbaric oxygen therapy may improve post-stroke depression when combines with dexamethasone or fluoxetine.

• There is conflicting and limited evidence regarding the effect of music therapy on depressive symptoms.

• Limited Evidence suggests that speech therapy does not appear to improve depression post-stroke however, more studies are needed.

• Exercise training, whether progressive group programs, treadmill training or aerobic training, does not appear to be associated with a reduction in symptoms of depression post stroke. Further research is required.

• Ecosystem focused therapy may not be an effective treatment for post-stroke depression. Further research is required.

• More studies are needed to determine the effect of acupuncture on post-stroke depression.

• Although limited evidence suggests that Reiki Treatments may not improve post-stroke depression, more studies are needed to investigate its effect.

• More studies are needed to determine the effect of meridian acupressure on post-stroke depression.

• More studies are needed to determine the effect of massage therapy on post-stroke anxiety.

• More studies are needed to determine the effect of relaxing therapies on post-stroke anxiety and depression symptomology.

• More studies are needed to determine the effect of art therapy on post-stroke anxiety and depression.

**Post-Stroke Emotionalism**

• In the first 6 months following stroke, post-stroke emotionalism affects approximately one-quarter of stroke survivors.
• Antidepressants, and SSRI antidepressants in particular, are effective in the treatment of post-stroke emotionalism. Further study is required to determine optimum timing and duration for treatment.

Guidelines for Treatment of Post-Stroke Depression
• Guidelines for the treatment of post stroke depression recommend screening, assessment and treatment with an appropriate antidepressant for a period of approximately 6 months.
# Table of Contents

Abstract ........................................................................................................................................... 1

Key Points ......................................................................................................................................... 2

Table of Contents ............................................................................................................................... 7

18.1 Introduction ............................................................................................................................... 9

18.2 Prevalence and Natural History of Post-Stroke Depression ..................................................... 9

18.3 Risk Factors for Post-Stroke Depression ................................................................................. 12
  18.3.1 Stroke Location and Depression ......................................................................................... 17

18.4 Assessment of Post-Stroke Depression .................................................................................... 22

18.5 Consequences Associated with Post-Stroke Depression ......................................................... 25
  18.5.1 Functional Impairment and Depression Post-Stroke ............................................................ 26
  18.5.2 Depression and Social Activities Post-Stroke .................................................................... 28
  18.5.3 Cognitive Impairment and Depression Post-Stroke ............................................................. 29
  18.5.4 Mortality and Depression Post-Stroke ................................................................................. 31

18.6 Prevention of Post-Stroke Depression ...................................................................................... 33
  18.6.1 Care Provision and the Prevention of Post-Stroke Depression ........................................... 36
  18.6.2 Dietary Supplementation .................................................................................................... 38
  18.6.2.1 Omega-3 Fish Oil ........................................................................................................... 38
  18.6.2.2 B-Vitamins .................................................................................................................... 39

18.7 Pharmacologic Treatment of Post-Stroke Depression ............................................................... 40
  18.7.1 Heterocyclic Antidepressants .............................................................................................. 41
  18.7.2 Selective Serotonin Reuptake Inhibitors (SSRIs) ................................................................. 43
  18.7.2.1 Adjunctive Light Therapy ............................................................................................... 45
  18.7.3 Selective Noradrenaline Reuptake Inhibitors (NARI) ........................................................ 46
  18.7.4 Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs) .............................................. 47
  18.7.5 Gamma Aminobutyric Acid Compounds (GABA) ............................................................. 48
  18.7.6 Psychostimulants ................................................................................................................ 48
  18.7.7 Melatonin Agonist ................................................................................................................ 49
  18.7.8 Statins .................................................................................................................................. 50
  18.7.9 Alternative Medicine .......................................................................................................... 50
  18.7.10 Care Management ............................................................................................................. 51

18.8 Impact of Pharmacologic Treatment of PSD on Rehabilitation Outcomes ......................... 52
  18.8.1 Functional Recovery Associated with Pharmacologic Treatment of Post-Stroke Depression 52
  18.8.2 Mortality and Pharmacologic Treatment of Post-stroke Depression .................................. 55

18.9 Non-Pharmacologic Treatment of Post-Stroke Depression ................................................ 56
  18.9.1 Electroconvulsive Therapy ................................................................................................. 56
  18.9.2 Repetitive Transcranial Magnetic Stimulation ................................................................. 57
  18.9.3 Cognitive Behavioural Therapy ......................................................................................... 58
  18.9.3.1 Combined Therapy ....................................................................................................... 60
  18.9.4 Music Therapy .................................................................................................................... 61
  18.9.5 Speech Therapy .................................................................................................................. 62
  18.9.6 Physical Activity ................................................................................................................ 63
  18.9.7 Ecosystem Focused Therapy .............................................................................................. 65
  18.9.8 Acupuncture ....................................................................................................................... 66
  18.9.9 Reiki Treatments ................................................................................................................ 67
  18.9.9.1 Meridian Acupressure ................................................................................................... 68
18.1 Introduction

A variety of emotional and behavioural disorders may develop following stroke. The DSM-IV categorizes post-stroke depression as a “mood disorder due to general medical conditions” with the specifiers of: (a) depressive features; (b) major depressive-like episodes; (c) manic features; or (d) mixed features. The two types of depressive disorders most associated with stroke are major depression and minor depression, the latter of which has been defined for research purposes by the DSM-IV criteria as a “depressed mood or loss of interest and at least 2 but fewer than 4 symptoms of major depression.”

Depression is often observed in patients with severe physical illnesses. While the endogenous features of depression are present in these patients, the interpretations of vegetative signs are not clear. There appears to be less emphasis on feelings of low self-esteem, guilt and self-blame when depression accompanies physical illness while hypochondrial concerns, lethargy and behaviour disturbances are most characteristic (Morris & Raphael 1987). Three possible explanations for the association between physical illness and depression have been sought. First, and least likely, is a coincidental relationship. The second possible 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 (losses to self-esteem, independence, employment, etc.). The third possible explanation is a neurotransmitter imbalance as a result of cerebral damage caused by the stroke.

18.2 Prevalence and Natural History of Post-Stroke Depression

Depression is a well-documented sequela of stroke. Based on pooled data from published prevalence studies, Robinson reported a mean prevalence of depression among in-patients in acute or rehabilitation settings of 19.3% (Robinson 2003) to 21.6 (Robinson & Spalletta 2010) for major depression (Table 18.2.1). Among individuals in community settings, mean prevalence for major depression was reported to be 14% (Robinson & Spalletta 2010) to 14.1% (Robinson 2003). For patients included in outpatient studies, mean reported prevalence was 23.3% (Robinson 2003) to 24% (Robinson & Spalletta 2010) for major depression. Overall mean prevalence ranged from 31.8% in the community studies to 35.5% in the acute and rehabilitation hospital studies.

Table 18.2.1 Prevalence Studies included in Robinson (Robinson 2003)

<table>
<thead>
<tr>
<th>Community Studies:</th>
<th>Acute &amp; Rehabilitation Hospital Studies:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Community Studies:</strong></td>
<td><strong>Acute &amp; Rehabilitation Hospital Studies:</strong></td>
</tr>
<tr>
<td>Wade et al. (1987)</td>
<td>Folstein et al. (1977)</td>
</tr>
<tr>
<td>Kotila et al. (1998)</td>
<td>Sinyor et al. (1986)</td>
</tr>
<tr>
<td><strong>Outpatient Studies:</strong></td>
<td>Ebrahim et al. (1987)</td>
</tr>
<tr>
<td>Collin et al. (1987)</td>
<td>Morris et al. (1990)</td>
</tr>
<tr>
<td>Astrom et al. (1993)</td>
<td>Fedoroff et al. (1991)</td>
</tr>
<tr>
<td>Herrmann et al. (1998)</td>
<td>Starkstein et al. (1992)</td>
</tr>
<tr>
<td>Schwartz et al. (1993)</td>
<td></td>
</tr>
</tbody>
</table>
In a systematic review of prospective, observational studies of post-stroke depression, Hackett et al. reported that 33% of stroke survivors exhibit depressive symptoms at some time following stroke (acute, medium-term or long-term follow-up) (Hackett et al. 2005c). This pooled estimate was based on data collected from 51 studies in population, hospital and rehabilitation-based settings. The authors stated that this is likely to be an underestimation of the frequency with which post-stroke depression occurs. Errors in estimation may be attributed to under-reporting of unusual mood, difficulties in the assessment of depression in neurologically impaired individuals and variability in the methods used to assess and define depression or “caseness” within the literature (Hackett et al. 2005c).

In a large, case-control study, Linden et al. (2007) reported identified depression in 34% of patients (n=149) one year post stroke compared to 13% of sex and age-matched controls (n=745). All types of depressive disorders, both major and minor, were more frequent among individuals with stroke. Major depressive disorders were most frequent among individuals with stroke who were more than 80 years of age (Linden et al. 2007). Other studies have reported that the risk for depression among individuals aged 65 or over, living in the community and who have experienced a stroke 2 years previously, is 6 times greater than for their stroke-free counterparts (Whyte et al. 2004).

Estimates of prevalence may be affected by the time from stroke onset until assessment. Patients who are assessed during the subacute phase may be in a period of transition during which they are attempting to adjust to the consequences of stroke. Depression at this time may simply be a reflection of the difficulties associated with this transition. In fact, the highest rates of incident depression have been reported in the first month following stroke (Aben et al. 2006, 2003; Andersen et al. 1995a; Bhogal et al. 2004; Bour et al. 2010; Morrison et al. 2005). In a study of 190 individuals with first-ever stroke, Bour et al. reported a decrease in incident cases of depression over the course of the first year following the stroke event (Bour et al. 2010). Cumulative incidence of PSD was 18.8% at 1 month and 23.1%, 26.7%, 31%, and 36.2% at 3, 6, 9 and 12 months respectively.

Paolucci et al. (2005) reported that, of 1064 patients included in the DESTRO study, 36% developed depression. Eighty percent of these became depressed within the first three months of the stroke event (Paolucci et al. 2005). In that study, dysthymia (mild depression) was the most common form of depression, occurring in 80.7% of cases, whereas major depression was diagnosed in only 2.9% .While the incidence of major depression post-stroke may decrease over the first 24 months following stroke (Astrom et al. 1993; Verdelho et al. 2004), minor depressive symptoms may persist or increase over the same time period (Berg et al. 2003; Burvill et al. 1995; Verdelho et al. 2004).

Prevalence of PSD should not be regarded as static. While there may be a general trend toward improvement in depressive symptomatology over the first year following stroke (Ostir et al. 2011), and incidence rates may decline over time (Bour et al. 2010, 2011), PSD may be persistent for a significant proportion of individuals identified as depressed (Ayerbe et al. 2011; Berg et al. 2003; Farner et al. 2010; Ostir et al. 2011). Ostir et al. (2011) examined patterns of change in depressive symptomatology in the first year following first-ever stroke in 544 individuals (Ostir et al. 2011). At the time of discharge from inpatient rehabilitation, 27.6% of patients were identified as depressed. Over the course of the following 12 months, the authors identified a general, significant trend toward recovery in terms of depressive
symptomatology. However, approximately one-fifth of individuals identified as depressed at baseline remained depressed at one year; while for approximately one-third of this group, depression remained unresolved and they “moved in and out of depression” during the follow-up period (Ostir et al. 2011).

Ayerbe et al. (2011) followed individuals (n=3689) for 5 years as part of a population-based study (South London Stroke Register). Over this period, the prevalence of PSD was reported to be 33%, 28%, 32% and 31% at 3 months, 1 year, 3 years and 5 years, respectively (where depression was defined as a score >7 on the depression subscale of the Hospital Anxiety and Depression Scale). Although some cases resolved, 15-20% of individuals identified as depressed at each follow-up were new cases. In addition, as many as 55% of individuals identified as depressed at one assessment remained depressed on follow-up (Ayerbe et al. 2011). Retrospective research over 15 years (1995 to 2009) by Ayerbe et al. (2013) revealed a cumulative incidence of 55.4% and a prevalence ranging from 29-39%. Of greater concern was the percentage of recurrent episodes of PSD with a 100% recurrence rate found at 14 and 15 years. These findings indicate that depression is a long-term concern for many patients post-stroke, particularly those who experience at least one episode of depressive symptoms.

Similarly, Farner et al. (2010) reported persistent depression in more than half (55%) of the individuals identified as depressed during inpatient rehabilitation post stroke. Significant predictors of persistent depression included lower levels of pre-stroke social activity, greater severity of stroke and lower levels of function at baseline. At the same time, 35% of individuals with no significant depressive symptomatology at baseline were identified with incident depression over the 13-month follow-up period.

Given that depression is a psychological concern, other psychological aspects may be attributable to the development and sustainment of depression. Van Mierlo et al. (2015) reported that higher scores in neuroticism on the Eysenck Personality Questionnaire Revised Short Scale, pessimism on the Life Orientation Test-Revised, the Helplessness subscale on the Illness Cognition Questionnaire, and the Utrecht Coping List-Passive scale were significantly associated with the prevalence of depression. The findings from Van Mierlo et al. (2015) indicated that patients of specific personality traits and cognitions are more susceptible to depression than those with more optimistic, extraverted and self-efficacious personality traits.

Depression has also been found to be comorbid with other symptoms of psychological distress. White et al. (2014) reported that comorbid depression and anxiety at baseline was 69% and 34% at 12 month follow-up. Although rates of depression remained consistent over the 12 month study period, anxiety decreased from 47% at baseline to 14% at the study’s end. Severity of depression at any time during the study period was significantly associated with baseline anxiety ratings and severity of anxiety during the study period was significantly associated with baseline depression ratings. At 5 years, a multi-centre study reported comorbidity of depression and anxiety in 20% of patients (Lincoln et al. 2013). Of interest, patients in Switzerland were significantly less depressed and anxious than patients in the United Kingdom and Belgium but did not differ significantly from patients in Germany. Although intensity of rehabilitation was greater in Switzerland and Germany, the authors argue that external factors such as social support and expectation may have accounted for these differences over such an extended period of time.

**Conclusions Regarding the Prevalence and Natural History of PSD**

At least one-third of stroke patients will experience depression. While the patterns of incidence and recovery change over time, for many individuals PSD may be persistent.
There is level 4 evidence that personality traits such as neuroticism and pessimism, and a passive coping style is significantly associated with the development of depression.

There is level 5 evidence that comorbidity of depression and anxiety occur in at least one-third of stroke patients and, despite recovery over time, are prevalent in one-fifth of patients after 5 years.

**Depression is a common complication post-stroke affecting approximately one-third of patients.**

**Comorbidity of depression and anxiety could potentially occur in one-third of stroke patients and could still be prevalent in one-fifth of patients after five years.**

**The highest rates of incident depression are reported in the first month post stroke and, while incidence may decline over time and there may be a general trend toward improvement, PSD may persist for years in a significant proportion of individuals.**

### 18.3 Risk Factors for Post-Stroke Depression

Although post-stroke depression (PSD) is a common consequence of stroke, risk factors for the development of PSD have not been clearly delineated. In a systematic review, Hackett and Anderson (2005a) included data from a total of 21 studies (Table 18.3.1). Of the many different variables assessed, physical disability, stroke severity and cognitive impairment were most consistently associated with depression. The authors noted that major methodological limitations within the available literature make it difficult to form a definitive conclusion. Methodological limitations cited include selection biases, poor methodology and reporting, problems in choosing variables to include as potential predictors and inadequate sample size from which to derive appropriate predictive models for depression (Hackett & Anderson 2005a).

In an earlier review of 9 prospective studies examining post-stroke depression, the risk factors identified most consistently as increasing an individual’s risk for post-stroke depression included a past history of depression or psychiatric illness, social isolation, functional impairment, living alone and dysphasia (Ouimet et al. 2001). Several studies later confirmed the importance of severity of initial neurological deficit and physical disability as predictors of the development of depression after stroke (Bour et al. 2010; Carota et al. 2005; Christensen et al. 2009; Hackett & Anderson 2005a; Hackett et al. 2005b, 2005c; Ouimet et al. 2001), with one study also demonstrating a high prevalence of PSD (41%) among a group of individuals with minor ischemic stroke (NIHSS ≤5) (Altieri et al. 2012). In addition, Storor and Byrne (2006) examined post-stroke depression in...
the acute phase (within 14 days of stroke onset) and identified significant associations between pre-stroke neuroticism (OR = 3.69, 95% CI 1.25 – 10.92) and a past history of mental disorders (OR = 10.26, 95% CI 3.02 – 34.86) and the presence of depressive symptoms. Both anxiety and depression at 4 months post stroke have been associated with self-reported symptoms of anxiety at the time of admission for the stroke event (Sagen et al. 2010).

The potential influences of socioeconomic status (SES), age and gender on the development of depression following stroke have all been examined, with inconsistent results (Ouimet et al. 2001). Lower SES was found to be significantly predictive of developing PSD (Saxena & Suman 2015) and in developing depression and anxiety (Broomfield et al. 2014). Although one could predict intuitively that lower SES and increasing age are associated with the risk for PSD, this is not necessarily the case. Andersen et al. (1995b) reported that SES had no influence on the risk for post-stroke depression and recent studies suggest that younger rather than older age is associated with increased risk of PSD (Andersen et al. 1995b; Carota et al. 2005; Eriksson et al. 2004) and anxiety (Ayerbe et al. 2014c). Younger age was also found to be a significant predictor of psychological distress including anger, indifference, emotional dyscontrol and helplessness (Huang et al. 2014). Conversely, older age has been found to be significantly predictive of developing PSD in a number of studies (Hou et al. 2013). Bour et al. (2010) demonstrated that older age may be associated with recurrent cases of depression (vs. transient or persistent cases, p=0.06). However numerous studies have failed to yield a significant difference between age groups and the prevalence of PSD (Huang et al. 2014).

Given the substantially higher prevalence of depression among women when compared to men in the general population (Ouimet et al. 2001; Salokangas et al. 2002; Wilhelm & Parker 1994), a higher prevalence of PSD among women might be expected. While the results from some studies support the association between female sex and PSD (Desmond et al. 2003; Eriksson et al. 2004; Ouimet et al. 2001; Paolucci et al. 2005; Paradiso & Robinson 1998; Poynter et al. 2009), others do not (Berg et al. 2003; Ouimet et al. 2001; Poynter et al. 2009; Spalletta et al. 2005; Whyte et al. 2004). More recently, studies have found that male gender coupled with previous stroke (Tang 2013c) and high health ambiguity scores on the Mischel Uncertainty in Illness Scale (McCarthy et al. 2013) were significantly predictive of PSD. However, further studies have found no significant differences between genders (Hou et al. 2013; Huang et al. 2014; Kouwenhoven et al. 2013; Saxena & Suman 2015). In part, sex-based differences could be attributed to response bias created by the greater tendency for women to remember and report symptoms of depression (Wilhelm & Parker 1994). In addition, certain assessment tools may include items that exacerbate gender-based response biases such as “sadness” or “crying” that may be connected to gender-bound role behaviour (Salokangas et al. 2002).

However, there may be real differences between men and women in terms of the relative importance of risk factors for PSD. Among men, physical impairment may be a more influential risk factor for depression (Berg et al. 2003; Paradiso & Robinson 1998), while among women, previous history of psychiatric disorder may be more important (Paradiso & Robinson 1998). As in the evaluation of any potential risk factor, conflicting findings could be the result of variations in subject sampling, assessment techniques, definitions of depression, or time passed since stroke onset (Paradiso & Robinson 1998; Rigler 1999).

As part of the DESTRO study, a multicentre observational study of depression in stroke, Paolucci et al. (2005) identified female sex (OR=1.49), previous stroke (OR = 1.55), previous depression (OR=3.97) and severe disability (Modified Rankin Scale score >3, OR = 2.70) as factors likely to facilitate the development of depression following stroke. The risk for post-stroke depression was found to increase exponentially in individuals with more than one risk factor. This ranged from 25% in males with one previous stroke
episode, mild disability but no previous psychiatric episodes to 89.1% in women with previous stroke, previous depression and moderate to moderate/severe disability (Paolucci et al. 2005). This information could be used as the basis for a simple decision-tree, used to guide a selective screening process directed at those individuals at most risk for developing PSD.

In a report from the Auckland Regional Community Stroke Study (Hackett & Anderson 2006), the authors described an attempt to create a simple, predictive tool for the identification of individuals most at risk for abnormal mood. Unfortunately, the resulting model, which included female gender, age, more than two co-morbid conditions, prior treatment for depression and requiring “much help” (based on baseline Barthel Index score) could correctly identify mood status, assessed on the General Health Questionnaire at 6 months, in only 54% of patients. Of the factors included in the model, only two were significant predictors of mood; prior treatment for depression (OR = 2.4, 95% CI 1.34 – 3.43) and requiring “much help” with activities of daily living (OR = 2.35, 95% CI 1.33 – 4.14) (Hackett & Anderson 2006). The ability of the model to predict risk for depression might be increased by the inclusion of other factors such as fatigue and performance of instrumental activities of daily living. However, van de Port et al. (2007) demonstrated that use of these two predictors (prior treatment for depression and requiring much help with ADLs) in a multivariate model could correctly classify depression in 76% of patients 3 years post stroke.

Tables 18.3.2 to 19.3.5 illustrate a summary of the studies evaluating various risk factors for post-stroke depression, anxiety, multiple psychiatric comorbidities, and suicide.

### Table 18.3.2 Summary of Risk Factors for Post-Stroke Depression

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design (PEDro Score)</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Main Outcome(s) Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hou et al. (2013)</strong></td>
<td>Case Control (N_{Start}=7767) (N_{End}=7767)</td>
<td></td>
<td>Data was collected from randomly selected beneficiaries with insurance between the years of 2000 and 2009.</td>
<td>* Older Age &gt;64yr (+) * Length of Stay 22-28d (+) and &gt;28d (+) * Hemorrhagic stroke (+) * Gender (-)</td>
</tr>
<tr>
<td><strong>Kouwenhoven et al. (2013)</strong></td>
<td>Case Series (N_{Start}=109) (N_{End}=109)</td>
<td></td>
<td>One of two hospitals in Eastern Norway participated in a longitudinal study of fatigue between 2007 and 2008. Data was collected from medical records and standardized interviews.</td>
<td>* Fatigue (+) * Gender (-) * Age (-) * Type of lesion &amp; lesion location (-)</td>
</tr>
<tr>
<td><strong>McCarthy et al. (2013)</strong></td>
<td>Observational (N_{Start}=36) (N_{End}=36)</td>
<td></td>
<td>Patients were recruited to participate in face-to-face interviews regarding their psychological state and health ambiguity.</td>
<td>* Male gender &amp; Health ambiguity (high MUIS score) (+)</td>
</tr>
<tr>
<td><strong>Ojagbemi et al. (2013)</strong></td>
<td>Observational (N_{Start}=30) (N_{End}=30)</td>
<td></td>
<td>All patients completed a set of questionnaires to examine the association between depression and cognitive deficits.</td>
<td>* Female gender (+) * Age (-) * Type of lesion &amp; lesion location (-) * Level of education (-)</td>
</tr>
<tr>
<td><strong>Paul et al. (2013)</strong></td>
<td>Case Control (N_{Start}=241) (N_{End}=130)</td>
<td></td>
<td>Patients living in the city of Kolkata in India completed a series of questionnaires between 2006 and 2010 and were followed up at four intervals of 8mo to 12mo.</td>
<td>* Older age at presentation (+) * Older age at first stroke (+) * Lower income (+) * Lower education level (+)</td>
</tr>
<tr>
<td><strong>Tang et al. (2013a)</strong></td>
<td>Observational</td>
<td></td>
<td>Chinese patients with acute ischemic stroke admitted to the acute stroke unit of a</td>
<td>* Female gender (+) * History of depression (+)</td>
</tr>
<tr>
<td>Study</td>
<td>Type</td>
<td>Sample Size</td>
<td>Methods</td>
<td>Associated Factors</td>
</tr>
<tr>
<td>-------</td>
<td>------</td>
<td>-------------</td>
<td>---------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Tang et al. (2013c)</td>
<td>Longitudinal</td>
<td>N\textsubscript{Sear}=223, N\textsubscript{Ent}=223</td>
<td>Patients completed a set of questionnaires and donated a 9ml blood sample at 3mo post-stroke.</td>
<td>Lower educational level (+), Frontal Lobe Atrophy (+), Age (-), Male gender &amp; Previous stroke (+), Male gender &amp; Serotonin Receptor 2C Gene (HTR2C) (+), Common haplotypes of HTR2C Gene (-), Cognitive dysfunction (+).</td>
</tr>
<tr>
<td>Sun et al. (2014)</td>
<td>Observational</td>
<td>N\textsubscript{Sear}=465, N\textsubscript{Ent}=465</td>
<td>Patients who had visited a hospital neurology department completed a set of questionnaires assessing depression and neurological deficits.</td>
<td>Female gender (+), Left hemisphere stroke (+), &gt;1mo since onset of stroke (+), Age (-), Socioeconomic Status (+), Gender (-), Age (-), Smoking/Alcohol consumption (-), Lesion location (-), Hypertension, diabetes, ischemic heart disease (-), History of depression (-).</td>
</tr>
<tr>
<td>Li et al. (2014)</td>
<td>Observational</td>
<td>N\textsubscript{Sear}=256, N\textsubscript{Ent}=191</td>
<td>Patients donated serum samples upon admission and participated in a psychiatric evaluation conducted by a psychiatrist.</td>
<td>Female gender (+), Higher serum leptin levels (+), Higher Body Mass Index (+), Older age (+), Lower monthly income (+), Lower care satisfaction (+), Diabetes, coronary heart disease, hyperlipidemia (-).</td>
</tr>
<tr>
<td>Ojagbemi et al. (2014)</td>
<td>Observational</td>
<td>N\textsubscript{Sear}=260, N\textsubscript{Ent}=260</td>
<td>Patients were consecutively recruited to undergo semi-structured interviews in addition to completing a series of questionnaires.</td>
<td>Female gender (+), Moderate disability (+), Cognitive dysfunction (+).</td>
</tr>
<tr>
<td>Jiang et al. (2014)</td>
<td>Observational</td>
<td>N\textsubscript{Sear}=329, N\textsubscript{Ent}=329</td>
<td>Patients underwent interviews based on neuro-psychiatric factors and socio-economic characteristics, as well as MRI and other lab measures to investigate the prevalence and correlation factors of post-stroke depression (PSD) in stroke patients.</td>
<td>Hypertension (+), Single left hemisphere stroke (+), Single lesion (+), Total anterior circulation infarct (+), Lower yearly income (+), Lower care satisfaction (+), Diabetes, coronary heart disease, hyperlipidemia (-).</td>
</tr>
<tr>
<td>Saxena et al. (2015)</td>
<td>Observational</td>
<td>N\textsubscript{Sear}=107, N\textsubscript{Ent}=107</td>
<td>Consecutive acute stroke inpatients admitted to a hospital in central India were assessed for depression through a face-to-face interview-based questionnaire.</td>
<td>Socioeconomic Status (+), Gender (-), Age (-), Smoking/Alcohol consumption (-), Lesion location (-), Hypertension, diabetes, ischemic heart disease (-), History of depression (-).</td>
</tr>
</tbody>
</table>

Consecutive acute stroke inpatients admitted to a hospital in central India were assessed for depression through a face-to-face interview-based questionnaire.
Data collected as part of a multicenter observational study conducted on young stroke patients aged 18-55yr in 2007 was reanalysed and reviewed to determine depression rates and potential associated factors.

- Indicates not a significant risk factor
+ Indicates statistically significant risk factor

### Table 18.3.3 Summary of Risk Factors for Anxiety

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design (PEDro Score)</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Main Outcome(s) Result</th>
</tr>
</thead>
</table>
| **Tang et al.** (2013b) | Hong Kong Observational | NStart=374 NEnd=374 | Patients were followed-up to complete a set of questionnaires investigating quality of life, symptoms of anxiety and depression, and cognitive function. | • Female gender (+)  
• Age (-)  
• Years of education (-)  
• Previous stroke (-)  
• Hypertension, diabetes, ischemic heart disease (-) |
| **Ayerbe et al.** (2014a) | Case Series | NStart=2179 NEnd=2179 | Data from patients registered in the South London Stroke Register between 1995 and 2009. | • Younger age <65yr (+)  
• Female gender (+)  
• Disability (+) |
| **Ayerbe et al.** (2014c) | Case Series | NStart=4022 NEnd=4022 | Data was collected and analysed from patients registered on the South London Stroke Register between January 1995 and December 2009 and followed-up until August 2010. | • Younger age <65yr (+)  
• Female gender (+) |

### Table 18.3.4 Summary of Risk Factors for Multiple Psychiatric Comorbidities

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design (PEDro Score)</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Main Outcome(s) Result</th>
</tr>
</thead>
</table>
| **Ajiboye et al.** (2013) | Observational | NStart=83 NEnd=83 | Patients participated in a clinical psychiatric interview and were assessed for potential psychiatric disorders including depression, anxiety, phobias, somatoform disorder, delusional disorder, and vascular dementia. | • Age (-)  
• Gender (-)  
• Type and location of stroke (-)  
• Duration of time since stroke (-) |
| **Broomfield et al.** (2014) | Case Series | NStart=4079 NEnd=4079 | Case review data was collected and analysed for depression and anxiety from patients registered on the Glasgow Local Enhanced Services between April 2012 and March 2013. | • Female gender (+)  
• Younger age (+)  
• Lower Socioeconomic Status (+)  
• Smoker (+)  
• Chronic Obstructive Pulmonary Disease (anxiety only) (+) |
| **Huang et al.** (2014) | Observational | NStart=178 NEnd=178 | Questionnaires were completed by first-time stroke patients to determine the influence of psychological distress (anger, helplessness, emotional dyscontrol, indifference, etc) on functional outcomes. | • Male gender (anger, emotional dyscontrol) (+)  
• Younger age <60yr (+)  
• Stroke duration >3mo (+)  
• Non-Lacunar Circulation Infarcts (+) |
Table 18.3.5 Summary of Risk Factors for Suicide, Suicidal Ideation, and Mortality

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design (PEDro Score) Sample Size</th>
<th>Intervention</th>
<th>Main Outcome(s) Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eriksson et al., (2015)</strong></td>
<td>Case Series N_Start=336 N_End=220</td>
<td>Data was collected and analysed from patients registered on the Swedish Stroke Register (Riksstroke) between January 2001 and December 2012.</td>
<td>• Male gender (+) • Aged 18-54 (+) • Greater usage of anti-depressants (+)</td>
</tr>
<tr>
<td><strong>Nishida et al., (2015)</strong></td>
<td>Case Control N_Start=23 N_End=23</td>
<td>Patient records of autopsies performed between 2006 and 2013 were reviewed. Specifically, brains of deceased patients from the EG (suicide) and CG (non-suicide) that had undergone neuropathological examination were assessed.</td>
<td>• Presence of Argyrophilic Grain Disease (AGD) and Progressive Supranuclear Palsy (PSP) (+) • Presence of AGD only (-) • Presence of PSP only (-)</td>
</tr>
<tr>
<td><strong>Tang et al., (2015)</strong></td>
<td>Observational N_Start=518 N_End=518</td>
<td>Participants’ socio-demographic and clinical characteristics were obtained to examine the association between apathy and suicide-related ideation post-stroke.</td>
<td>• Geriatric Depression Scale (GDS) score (+) • Neuropsychiatric Inventory - Apathy Subscale (NPI: Apathy) (+)</td>
</tr>
</tbody>
</table>

- Indicates not a significant risk factor
+ Indicates statistically significant risk factor

Conclusions Regarding Risk Factors for Post-Stroke Depression

Commonly identified risk factors for depression include female gender, older age, a previous history of depression, functional limitations and cognitive impairment.

Prior treatment of depression and the need for assistance with activities of daily living may be the factors most predictive of risk of post stroke depression.

Younger age was found to be a commonly identified risk factor for developing multiple comorbid psychiatric concerns such as depression and anxiety, and psychological distress including anger, helplessness, emotional dyscontrol, and indifference.

The risk factors most commonly associated with increased risk for post-stroke depression (PSD) include female gender, younger age, past history of depression or psychiatric illness, functional limitations, and cognitive impairment.

18.3.1 Stroke Location and Depression

The association between the brain lesion as a result of stroke and post-stroke depression has been the topic of much research. While it has been suggested that lesion location may account for up to 50% of the variance in the development of PSD (Robinson et al. 1986), the complex association between lesion location and the susceptibility to post-stroke depression is not well understood (Ghika-Schmid & Bogousslavsky 1997). Feng et al. (2014) report that previous research indicates that the frontal subcortical circuit, with the frontal left lobe and basal ganglia as key areas, is part of a network of circuits that
modulate emotional behaviour and infarcts to this circuit have been found to be associated with PSD. However, Feng et al. (2014) also state that conflicting reviews and studies have found no link between lesion location and PSD.

The John Hopkins Group (Lipsey et al. 1983; Robinson et al. 1983,1984,1987; Robinson 1986; Robinson & Price 1982; Robinson & Szetela 1981) carried out a series of studies exploring the relationship of post-stroke depression to the location of the lesion within the brain itself. They found that in a selected group of stroke patients, similar to those admitted to a stroke rehabilitation unit, depression appeared to be more frequent in patients with left hemispheric lesions (Robinson et al. 1986, 1987; Robinson & Price 1982; Robinson & Szetela 1981). Among these patients, the severity of depression correlated inversely with the distance of the lesion from the frontal poles (Robinson 1986; Robinson et al. 1987,1984,1983; Robinson & Price 1982; Robinson & Szetela 1981; Starkstein et al. 1987). Patients with subcortical, cerebellar or brainstem lesions had much shorter-lasting depressions than patients with cortical lesions (Starkstein et al. 1987; Starkstein et al. 1988).

Table 18.3.1.1 Lesion Location & Post-Stroke Depression in Carson et al. (2000) Systematic Review

<table>
<thead>
<tr>
<th>Folstein et al. 1977</th>
<th>Astrom et al. 1993</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feibel et al. 1982</td>
<td>Schwartz et al. 1993</td>
</tr>
<tr>
<td>Finkelstein et al. 1982</td>
<td>Agrell et al. 1994</td>
</tr>
<tr>
<td>Robinson et al. 1983</td>
<td>Grasso et al. 1994</td>
</tr>
<tr>
<td>Agarwal et al. 1987</td>
<td>Andersen et al. 1995</td>
</tr>
<tr>
<td>Collins et al. 1987</td>
<td>Gonzalez-Torreillas et al. 1995a, 1995b</td>
</tr>
<tr>
<td>Ebrahim et al. 1987</td>
<td>Herrmann et al. 1995</td>
</tr>
<tr>
<td>Kotila et al. 1987</td>
<td>Iacobani et al. 1995</td>
</tr>
<tr>
<td>Wade et al. 1987</td>
<td>Ng et al. 1995</td>
</tr>
<tr>
<td>Eastwood et al. 1989</td>
<td>Buvill et al. 1996</td>
</tr>
<tr>
<td>Bacher et al. 1990</td>
<td>Nagaraja et al. 1997</td>
</tr>
<tr>
<td>House et al. 1990</td>
<td>Kase et al. 1998</td>
</tr>
<tr>
<td>Malec et al. 1990</td>
<td>MacHale et al. 1998</td>
</tr>
<tr>
<td>Morris et al. 1990, 1996</td>
<td>Pohjasvannra et al. 1998</td>
</tr>
<tr>
<td>Van Rooijen et al. 1990</td>
<td>Gainotti et al. 1999</td>
</tr>
<tr>
<td>Gordon et al. 1991</td>
<td>Hibbard et al. 1992</td>
</tr>
</tbody>
</table>

There have been a number of systematic reviews and meta-analyses examining the evidence with regard to the possible relationship between lesion location and PSD.

Singh et al. (1998) conducted a critical appraisal on the importance of lesion location in post-stroke depression. The authors systematically selected 26 original articles that examined lesion location and post-stroke depression. Thirteen of the 26 articles satisfied inclusion criterion. Six of those studies found no significant difference in depression between right and left hemisphere lesions. Two studies found that right-sided lesions were more likely to be associated with depression and 4 studies found that left-sided lesions were more likely to be associated with post-stroke depression. Only one study matched patients with and without depression for lesion location and size to identify non-lesion risk factors. The authors noted that all of the studies reviewed were methodologically flawed. None of the studies were comparable with respect to sample, timing and analysis of CT scan and psychiatric evaluation. Consequently, Singh et al. were unable to make any definitive conclusions concerning stroke lesion location and the risk for depression (Singh et al. 1998).

Carson et al. (2000) undertook a systematic review examining the association between post-stroke depression and lesion location. All reports on the association of post-stroke depression with location of brain lesions were included in the review. In total 48 reports were included for review (Table 18.3.1.1). The authors of the review identified 38 reports that found no significant difference in risk of depression between lesion sites; 2 reported an increased risk of post-stroke depression with left-sided lesions; 7 reported increased risk with right-sided lesions; and one report demonstrated an association between depression and lesions in the right parietal region or the left frontal region. However, 4 studies were observed to be from the same samples of patients and were treated as one report. Thus 35 reports were
analyzed. When data from all reports were pooled, lesion location was not associated with depression. The null effect remained regardless of whether a fixed-effect model (0.95, 95% CI 0.83-1.03) or a random-effect model (0.95, 95% CI 0.83-1.10) had been used. Based on the results generated by their systematic review, the authors concluded that the risk of post-stroke depression was not affected by location of the brain lesion.

Carson et al. (2000) identified several sources of bias that may have led to the different results of the individual studies. The main source of bias appears to be the heterogeneity of study patients. There was evidence to suggest that patients selected from the community, but not those selected from hospitals or rehabilitation units, experience an increased risk of depression with right-sided lesions. This was also corroborated by a systematic review from Bhogal et al. (2004). The exclusion of aphasic patients that usually occurs in reports that follow patients from hospitals and rehabilitation units may have accounted for this finding. Furthermore, differences among individual studies were most apparent when carried out in the first 28 days of stroke; these were studies most often conducted in inpatient units. Studies examining lesion location and post-stroke depression are summarized in Table 18.3.1.2.

**Table 18.3.1.2 Summary of Studies Evaluating Stroke Location and Depression**

<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>Robinson &amp; Szetela (1981) Observational</td>
<td></td>
<td>E1: Stroke patients E2: Traumatic Brain Injury patients</td>
<td>• HAMD (+) • ZDS (+) • VAS Mood Slip (+) • Nurses Mood Scale (+)</td>
</tr>
<tr>
<td>Sinyor et al. (1996) Observational</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=35 N&lt;sub&gt;End&lt;/sub&gt;=35</td>
<td>E1: Left hemispheric stroke patients E2: Right hemispheric stroke patients</td>
<td>• Hopkins Symptom Checklist Depression subscale (+) • ZDS (-) • Beck Hopelessness Scale (-) • Composite Depression Index (-) • Nurses Rating Scale (-)</td>
</tr>
<tr>
<td>Chatterjee et al. (2010) Observational</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=182 N&lt;sub&gt;End&lt;/sub&gt;=127</td>
<td>E: Depressed patients C: Non-depressed patients</td>
<td>• Location of lesion (Subcortical vs Cortical vs No lesion) (+) • White Matter Change (WMC) in Basal Ganglia (+) • WMC Frontal (+) • WMC Parieto-occipital (-) • Side of lesion (-)</td>
</tr>
<tr>
<td>Wu et al. (2014) Observational</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=243 N&lt;sub&gt;End&lt;/sub&gt;=243</td>
<td>E: Depressed patients C: Non-depressed patients</td>
<td>• Silent lacunar infarction (SLI) in basal ganglia (+) • SLI in Thalamus (-) • SLI in deep white matter (-) • SLI in Brainstem (-)</td>
</tr>
</tbody>
</table>

- Indicates non-statistically significant differences between treatment groups
+ Indicates statistically significant differences between treatment groups

**Discussion**

Based on the results of a meta-analysis conducted by Bhogal et al. (2004), there appears to be some evidence that depression following stroke may be related to the anatomical site of brain damage, although the nature of this anatomic relationship is not completely clear (Figure 18.3.1.1).
Aben et al. (2006), attempted to replicate the finding that left-sided strokes and/or anterior strokes are associated with an increased risk for PSD. The findings could support neither this hypothesis nor the hypothesis that post-stroke depression results from generalized vascular damage (Aben et al. 2006). Finally, the two large systematic reviews by Singh et al. and Carson et al. referred to previously, failed to find a relationship between the stroke lesion site and depression (Carson et al. 2000; Singh et al. 1998). As important as the contribution of Robinson and his group is to our understanding of post-stroke depression, there are potential weaknesses in their research in part related to selection biases in the patient population, which might account for why their findings have not been consistently replicated. These weaknesses were outlined in two studies (Ebrahim 1990; Malec et al. 1990). In an empirical study, Ebrahim et al. (1987) did not find any significant difference between right and left hemispheric strokes in the development of PSD.

Despite the lack of evidence from systematic reviews concerning the hemispheric side of the lesion, individual studies have demonstrated potential associations between PSD and hemisphere. Astrom et al. (1993); Morris et al. (1996); Rajashekaran et al. (2013); and Rashid et al. (2013) all reported findings indicating involvement of the left hemisphere with PSD. In particular, Rashid et al. (2013) reported a significant relationship between lesion laterality and PSD. Furthermore, Morris et al. (1996) did not find any associations between lesion location and size with PSD, but it was reported that patients with smaller lesions in the left hemisphere reported PSD more frequently than patients with comparable lesions in the right hemisphere. However, MacHale et al. (1998) reported the opposite in that their study revealed an association between PSD and the right hemisphere and Chatterjee et al. (2010) did not find any significant differences between left and right hemispheric strokes with regard to the incidence of PSD. A systematic review conducted by Wei et al. (2015) revealed a significant link between right hemispheric stroke and PSD within studies with a subacute stroke population and no association between PSD and left hemispheric stroke. With the wide array of research and systematic reviews all providing contrasting evidence, the debate is no closer to conclusion. However, as indicated by Carson et al. (2000) and Bhogal et al. (2004), reducing biases within the methodologies of research studies could be one step towards achieving a more succinct basis of evidence for future research.

The role of the frontal lobes has been the subject of many investigations as to whether lesions at the front of the brain are associated with the prevalence of PSD. The correlation of major depression to the proximity of the lesion to the frontal pole has been confirmed by Sinyor et al. (1986) and Eastwood et al. (1989). Robinson and Szetela (1981) found a significant correlation between PSD and closeness of the lesion to the frontal lobes. A multi-centre study by Shi et al. (2014) reported that not only was PSD significantly more frequent amongst patients with frontal lesions, but these patients were also at greater risk of a recurrence of depression at 3 and 6 months post-stroke compared to non-frontal stroke patients. It has been suggested that the association between frontal lesions and depression may be due to a reduction in biogenic amine release from the monoaminergic pathways, or a change in frontal lobe glutamine levels after a stroke (Esparrago Llorca et al. 2015).

Interestingly, in one study, patients who had both an anxiety disorder and a major depression showed a significantly higher frequency of cortical lesions, while patients with major depression had a significantly higher frequency of subcortical (basal ganglia) stroke (S.E. Starkstein et al. 1987). A number of authors (Chatterjee et al. 2010; Santos et al. 2009; Wai Kwong. Tang et al. 2010) have since demonstrated that accumulation of lacunar infarcts and lesions within the basal ganglia, are associated with the presence of depression following stroke suggesting that older individuals with cerebral small vessel disease may be at greater risk for PSD. However, Sato et al.’s (1999) multi-centre observational study did not find any evidence of a special role for the basal ganglia’s involvement in the prevalence of PSD. There is also
18. Post Stroke Depression and Mood Disorders

Evidence that suggests lacunar infarcts of the thalamus have been found to play a causal role in the development of PSD (Murakami et al. 2013; Santos et al. 2009; Wu et al. 2014). The concept of neurotransmitters was discussed in the systematic review by Feng et al. (2014) in that disruption of neurotransmitters passing through the thalamus and basal ganglia from the midbrain to the frontal cortex results in the decrease of serotonin, dopamine and norepinephrine thus potentially contributing to depressive symptoms.

It has been speculated that the role of the location of the brain lesion in the development of post-stroke depression is mediated by the depletion of catecholamines believed to play a major role in the etiology of depression (Robinson 1986). It has been suggested that when cerebral catecholaminergic neurons are injured, they markedly reduce neurotransmitter production during the regenerative process causing a decline in neurotransmitter availability, not only in the injured area, but also throughout the cerebrum.

**Figure 18.3.1.1 Odds Ratio of Post-Stroke Depression and Affected Hemisphere**

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95%CI Random)</th>
<th>Weight %</th>
<th>OR (95%CI Random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agrollt et al.</td>
<td>6.7</td>
<td>0.74(0.30,1.72)</td>
<td></td>
</tr>
<tr>
<td>Anderson et al.</td>
<td>6.8</td>
<td>0.45(0.20,1.02)</td>
<td></td>
</tr>
<tr>
<td>Ascor et al.</td>
<td>4.1</td>
<td>30.00(5.51,163.35)</td>
<td></td>
</tr>
<tr>
<td>Collins et al.</td>
<td>6.7</td>
<td>0.57(0.25,1.31)</td>
<td></td>
</tr>
<tr>
<td>Garblotte et al.</td>
<td>7.1</td>
<td>0.56(0.29,1.20)</td>
<td></td>
</tr>
<tr>
<td>Herrmann et al.</td>
<td>5.2</td>
<td>1.20(0.33,4.00)</td>
<td></td>
</tr>
<tr>
<td>House et al.</td>
<td>5.3</td>
<td>0.53(0.15,1.80)</td>
<td></td>
</tr>
<tr>
<td>Lipsey et al.</td>
<td>1.6</td>
<td>15.99(0.99,365.16)</td>
<td></td>
</tr>
<tr>
<td>MacHale et al.</td>
<td>4.8</td>
<td>0.17(0.04,0.70)</td>
<td></td>
</tr>
<tr>
<td>Morris (a)</td>
<td>5.1</td>
<td>1.71(0.45,6.43)</td>
<td></td>
</tr>
<tr>
<td>Morris (b)</td>
<td>7.3</td>
<td>1.30(0.67,2.52)</td>
<td></td>
</tr>
<tr>
<td>Nagaraja et al.</td>
<td>4.4</td>
<td>0.96(0.20,4.72)</td>
<td></td>
</tr>
<tr>
<td>Pohjasaaretta et al.</td>
<td>7.7</td>
<td>1.34(0.62,2.19)</td>
<td></td>
</tr>
<tr>
<td>Roobinson et al.</td>
<td>4.8</td>
<td>1.52(0.36,8.48)</td>
<td></td>
</tr>
<tr>
<td>Sharpa et al.</td>
<td>3.7</td>
<td>1.45(0.22,0.34)</td>
<td></td>
</tr>
<tr>
<td>Shmota &amp; Robinson</td>
<td>5.7</td>
<td>6.51(0.00,20.33)</td>
<td></td>
</tr>
<tr>
<td>Singh et al.</td>
<td>5.8</td>
<td>0.23(0.07,0.68)</td>
<td></td>
</tr>
<tr>
<td>Storketoin (1)</td>
<td>4.2</td>
<td>4.24(0.80,22.49)</td>
<td></td>
</tr>
<tr>
<td>Storketoin (2)</td>
<td>2.8</td>
<td>22.50(2.11,240.49)</td>
<td></td>
</tr>
</tbody>
</table>

Total(95%CI) 100.0 1.22(0.73,1.97)

Test for heterogeneity ch-square=63.64 df=18 p=0.00001
Test for overall effect z=0.01 p=0.4

The region close to the frontal pole has been reported to have the greatest concentration of catecholaminergic fibres. This was thought to correspond to the observation that injuries to the frontal region of the cortex produce the greatest vulnerability to post-stroke mood disorder. Three groups were unable to replicate the interhemispheric differences found by the John Hopkins’ group (Eastwood et al. 1989; Ebrahim et al. 1987; Sinyor et al. 1986). Robinson and colleagues failed to confirm their previously established interhemispheric differences when looking at a larger number of patients (Robinson et al. 1983). Folstein et al. (1977) found that patients with right-sided lesions were more likely to suffer psychological symptoms of irritability, loss of interest, difficulty in concentrating, subjective memory loss and depressed mood when compared to controls or patients with left hemispheric lesions.
The site and size of the brain lesion in stroke does not appear to be strongly correlated with depression although the data is not consistent and it continues to be difficult to determine whether positive findings can be accounted for by the clinical consequences of the stroke or the neurophysiological changes that may lead to depression. Recent reports have suggested that psychosocial risk factors including age, sex and functional impairment or a previous history of psychiatric disturbance are greater contributors to the development of PSD than lesion location (Aben et al. 2006; Berg et al. 2003; Carota et al. 2005; Singh et al. 2000).

Conclusions Regarding Stroke Location and Depression

There is level 1a evidence from one meta-analysis that there may not be a definitive relationship between the site of the brain lesion and depression.

There remains a wide diversity of findings in studies looking at the relationships between stroke location and depression. Not all studies have confirmed this relationship and meta-analyses have failed to establish a definitive relationship between the site of the stroke and depression.

There is conflicting evidence regarding the hemispheric side of the lesion and rates of depression. Level 4 evidence from one study and level 5 evidence from three studies suggest left hemispheric strokes are more susceptible to developing depression. Level 5 evidence from one observational study suggests right hemispheric strokes are more susceptible.

There is level 5 evidence suggesting mixed results with only one outcome measure out of five revealing a significant difference in levels of depression. There is level 5 evidence of a lack of an association between the hemispheric side of the lesion and depression.

There is level 5 evidence that strokes involving the basal ganglia are associated with the development of PSD.

There is level 5 evidence suggesting that patients with stroke experience greater levels of depression and mood disturbance than traumatic brain injury patients.

Despite an abundance of research, the influence of stroke location on the risk for developing post-stroke depression has not been determined.

Stroke involvement of the basal ganglia may be associated with development of PSD.

18.4 Assessment of Post-Stroke Depression

The detection of depression is not always consistent. Given the fluctuation in the incidence of depression post stroke, timing of assessment may be an important factor in screening and diagnosis, particularly during the initial post-stroke transition phase (see section 18.2). Apart from timing, the standards against which depression is assessed are also important. At present, the criteria provided by the DSM-V are the gold standard against which diagnosis is made and form the basis for the evaluation of assessment tools.
The DSM-V no longer categorizes major and minor depression. According to the updated DSM-V, major depression disorder is present when at least 4 accessory symptoms, besides depressed mood or anhedonia are reported. Minor depression is now incorporated under the category of Other Specified Depressive Disorders: Depressive Episode and insufficient symptoms. The DSM-V criteria for the diagnosis of PSD relate to those for Depressive Disorder Due to Medical Conditions. Stoke is now a condition listed in the DSM-V as “directly”, causing depression. If full criteria are met, it can be called Depressive Disorder due to Stroke (American Psychiatric Association 2013). Gainotti et al. (1997) reported distinct differences between functional depression and post-stroke depression and demonstrated that the motivated or reactive aspects of depression are more prevalent in PSD. However, it has also been suggested that the DSM criteria for depression are equally valid among psychiatric and stroke patients. More recently, Cumming et al. (2010) demonstrated that the experience of depression in individuals with stroke is similar, though not identical, to age and sex-matched controls without stroke. Depressed individuals in the control group were significantly more likely than individuals with PSD to report symptoms of anhedonia (p=0.002) and disturbed sleep (p=0.008). There were, however, no difference in scores on either the somatic or psychological factors of depression between the depressed controls and PSD groups (Cumming et al. 2010).

Self-Report Assessment
Lincoln et al. (2003) noted that there was poor agreement between psychiatric diagnosis and self-report questionnaires. It has been reported that, in terms of screening or classifying patients on the basis of depressive symptomatology, rating scales are quite sensitive, but lack specificity (Aben et al. 2002; Lincoln et al. 2003; Schramke et al. 1998), perhaps due to the inclusion of somatic symptoms.

Dam et al. (1989) suggested that discrepancies in diagnosis between psychiatric interviews and self-report scales 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. Schramke et al. (1998) reported that patients with left hemisphere lesions were assessed as experiencing greater levels of distress than patients with right hemisphere lesions on the Center for Epidemiologic Studies Depression Scale (CES-D) and the Hamilton Rating Scale for Depression (HAMD). However, this difference between groups reached significance only on assessments made with the CES-D, a self-report measure (Schramke et al. 1998). Self-report measures rely on the assumption that the individuals being evaluated are sufficiently self-aware to provide an accurate self-assessment and report. As Lincoln et al. (2003) pointed out, this is not necessarily true of individuals who have experienced a stroke, who may either minimize or exaggerate changes.

Schubert et al. (1992) carried out a chart review of 15 stroke patients on a medical ward. Charts were examined for detection of depression by the rehabilitation team. Chart evaluation revealed no notation of depression or mention of possible depressed mood by the rehabilitation team. Assessment of these patients using the Beck Depression Inventory identified 50% of the patients as mildly depressed. Review of the psychiatric charts revealed that 68% of patients were had received some psychiatric diagnosis: 26% were diagnosed with major depression and 42% with adjustment disorder with depressed mood.

Screening for Depression
Although, formal screening for post-stroke depression may be superior to simple observation and is included among the recommendations appearing in current guidelines (see section 18.11), reported compliance is low. The UK National Clinical Guidelines for Stroke recommend screening for depression within the first month of a stroke event; however, the National Sentinel Audit for the years 2001 – 2002 revealed a compliance rate of only 50% (Bowen et al. 2005). When hospitals with psychologist input were
examined separately, the rate of compliance was 60%. An examination of reasons for non-compliance was based on survey responses received from 75 healthcare professionals affiliated with 16 stroke units in the UK (Hart & Morris 2008). These suggested that while compliance for screening was low, attitudes toward the practice were positive. While nurses most often performed the screening, neither the profession of the individual responsible for this task nor the availability of psychologist input had an effect on compliance. Identified barriers to screening included time pressures and concerns about screening tests, while being knowledgeable about screening, having screening in the job role and belief in the value of screening were identified as facilitators (Hart & Morris 2008).

Several studies evaluating detection methods for post-stroke depression are summarized in table 18.4.1.

<table>
<thead>
<tr>
<th>Study Design (PEDro Score)</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Main Outcome(s)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>da Rocha e Silva et al. (2013)</td>
<td>N&lt;sub&gt;start&lt;/sub&gt;=64, N&lt;sub&gt;end&lt;/sub&gt;=64</td>
<td>E1: Stroke patients with Post-Stroke Depression (PSD) E2: Stroke patients without PSD C: Non-stroke patients with major depression</td>
<td></td>
<td>• BDI (+) • HAM-D (+) • HAM-A (+) • HADS (+)</td>
</tr>
<tr>
<td>de Man-Van Ginkel et al. (2013)</td>
<td>N&lt;sub&gt;start&lt;/sub&gt;=410, N&lt;sub&gt;end&lt;/sub&gt;=382</td>
<td>E: Patients with depression C: Patients without depression</td>
<td></td>
<td>• SSL-6 (+)</td>
</tr>
</tbody>
</table>

- Indicates non-statistically significant differences between treatment groups
+ Indicates statistically significant differences between treatment groups

Discussion
Screening can result in an early diagnosis and therefore prompt treatment of PSD. White et al. (2013) developed an electronic screening tool that allowed clinicians to observe a summary of potential depressive symptomology in patients. Despite only receiving a summary, the clinicians in the study said that it encouraged and motivated them to open dialogue regarding PSD and monitor symptoms more frequently. The clinicians added that the reason for screening occurring infrequently was due to time constraints. In this case, a self-report assessment may be a more viable approach to save time for clinicians. However, a systematic review by Salter et al. (2013) stated that communicative issues and bias can skew the results when screening is performed by the patient. 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).

A meta-analysis conducted by Meader et al. (2014) revealed favourable verification of the Centre of Epidemiological Studies-Depression Scale (CESD), Hamilton Depression Rating Scale (HAM-D), and Patient Health Questionnaire-9 (PHQ-9) in detecting PSD and major depression during the acute and post-acute stages. Support for the PHQ-9 as an effective screening tool has also been reported by Williams et al. (2004) and de Man-van Ginkel et al. (2013). Despite the Depression subscale of Hospital Anxiety and Depression Scale (HADS) being widely used, it has been found to demonstrate poor sensitivity (Kang et al. 2013; Lees et al. 2014) but a good level of specificity (Lees et al. 2014; Meader et al. 2014). In comparing diagnoses of PSD and major depression (MD) in non-stroke patients, da Rocha e Silva et al. (2013) reported that the two conditions were dissimilar enough in that high scores on the HAM-D, Hamilton Rating Scale
for Anxiety (HAM-A), Hospital Anxiety and Depression Scale (HADS) and Beck Depression Inventory (BDI) were significantly different between the two groups.

A new screening tool known as the Post-stroke Depression Prediction Scale (DePreS) has been proposed by de Man-Van Ginkel et al. (2013). Although the authors reported a good predictive performance (sensitivity score 0.73 and a specificity of 0.75), further research and testing of the DePreS in the field is required to fully examine the efficacy of this tool.

Screening and diagnosing PSD is not without its limitations. A systematic review by Gabaldon et al. (2007) highlights the issue of verbal and communication deficits in that there is a lack of tests specifically designed for stroke patients. The authors add that the Stroke Aphasic Depression Questionnaire, the Aphasic Depression Rating Scale and the Visual Analog Mood Scales can accommodate patients with communicative deficits, however, these tests evaluate depressive symptoms but do not provide a clinical diagnosis. Moreover, the use of psychiatric tests may lead to bias due to the lack of clarity in symptoms specific to stroke and symptoms specific to stroke (Gabaldon et al. 2007). Further evidence can be observed from Kang et al.’s (2013) study as misclassification of PSD was significantly associated with lower Mini Mental State Examination (MMSE) and Barthel Index (BI) scores at two weeks post-stroke. It is therefore plausible that symptoms considered to be depressive may be specific to functional deficits post-stroke thus greater caution is required when screening for PSD.

**Conclusions Regarding Detection and Diagnosis of Post-Stroke Depression**

*There is level 1a evidence from one meta-analysis that the PHQ-9 is an effective diagnostic tool for post-stroke depression as well as favourable findings for use of the CES-D and the HAM-D.*

*There is level 5 evidence that PSD is significantly different from a diagnosis of major depression and that a new tool for PSD, the Post-Stroke Depression Predict Scale (DePres), may be of use when detecting post-stroke depression.*

*There is level 5 evidence that the Hospital Anxiety and Depression Scale (HADS) demonstrates low sensitivity but mixed conclusions were drawn regarding specificity with one study reporting a low specificity score whilst the other reported a higher score.*

Detection and diagnosis of post-stroke depression is often inconsistent. Compliance with guidelines for screening is poor. Identified barriers to routine screening include time pressures and concerns about screening tools.

*There is evidence to suggest that the PHQ-9 is an effective diagnostic tool, as well for the CES-D and HAM-D, for PSD.*

**18.5 Consequences Associated with Post-Stroke Depression**

**18.5.1 Functional Impairment and Depression Post-Stroke**
The relationship between functional deficits and depression is an ongoing topic for debate. The degree to which functional ability influences depression or depression impacts functional ability is uncertain.
However, post-stroke depression has been associated with rate of recovery and success of rehabilitation. Individual studies examining the impact of PSD on functional limitations are summarized in Table 18.5.1.1.

| Table 18.5.1.1 Summary of Studies Evaluating Functional Ability and Depression Post-Stroke |
|---|---|---|---|---|---|
| Author, Year | Study Design (PEDro Score) | Intervention | Main Outcome(s) Result |
| **Cully et al. (2005)** | Case Control | E: Stroke patients (depressed and non-depressed) C: Non-stroke patients (depressed and non-depressed) | • FIM Sphincter Control (+) • FIM Body Mobility (-) • FIM Communication (-) • FIM Self-Care (-) |
| | | NStart=509 NInt=509 | |
| **Nannetti et al. (2005)** | Case Control | E: Depressed patients treated with Physiotherapy C: Non-depressed patients treated with Physiotherapy | • Fugl-Meyer Assessment (+) • Barthel Index (+) |
| | | NStart=121 NInt=117 | |
| **Schmid et al. (2011)** | Case Control | E: Functionally independent and Depressed C: Functionally dependent and Depressed | • MMSE (+) • NIHSS (+) • Cumulative Illness Rating Scale (+) |
| | | NStart=367 NInt=367 | |
| **Brodaty et al. (2013)** | Observational | E: Patients admitted to inpatient stroke unit C: Community-dwelling volunteers | • Apathy Evaluation Scale (AES) (+) |
| | | NStart=330 NInt=253 | |
| **Rabi Zikic et al. (2014)** | Observational | E: Depressed patients C: Non-depressed patients | • HAMD (+) • SF-36 (+) • Barthel Index (+) |
| | | NStart=60 NInt=60 | |

- Indicates non-statistically significant differences between treatment groups
+ Indicates statistically significant differences between treatment groups

**Discussion**

Depression post stroke is associated with functional ability and may have a negative impact on recovery. Although patients with post-stroke depression may experience significant recovery, functional ability may remain at a lower level than non-depressed patients, despite rehabilitation interventions. Goodwin and Devanand (2008) demonstrated that co-occurrence of stroke and depression is associated with greater physical limitations than either condition on its own. In addition, Nannetti et al. (2005) revealed that despite receiving the same form of treatment in physiotherapy, stroke patients with depression reported significantly poorer functional ability compared to stroke patients without depression. This duality of depression and functional impairment has been replicated in a number of recent observational and case series studies (Brown et al. 2012; De Ryck et al. 2014a, 2014b; Yeon-Jae et al. 2014). Physical impairment and post-stroke depression appear to act upon each other, and each influences the recovery of the other.

Cully et al. (2005) reported no significant functional differences between stroke patients and non-stroke patients (except for sphincter control on the Functional Independence Measure) but when depressed and non-depressed patients were compared, stroke or otherwise, significant differences in functioning emerged. The authors assert that depressive symptoms do not discriminate between diagnoses and that routine screening would be recommended. Moreover, these findings support that a relationship exists between functional impairment and depression but not specifically among stroke populations.
Van de Port et al. (2006) recently published the results of a prospective cohort study (n=205), which demonstrated that mobility decline was experienced by 21% of participants between 1 and 3 years post stroke. Significant predictors of this decline in mobility status were level of activity, cognitive problems, fatigue and depression. Given that the relationship between depression and physical impairment may be reciprocal, depression may contribute to a progressive deterioration in mobility, which may in turn contribute to increased feelings of depression.

Since depression is a treatable condition, which impacts both function and functional recovery, it should be taken into account in the evaluation and treatment of all stroke patients (Ramasubbu 1998). Although it is difficult to determine whether depression is a significant independent factor in the development of dependency, improvement in depressive symptomatology has been associated with reduced odds for dependency at 3 months post stroke (Schmid et al. 2011). As Ramasubbu et al. (1998) pointed out, early recognition and treatment of depression may “optimize rehabilitation potential” and reduce “significant human and financial costs associated with post-stroke functional impairment”.

The relationship between physical impairment and depression proves to be a complex association with different variables and conditions often providing differing insights. Brodaty et al. (2013) investigated this relationship in the development of apathy among patients and healthy volunteers and reported that depression and functioning (as measured by activities of daily living) were significant predictors among stroke patients. In healthy volunteers, only functioning was a significant predictor. Moreover, apathy was significantly more prevalent among stroke patients compared to the healthy controls. Furthermore, apathy scores increased over time within the stroke group. This increase and overall greater prevalence in apathy can lead to a hampering of rehabilitation and result in caregiver burden (Brodaty et al. 2013).

Although there would appear to be a consensus in the reciprocal relationship between functional impairment and depression, contrasting evidence has suggested the contrary. Despite depressed patients scoring significantly higher on the Hamilton Depressing Rating Scale (HAMD) and lower on the Barthel Index, Rabi Zikic et al. (2014) did not find any correlation between the two sets of scores, indicating that depression cannot be predicted by functional impairment. The authors add that patients who were the most severely disabled at baseline were not the most depressed patients at follow-up. Although comorbidity may be inconclusive, the authors reported that functional disability was more severe in depressed patients and that a multidisciplinary approach to treatment should be implemented.

**Conclusions Regarding Functional Impairment and Depression Post-Stroke**

There is level 3 evidence that depression may have a significant and negative impact on functional ability following stroke.

There is level 3 evidence that functional dependence is associated with greater levels of depression, illness comorbidity and cognitive deficits when compared to functional independence.

There is level 5 evidence that patients admitted to an inpatient stroke unit demonstrate significantly greater levels of apathy compared to patients living in the community.

**Depression post-stroke has a negative impact on functional recovery.**
Functional dependence may be associated with greater levels of depression, cognitive deficit, and illness comorbidity.

Early identification and treatment of post-stroke depression may serve to enhance functional recovery.

18.5.2 Depression and Social Activities Post-Stroke

One study examining the association between social isolation and participation and the experience of post-stroke depression is reviewed in Table 18.5.2.1.

Table 18.5.2.1 Summary of Studies Evaluating Depression and Social Activities Post Stroke

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design (PEDro Score)</th>
<th>Intervention</th>
<th>Main Outcome(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labi et al. (1980)</td>
<td>Case Control</td>
<td>E: Stroke patients</td>
<td>• Decrease in socialization outside of home (+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C: Age and gender-matched controls</td>
<td>• Decrease in socialization in the home (+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Decrease in hobbies/interests (+)</td>
</tr>
</tbody>
</table>

- Indicates non-statistically significant differences between treatment groups
+ Indicates statistically significant differences between treatment groups

Discussion

Although there may be a tendency for individuals who were isolated prior to stroke to remain isolated (Hinojosa et al. 2011), depression is associated with reduced social activity and integration (G. Andersen 1995a; Baseman et al. 2010; Hinojosa et al. 2011; Sienkiewicz-Jarosz et al. 2010). Decreases in socialization outside and inside the home and a decrease in social hobbies and interests have been found to result in an increase of depression (Labi et al. 1980). A multi-centre study conducted by Sienkiewicz-Jarosz et al. (2010) reported that approximately 2/3 of individuals with stroke who experienced symptoms of depression reported a reduction in social contact. These individuals also expressed a significantly greater reduction in both frequency and satisfaction with contacts with both friends and family than non-depressed individuals with stroke. Frequent social contact has been found to be beneficial in reducing incidence and symptoms of depression as patients who recorded socialising with friends and frequently visiting or staying with family reported significantly lower Hamilton Rating Scale of Depression (HAMD) scores (Jean et al. 2013).

Community reintegration is an important aspect of improving social participation of patients post stroke. A negative correlation was found between PSD scores and the level of satisfaction with community reintegration by Baseman et al. (2010) and Obembe et al. (2013) who reported higher satisfaction with integration was associated with lower incidence of PSD. It is unclear as to the directionality of this correlation (i.e. lower PSD resulting in more social integration, or more integration resulting in lower PSD symptomology), however, the association between the two is telling. It is also important to note that social integration needs to be approached with caution. Similarly, Van Puymbroeck et al. (2014) found a positive correlation between high depression scores and a higher number of limitations towards activity, indicating that a lack of activity is associated with depressive symptoms. However, the findings from Jean et al.’s (2013) study suggests that a cautious approach to community reintegration may be beneficial as patients who returned to work or played sports reported significantly higher HAMD scores compared to those who took up passive activities such as listening to music and non-physical leisure.
The effects of stroke may alter how patients perceive themselves, their capabilities and self-image (Labi et al. 1980). These perceptions are associated with depression (Feibel & Springer 1982) and are also associated with social withdrawal, which may in turn, further exacerbate depression after stroke. Andersen et al. (1995) demonstrated that social factors explained only 3% of the variance in mood; however, even after intensive intervention for depression, social function among depressed stroke survivors was still significantly lower than among non-depressed stroke survivors during the first year following the stroke event. The significant relationship identified between lower social function prior to stroke and depression (Andersen et al. 1995b) highlights the difficulty in separating the risk factors for post-stroke depression from its consequences.

**Conclusion Regarding Depression and Social Activities Post-Stroke**

_There is level 3 evidence that decreased socialization outside of the home, inside the home, and in hobbies and interests lead to significant increases in depressive symptoms among stroke patients compared to age and gender-matched controls._

_There is level 5 evidence that patients who socialize with friends, spend time with relatives and/or a partner, and participate in passive activities such as listening to music exhibit lower levels of depression while returning to work and/or playing sports was associated with higher levels of depression._

_There is a significant association between the presence of depression and greater social isolation._

_Returning to work and/or playing sports may be associated with higher levels of depression compared to engaging in passive activities._

### 18.5.3 Cognitive Impairment and Depression Post-Stroke

Cognitive impairments have been associated with stroke and some believe they contribute to post-stroke depressive disorders. However, the reciprocal relationship may also apply. Observational studies have suggested that depressive disorders can contribute to cognitive impairment in post-stroke patients. Individual studies examining the association between cognitive impairment and post-stroke depression are summarized in Table 18.5.3.1.

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design (PEDro Score)</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Main Outcome(s) Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prokopenko et al. (2013)</td>
<td>RCT (8)</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=43 N&lt;sub&gt;End&lt;/sub&gt;=43</td>
<td>E: Individual computer program training consisting of Schulte’s table tasks and figure-background tests. C: Standard treatment.</td>
<td>• HADS Anxiety (-) • HADS Depression (-) • CDT (+) • FAB (+) • ST (+)</td>
</tr>
<tr>
<td>Dam et al. (2001)</td>
<td>Observational</td>
<td>N&lt;sub&gt;Start&lt;/sub&gt;=127 N&lt;sub&gt;End&lt;/sub&gt;=99</td>
<td>E: Stroke patients C: Prolapsed Intervertebral Disc patients</td>
<td>• Research diagnostic criteria (RDC) diagnosis of depression (-) • HAMD (-) • BDI (-)</td>
</tr>
</tbody>
</table>
Discussion

Overall, there appears to be a relationship between cognitive impairment and the presence of depression, although the reported results vary and the relationship appears complex.

As is the case for many of the factors with which PSD has been associated, it is difficult to determine whether cognitive impairment results from depression, is a risk factor for depression, or both (Andersen et al. 1995b; Bour et al. 2010; Saxena et al. 2008). Mostly recently, Bour et al. (2010) demonstrated that, over time, the presence of depression was a significant predictor for executive dysfunction, while the presence of executive dysfunction was also associated with depression. Sibolt et al. (2013) expanded on this concept by investigating a subtype of depression known as Depression-Executive Dysfunction Syndrome (DES), a duality of depressive and cognitive impairment symptoms. The authors reported a significantly higher and faster recurrence rate of ischemic stroke among patients diagnosed with DES but executive dysfunction alone was not associated with recurrence rates. These findings would coincide with theory that a relationship exists between cognitive impairment and depression among stroke patients.

In comparing cognitive impairment and depression between two distinct groups of patients at seven year follow-up, Dam et al. (2001) did not reveal any significant differences in cognitive abilities between stroke patients and patients with prolapsed intervertebral spinal discs. However, stroke patients demonstrated greater levels of depressive symptoms and irritability, and depressed stroke patients were significantly more cognitively impaired than non-depressed stroke patients. Moreover, these symptoms were still apparent in stroke patients up to seven years post-stroke, indicating that depressive symptomology is a long-term concern with cognitive functioning also at risk of impairment during this time.

Based on a large sample of older adults (n=6,476) Chodosh et al. (2010) demonstrated that incident and prevalent depression along with stroke and functional deficits may be significant contributors to poorer cognitive functioning in a stepwise fashion; that is, depression or stroke may have a negative impact on cognitive function at the time of their onset. However, the presence of depression was not associated with continued deterioration in cognitive function over time. The authors note that depression, chronic disease and physical function probably have multidirectional relationships that confound our attempts to understand causation.

However, Murata and colleagues (2000) demonstrated that, in 41 stroke patients with major depression diagnosed in an acute hospital setting, improvement in depression over 3 to 6 months was associated with significantly greater increases in cognitive function when compared to depressed individuals with no mood improvements. The authors suggest that, since patients with major depression whose mood improved experienced greater cognitive improvement than any other group of study participants, depression leads to cognitive impairment and produces a “dementia of depression”. Further study is required to clarify the association between cognitive impairment and depression following stroke.

In a randomized controlled trial by Prokopenko et al. (2013), patients were asked to complete Schulte Tables as part of a cognitive computer training program and were assessed for depression, anxiety and cognitive impairment. Although the treatment group demonstrated significantly greater improvements in all cognitive measures compared to the control group after the two week study period, there were no significant differences in depression and anxiety scores between groups. Furthermore, Aben et al. (2014)
provided similar results after stroke patients completed a memory self-efficacy training program. Patients who completed the program demonstrated significantly greater improvements in memory self-efficacy compared to the control group patients but no significant differences were noted in levels of depression. These findings would suggest that cognitive impairment and depression may not be in tandem, rather, they are mutually exclusive.

Conclusions Regarding Cognitive Impairment and Depression Post-Stroke

There is level 1a evidence that cognitive impairments can be improved with cognitive training interventions but these do not result in improvements for depression.

There is level 5 evidence that executive dysfunction and depression-executive dysfunction syndrome are both associated with older age.

Executive dysfunction has been found to be associated with older age.

Post-stroke depression is associated with cognitive impairment and is likely reciprocal. Further research is required.

18.5.4 Mortality and Depression Post-Stroke
Recent attention has been paid to the association between depression and mortality. The presence of depressive symptomatology has been reported to be associated with an increase in stroke mortality. In a community-based sample followed for a period of 29 years, Everson et al. reported that the presence of 5 or more depressive symptoms was associated with a significant increase in risk for mortality from stroke in individuals who were healthy, and stroke free at the beginning of their surveillance (HR = 1.66, p<0.006) (Everson et al. 1998). This association remained significant after adjustment for education, alcohol consumption, smoking, body mass index, hypertension and diabetes (HR=1.54; p<02). Every point increase in depressive symptomatology was associated with an 8% increase in risk for stroke mortality (p<0.003) (Everson et al. 1998). Similarly, Kamphuis et al. (2006) reported that, in a 10-year prospective study of 799 men who had no cardiovascular disease and were aged 70 – 90 at baseline, the risk of death from stroke increased as depressive symptomatology increased. Each 5-point increase on the Zung Self-rating Depression Scale was associated with a 35% increase in the risk for death from stroke HR = 1.35 (95% CI 1.19 – 1.53 adjusted for country of origin, education, BMI, smoking, alcohol intake, cholesterol levels and level of physical activity). When compared to individuals with low symptomatology at baseline, individuals with high levels of depressive symptomatology were more than 3 times as likely to die from stroke (HR = 3.41 95% CI 1.69 – 6.90).

Depression has also been linked to higher mortality among elderly patients with physical illness; however, how moods are linked to mortality remains unclear (House et al. 2001; Lewis et al. 2001; Morris et al. 1993). Individual studies focusing on the association between post-stroke depression and mortality appear in Table 18.5.4.1.

Table 18.5.4.1 Summary of Studies Evaluating Mortality and Depression Post-Stroke

<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></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

18. Post Stroke Depression and Mood Disorders  www.ebrsr.com
**Discussion**

Overall, studies suggest that there is an association between psychological distress and mortality. Reynolds et al. (2008) demonstrated an association between the presence of symptoms of depression and shorter total life expectancy in both men and women aged 70 and 85. Although the reduction in life expectancy for individuals with depressive symptomatology and stroke (compared to stroke alone) did not reach significance, the presence of both variables was associated with a reduction in total life expectancy of approximately 1.5 years in both men and women aged 70. Moreover, Naess et al. (2013) reported a significant association between mortality and depression as well as fatigue and social factors such as smoking, alcoholism, unemployment and being unmarried. Future health concerns were also found to be at risk with high baseline scores in depression resulting in an increased risk of cardiovascular mortality (Peters et al. 2010). Results of the study by Williams et al. (2004) demonstrated an increased risk for mortality for those patients with PSD and also indicated that other mental health conditions such as schizophrenia, major affective disorders (not depression), anxiety disorders, personality disorders and substance abuse/dependence have a similar association with long-term mortality risk. Results from House et al. (2001) and Lewis et al. (2001) suggest that the identified association may not be between depression and mortality per se, but is between a more general psychological distress and mortality instead. In support of this, Almeida and Xiao (2007) revealed a link between dementia and psychotic disorders with mortality but no significant association between depression and mortality. Further study is required to clarify this association in individuals who have experienced stroke.

Furthermore, a potential consequence of depression going untreated could lead to the risk of developing suicidal ideation or even suicide itself. Attempted suicide was found to be significantly higher among depressed patients than non-depressed patients (Eriksson et al. 2015). As illustrated by Tang et al. (2015), patients with high scores in depression and a greater prevalence of apathy were significantly more likely to exhibit ideations of suicide than those with lower depression scores and apathy. Among the risk factors with which PSD and suicide post-stroke are associated includes male gender, younger age (18-54 years old) and within two years post-stroke (Eriksson et al. 2015).

**Conclusions Regarding Mortality and Depression Post-Stroke**

*There is level 3 evidence that the presence of mental health disorders post stroke, including depressive symptomatology, has been associated with an increased risk for mortality. Further study to clarify the association between psychological distress and mortality is required.*

*There is level 4 and level 5 evidence that presence of depression, presence of apathy, male gender, younger age, and use of anti-depressants are significant risk factors for suicide and suicidal ideation.*
The presence of mental health disorders post-stroke is associated with increased risk for mortality.

Depression and use of anti-depressants post-stroke have been found to be associated with greater rates of suicide and suicidal ideation.

18.6 Prevention of Post-Stroke Depression

Given the negative impact of post-stroke depression on stroke recovery, early initiation of antidepressant treatment in stroke patients to prevent the development of post-stroke depression has been investigated (Narushima et al. 2002; Palomaki et al. 1999). Individual studies examining the effectiveness of early initiation of antidepressant therapy in stroke patients are summarized in Table 18.6.1.

### 18.6.1 Summary of Studies Evaluating Prevention of Post-Stroke Depression

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design (PEDro Score)</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Main Outcome(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almeida et al. (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>• HADS-D (-)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Prescription of Anti-depressants (-)</td>
</tr>
<tr>
<td>Chollet et al. (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>• Symptoms of depression over 90d (+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Fugl-Meyer Motor Scale (FMMS) (+)</td>
</tr>
<tr>
<td>Palomäki et al. (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 (10mg, 60mg/d) C: Placebo</td>
<td>• HDS (0mo and 2mo) (+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• HDS (6mo, 12mo, 18mo) (-)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• BDI (-)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• SSS (-)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• CGI (-)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Barthel Index (-)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Rankin Scale (-)</td>
</tr>
<tr>
<td>Narushima et al. (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>• HAMD (+)</td>
</tr>
<tr>
<td>Tsai et al. (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 (50mg, 100mg/d) C: Placebo</td>
<td>• HAMD (+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Side effects (-)</td>
</tr>
<tr>
<td>Rasmussen et al. (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>• HAMD (+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• GDS (-)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• MMSE (-)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Barthel Index (-)</td>
</tr>
<tr>
<td>Robinson et al. (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 (5-10 mg/d) E2: Problem-solving Therapy C: Placebo</td>
<td>• Development of depression according to HAMD (+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Adverse events (-)</td>
</tr>
<tr>
<td>Mikami et al. (2013)</td>
<td></td>
<td></td>
<td>E1: Escitalopram (5mg/d)</td>
<td>• Apathy Scale (CG vs EG1) (+)</td>
</tr>
</tbody>
</table>

18. Post Stroke Depression and Mood Disorders

www.ebrsr.com
RCT (6)
N_{\text{Start}}=176
N_{\text{End}}=154

E2: Problem-solving Therapy
C: Placebo
• Apathy Scale (CG vs EG2) (+)
• Adverse events (-)
• FIM (apathy vs non-apathy patients) (-)
• RBANS (apathy vs non-apathy patients) (-)

Niedermaier et al. (2004)
RCT (5)
N_{\text{Start}}=70
N_{\text{End}}=62

E: Mirtazapine (30-45mg/d)
C: No medication.
• Development of depression according to HAMD (+)

- Indicates non-statistically significant differences between treatment groups
+ Indicates statistically significant differences between treatment groups

Discussion
Overall, individual studies offer conflicting evidence with regard to prevention of PSD through pharmacological intervention. However, a positive trend toward protection against depression associated with prophylactic treatment appears to be present. Given that all of the studies summarized in Table 18.6.1 included only patients with no depression at baseline and used the appearance of depression as a primary study outcome, a pooled analysis of data was conducted to evaluate the effectiveness of pharmacological intervention in the prevention of depression following stroke (Figure 18.6.1).

It should be noted that all but one study used an interview-based assessment to determine the presence of depression (Almeida et al. 2006). Pooled analysis of data demonstrated a significantly reduced risk for depression associated with pharmacological treatment (OR=0.38, 95%CI 0.24-0.61). Although there was no significant heterogeneity identified between studies, there are some notable differences such as variations in pharmacologic agents used, and length of treatment, that should be noted. Fluoxetine was found to be a successful choice of pharmacological treatment with two studies reporting significantly lower rates of depression (Chollet et al. 2011) and the severity of depressive symptoms (Narushima et al. 2002).

Figure 18.6.1. Effectiveness of Pharmacological Agents on Post-Stroke Depression

<table>
<thead>
<tr>
<th>Study name</th>
<th>Odds ratio Lower limit</th>
<th>Odds ratio Upper limit</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palomaki et al. (1999)</td>
<td>0.957 0.259</td>
<td>3.533</td>
<td>0.947</td>
</tr>
<tr>
<td>Narushima et al. (2002)</td>
<td>0.314 0.071</td>
<td>1.392</td>
<td>0.127</td>
</tr>
<tr>
<td>Rasmussen et al. (2003)</td>
<td>0.325 0.118</td>
<td>0.897</td>
<td>0.030</td>
</tr>
<tr>
<td>Niedermaier et al. (2004)</td>
<td>0.091 0.019</td>
<td>0.441</td>
<td>0.003</td>
</tr>
<tr>
<td>Almeida et al. (2006)</td>
<td>0.727 0.265</td>
<td>1.998</td>
<td>0.537</td>
</tr>
<tr>
<td>Robinson et al. (2008)</td>
<td>0.321 0.106</td>
<td>0.967</td>
<td>0.044</td>
</tr>
<tr>
<td>Tsai et al. (2011)</td>
<td>0.143 0.016</td>
<td>1.252</td>
<td>0.079</td>
</tr>
<tr>
<td>Chollet et al. (2011)</td>
<td>0.173 0.054</td>
<td>0.555</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>0.341 0.219</td>
<td>0.529</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Meta Analysis

Other medications such as Mirtazapine and Milnacipran also demonstrated a significant effect of preventing PSD prevalence compared to placebo groups (Niedermaier et al. 2004; Tsai et al. 2011). However, other medications such as Mianserin exhibited a short-term effect with a lower rate of depression in the treatment group at two month follow-up but no differences between groups at 6, 12
and 18 months (Palomaki et al. 1999). Sertraline revealed mixed results as Almeida et al. (2006) did not find a significant difference between treatment and placebo groups and Rasmussen et al. (2003) revealed an efficacious effect of preventing depression among treatment patients compared to a placebo group according to Hamilton Rating Scale for Depression scores but not on the Geriatric Depression Scale. In the case of the latter, it could be argued that the outcome measures may lack parity. Nonetheless, the evidence regarding the use of Sertraline is lacking.

Sudden cessation of preventative pharmacotherapy may be associated with an increased risk for post-stroke depression. In comparing Escitalopram with a placebo, patients in the placebo condition were significantly more likely to develop depression, even after controlling for previous mental health concerns (Robinson et al. 2008b). However, in a follow-up to Robinson et al. (2008b), Mikami et al. (2011) reported that six months following discontinuation of treatment with escitalopram, study participants were at a significantly increased risk for developing depression when compared to those who had been assigned to either the problem-solving therapy or placebo study conditions. Further research by Mikami et al. (2013) found that patients in the placebo study group were significantly more likely to develop apathy compared to patients in the Escitalopram and problem-solving therapy groups although the time to onset of apathy did not differ between groups (5.1 months, 6 months and 6.3 months respectively). This is somewhat contrasting to the authors’ previous finding that patients prescribed Escitalopram were at an increased risk of mental health concerns. To further illustrate the efficacy of Escitalopram, no significant adverse events were reported between all three groups.

Duration of treatment ranged from three months (Chollet et al. 2011; Narushima et al. 2002) to one year (Niedermaier et al. 2004; Palomaki et al. 1999; Rasmussen et al. 2003; Robinson et al. 2008b; Tsai et al. 2011). Cases of depression presented in figure 18.2 were those recorded at the end of treatment in each study. Two of the studies that did not demonstrate a significant effect in favour of treatment reported a shorter duration of intervention; 3 months (Narushima et al. 2002) and 24 weeks (Almeida et al. 2006).

**Conclusions Regarding Prevention of Post-Stroke Depression**

*There is level 1a evidence that early initiation of antidepressant therapy, in non-depressed stroke patients is associated with reduced risk for the development of post-stroke depression. Further study is required to assess both duration of treatment and optimal timing for the initiation of therapy.*

*There is level 1a evidence that Fluoxetine is an effective pharmaceutical treatment for preventing PSD with level 1b evidence from one RCT that Fluoxetine can also improve functional disabilities.*

*There is level 1a evidence that Escitalopram can assist with improving mood among stroke patients with one RCT revealing a successful prevention of depression compared to problem-solving therapy and a placebo group, and another RCT revealing a prevention of apathy compared to a placebo.*

*There is mixed evidence regarding the efficacy of Sertraline with level 1b evidence it does not prevent depression any better than a placebo while other level 1b evidence reporting successful prevention of depression compared to placebo.*

*There is level 1b evidence that Milnacipran may be effective in preventing depression compared to a placebo.*
There is level 2 evidence that Mirtazapine may be effective in preventing depression compared to not receiving pharmacological treatment.

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

Fluoxetine, Escitalopram, Milnacipran and Mirtazapine have been reported to be effective in preventing depression but there is mixed results concerning the efficacy of Sertraline.

18.6.1 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. The studies summarized in Table 18.6.1.1 have assessed the impact of care provision on the mental health and/or mood status of stroke patients.

18.6.1.1 Summary of Studies Evaluating the Impact of Care Provision Interventions on Post-Stroke Depression

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design (PEDro Score)</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Main Outcome(s)</th>
</tr>
</thead>
</table>
| Burton and Gibbon (2005) | RCT (7) | N_{Start}=176 N_{End}=128 | E: Follow-up visits from stroke nurse C: No contact | - BDI (+)  
- Barthel Index (+)  
- Nottingham Health Profile (+) |
| Watkins et al. (2007) | RCT (7) | N_{Start}=411 N_{End}=340 | E: Motivational Interviewing C: Usual Care | - GHQ-28 Mood (+)  
- Yale Self-report Screening Tool (+) |
| Watkins et al. (2011) | RCT (7) | N_{Start}=411 N_{End}=320 | E: Motivational Interviewing C: Usual Care | - GHQ-28 Mood (+)  
- Yale Self-report Screening Tool (-)  
- Stroke Expectations Questionnaire (-) |
| Hackett et al. (2013) | RCT (7) | N_{Start}=201 N_{End}=164 | E: Personalised postcards wishing the patients well and inviting patients to contact the hospital C: Did not receive postcards | - HADS Depression (-)  
- HADS Anxiety (-)  
- AQoL (-)  
- PHQ-9 (-) |
| Rochette et al. (2013) | RCT (7) | N_{Start}=186 N_{End}=139 | E: Multimodal support intervention in the form of weekly phone calls and follow-ups C: Provided with the name and phone number of a trained healthcare professional and asked to call when needed | - BDI-II (-)  
- LIFE-H (-)  
- EQ-5D (-)  
- QOLI (-)  
- Unplanned use of health services (-) |
| Drummond et al. (2013) | RCT (6) and Cohort | N_{Start}=93 N_{End}=86 | E: Pre-discharge home assessment visit by occupational therapist C: Pre-discharge hospital interview | - SADQ-10 (at 1wk) (+)  
- SADQ-10 (at 1mo) (-)  
- EQ-5D (-) |
| Lincoln et al. (2003) | RCT (5) | N_{Start}=250 N_{End}=187 | E: Support and information provided to patients and carers from Stroke Family Support Organiser service C: Usual Care | - GHQ-12 (-)  
- Barthel Index (-)  
- EADL (-) |
Claiborne (2006)  
RCT (5)  
N_{Start}=28  
N_{End}=28  
E: Home visit followed by weekly telephone appointments  
C: Usual Care  
- GDS (+)  
- Adherence to assigned regimens (+)  
- SF-36 Physical (-)

Ostwald et al. (2014)  
RCT (5)  
N_{Start}=159  
N_{End}=134  
E: Mailed letters containing resource information plus home visits  
C: Mailed letters containing resource information but no home visits  
- GDS (-)  
- PSS (-)  
- FIM Cognitive (-)  
- SIS Memory (-)  
- SIS Social Participation (-)

Joubert et al. (2006)  
RCT (4)  
N_{Start}=97  
N_{End}=80  
E: Shared Care – GPs of patients given goals and recommendations for risk factor management and appointments with patients  
C: Usual Care  
- PHQ-9 Depression (-)  
- Target blood pressure (-)  
- Number of walks per week (+)

- Indicates non-statistically significant differences between treatment groups  
+ Indicates statistically significant differences between treatment groups

**Discussion**

Based on the studies summarized above, there is evidence that involvement in ongoing contact, counselling and support may decrease deterioration of mental health and/or mood state following stroke (Burton & Gibbon 2005; Claiborne 2006; Joubert et al. 2008, 2006). Both studies by Joubert et al. (2008; 2006) and Claiborne (2006) included increased screening for the identification of depression. In the care coordination model of Claiborne (2006), social workers provided some counselling as necessary, or referred the patient for more extensive health services as deemed appropriate. A conflicting set of results was reported by Lincoln et al. (2003) as patients and caregivers who received support from a family support initiative did not demonstrate any significant differences compared to patients who received standard care. Overall, ensuring that mental health issues were identified and addressed was associated with improved mental health, quality of life and a reduction of depressive symptoms.

Ensuring patients are suitably homed after discharge has been found to be a potential factor in the development of PSD. Drummond et al. (2013) compared patients who received a pre-discharge home visit assessment with an occupational therapist in their home and patients who instead received a pre-discharge interview. Home visit assessments were found to be successful in the short-term with patients reporting significantly lower depression scores at one week post-discharge compared to the control group. However, no significant differences were found at one month post-discharge. It is also worth noting that there were significantly more hospital readmissions within the intervention group and more falls within the home (non-significant) which may have contributed to greater rates of depression. Greater planning and provisions within the home may assist maintaining a safe environment but further research is required to determine potential links with depression and mental health.

Two randomized control trials investigated the use of a community outreach approach via postal mail with educational resources and letters (Ostwald et al. 2014) and postcards inviting patients to contact the hospital should they need support (Hackett et al. 2013). Although both studies failed to find significant differences between the intervention and control conditions, both studies cited sampling issues. A similar method was utilised by Rochette et al.’s (2013) multi-centre trial who used telephone calls as opposed to postal mail with the intervention group receiving telephone calls and the control group encouraged to make calls to healthcare professionals when needed. Again, there were no significant differences between groups regarding depression rates. Despite the lack of significant group differences, both Ostwald et al. (2014) and Rochette et al. (2013) noted improvements among both groups of patients therefore indicating that community outreach programs may still hold some value for reducing the prevalence of PSD.
A single intervention evaluated the use of a specific intervention, motivational interviewing, and reported similarly positive results (Watkins et al. 2007; 2011). However, it was not clear whether the benefit associated with assignment to the motivational interviewing intervention could be attributed to the talk-therapy technique itself, or to the ongoing, increased, individualized attention and perceived support. Further study using an attentional control group may serve to clarify this issue.

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

- There is level 1a evidence that ongoing individualized contact and support provided via various care provision models is associated with less deterioration of mood and/or mental health state following stroke.

- There is level 1a evidence that outreach communication initiatives such as mailed postcards and letters to patients are ineffective in reducing depression however mixed evidence in regards to direct telephone calls with level 1b evidence that it is ineffective and level 2 evidence that weekly telephone appointments reduced depression scores.

- There is level 1a evidence that motivational interviewing resulted in significant improvements in reducing depression compared to usual care.

- There is level 1b evidence that outreach initiatives in the form of follow-up home visits from nurses resulted in significant improvements in depression and functioning compared to no contact or home visits.

- There is level 2 evidence that assistance from a stroke family support service did not result in a significant improvement in depression compared to usual care.

- There is level 2 evidence that goals and recommendations for general practitioners to manage risk factors and provide frequent appointments with patients did not reduce rates of depression significantly compared to usual care.

**Ongoing, individualized contact and supportive communication may reduce the risk for deterioration of psychological health following stroke.**

**There is mixed results regarding community outreach programs with evidence suggesting that home visits can reduce depression and functioning but other results suggest support provided by a liaison from a stroke family support service did not provide any greater improvement than usual care.**

**18.6.2 Dietary Supplementation**

**18.6.2.1 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 reports have
provided support for this apparent association, other studies have shown no association at all between omega-3 PUFAs and depression (Appleton et al. 2010).

Numerous trials have been conducted to assess the potential for omega-3 fatty acids as a treatment for or prophylactic measure against depression. In a recent meta-analysis, Appleton et al. (2010) identified 35 randomized controlled trials evaluating the impact of omega-3 fatty acids on depressive symptomatology. Of these 35 trials, the authors were able to include 29 studies in a pooled analysis which demonstrated a significant treatment effect in favour of omega-3 PUFAs. The positive treatment effect appeared to be limited to trials enrolling individuals with a diagnosed depressive disorder (SMD = 0.41, 95% CI 0.26-0.55) vs. trials that included individuals with no depression (SMD=0.22, 95% CI -0.01-0.44). It should be noted that all pooled analyses demonstrated significant heterogeneity, perhaps due to publication bias (Appleton et al. 2010).

Of the 35 trials identified in the Appleton et al. analysis, none were conducted in the population of individuals with stroke (Appleton et al. 2010). A single RCT has examined the impact of fish oil supplementation on mood following stroke (Table 18.6.2.1.1).

Table 18.6.2.1.1 Summary of Studies Evaluating Omega-3 Fish Oil Supplementation and Mood

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design (PEDro Score)</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Main Outcome(s)</th>
<th>Result</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 (+) GHQ-28 Depression (-) SF-36 Physical (-) SF-36 Mental (-)</td>
<td></td>
</tr>
</tbody>
</table>

- Indicates non-statistically significant differences between treatment groups
+ Indicates statistically significant differences between treatment groups

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, that this study did not focus on individuals with depression, for whom this treatment has been identified as effective in other participant populations.

Conclusions Regarding Omega-3 Fish Oil Supplementation and Mood Post-Stroke

There is level 1b evidence that fish oil supplementation following stroke has no impact on mood.

Dietary supplementation with omega-3 fatty acids has no impact on mood post stroke.

18.6.2.2 B-Vitamins
Depression and stroke share common cardiovascular risk factors. It has been suggested that elevated homocysteine may be one of these shared factors (Almeida et al. 2010). Previous studies have demonstrated that in older community-dwelling individuals, vitamin B12 deficiency may be associated with increased risk for depression (Kim et al. 2008; Tiemeier et al. 2002). As part of the Rotterdam study, Tiemeier et al. (2002) demonstrated that elderly individuals with lower levels of vitamin B12 (<258pmol/L) were significantly more likely to have a depressive disorder than individuals with normal levels of the vitamin (OR=1.63, 95% CI 1.03-2.58 adjusted for age, gender, general confounders, functional disability...
and the presence of cardiovascular risk factors). Similarly, in a sample of 40 individuals with first-ever lacunar stroke, Huijts et al. (2012) reported a significant association between vitamin B₁₂ deficiency and both symptoms of depression and severe fatigue. Elevated levels of homocysteine and reduced levels of folate may also be associated with depression (Kim et al. 2008; Tiemeier et al. 2002); however, this association may be mediated by the presence of functional limitations (Tiemeier et al. 2002).

A single study has examined the impact of B-vitamins on the risk for post stroke depression (Table 18.6.2.2.1).

### 18.6.2.2.1 Summary of Studies Evaluating B-Vitamin Supplementation in the Treatment of Post-Stroke Depression

<table>
<thead>
<tr>
<th>Author, Year Study Design (PEDro Score) Sample Size</th>
<th>Intervention</th>
<th>Main Outcome(s) Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almeida et al. (2010) RCT (10) (N_{\text{Start}}=563) (N_{\text{End}}=273)</td>
<td>E: B-Vitamins tablet (1/d) C: Placebo</td>
<td>• Mini-International Neuropsychiatric Interview (MINI) ±</td>
</tr>
</tbody>
</table>

- Indicates non-statistically significant differences between treatment groups
+ Indicates statistically significant differences between treatment groups

### Discussion

The results of a single RCT of high quality suggest that B-vitamin therapy may be protective for 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 vitamin therapy remains unknown as the average time from the index stroke event to study enrolment was 7 months. Given that the incidence of post stroke depression is highest in the first months following stroke, earlier initiation of preventive strategies might be more effective. In addition, the effectiveness of the vitamin therapy tested by Almeida et al. was not apparent until treatment had been administered for approximately 6 years (Almeida et al. 2010). Further study of duration, timing and dosage is required.

### Conclusions Regarding B-Vitamin Therapy

There is level 1b evidence that B-vitamin therapy, administered over a long period, may be associated with reduction in long-term risk for depression. Further study is required.

Long-term vitamin-B therapy may reduce risk for depression following stroke.

### 18.7 Pharmacologic Treatment of Post-Stroke Depression

Treatment of post-stroke depression may involve the use of medications, the rare use of electroconvulsive treatments and psychosocial therapies. Drug therapy for depression is based on the notion that depression is associated with an imbalance and under-activity of the cerebral noradrenergic and serotonergic systems.
In a meta-analysis of 16 studies (including 6 studies from the Chinese literature) examining the use of antidepressants in individuals with post-stroke depression, Chen et al. (2006) reported a significant treatment response regardless of the definition of response used by individual study authors. In addition, treatment was associated with a significant reduction in depressive symptomatology on all scales used to assess outcome. Chen et al. (2006) also identified a relationship between duration and benefit of treatment. Pooled analysis of studies with treatment durations of 1 and 2 weeks revealed no significant treatment effects. However, from 3 weeks onward, demonstrated effects were, generally, of increasing significance.

In a Cochrane review, Hackett et al. (2008) included 12 studies examining the use of pharmacological interventions for the treatment of PSD. Like the Chen et al. (2006) review, Hackett et al. (2008) included trials examining a variety of agents initiated at a variety of times post stroke and for varying intervals. Using pooled analysis where possible, the authors concluded that use of pharmacotherapy was associated with a small, but significant, positive treatment effect. However, this should be considered in light of increasing reports of adverse effects associated with the use of antidepressant medications.

18.7.1 Heterocyclic Antidepressants

Cyclic 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. Finklestein et al. (1987) conducted a retrospective review study of 60 stroke patients with depression who were treated with one of several cyclic antidepressant drugs including doxepine, maprotiline, trazadone, desipramine, amitriptyline, imipramine or who received no treatments. It was found that only 17% of the untreated patients attained an improvement in depression scores compared to 40% of the drug responders. Furthermore, drug responders showed a greater improvement in depression change scores than non-drug responders or untreated patients. Although this was a comparative retrospective study it demonstrates the potential value of anti-depressants post stroke.

There are several RCTs that have investigated the efficacy of heterocyclic drugs in the treatment of post-stroke depression (Table 18.7.1.1).

### Table 18.7.1.1 Summary of Studies Evaluating Heterocyclic Antidepressant in the Treatment of Post-Stroke Depression

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design (PEDro Score)</th>
<th>Intervention</th>
<th>Main Outcome(s) Result</th>
</tr>
</thead>
</table>
| Lipsey et al. (1984) | RCT (8) | E: Nortriptyline (20-100mg/d) C: Placebo | • HAMD (+)  
• Zung Self-Rating Depression Scale (+)  
• Present State Examination (-)  
• Overall depression score (HAMD, ZDS & PSE) (+) |
| | | N_{Start}=39  
N_{End}=34 | |
| Robinson et al. (2000) | RCT (8) | E1: Nortriptyline (25-100mg/d)  
E2: Fluoxetine (10-40mg/d) C: Placebo | • HAMA (+)  
• HAMD (+)  
• FIM (+)  
• John Hopkins Functional Inventory (+)  
• MMSE (-)  
• Social Function Exam (-) |
| | | N_{Start}=104  
N_{End}=83 | |
| Lauritzen et al. (1994) | RCT (7) | E: Imipramine (25-75mg/d) plus Mianserin (10mg/d) | • Melancholia Scale (+) |
18. Post Stroke Depression and Mood Disorders

Discussion

When compared to placebo, heterocyclic antidepressant medications demonstrated a significant treatment effect (Lipsey et al. 1984; Robinson et al. 2000). Robinson et al. (2000) compared a heterocyclic antidepressant with a serotonin reuptake inhibitor and found nortriptyline (a heterocyclic drug) to be more effective than the serotonin reuptake inhibitor fluoxetine.

Robinson et al. (2000) observed nortriptyline improved the Hamilton Depression Scale scores significantly more than fluoxetine and/or placebo. In addition, the response rate of nortriptyline was significantly greater than both fluoxetine and placebo (Robinson et al. 2000) (See Figure 18.7.1).

Double blind, placebo controlled randomized crossover trial of 104 patients. 104 patients with stroke were randomly assigned to receive fluoxetine (10mg/day gradually increased to 40 mg/day), nortriptyline (dose of 25 mg/day gradually increased to 100 mg/day) or matching placebo over 12 weeks. Patients received 12 weeks of active treatment followed by a cross-over period of 12 weeks to placebo.

Nortriptyline treated group showed significantly greater improvement on the HAMD than the other 2 groups. Nortriptyline produced a significantly higher rate than fluoxetine or placebo in treating post-stroke depression, in improving anxiety symptoms and in improving recovery of activities of daily living as measured by the FIM.

Figure 18.7.1 Nortriptyline versus fluoxetine in the treatment of depression and in short-term recovery after stroke (Robinson et al. 2000)

While the Lipsey et al. (1984) study results were promising, they noted confusion, drowsiness and agitation were significant side effects that may pose risks to elderly patients. Likewise, while the heterocyclic combination of imipramine and mianserin significantly improved melancholia scale scores, Lauritzen et al. (1994) noted that a significant number of patients dropped out of their study because of side effects. In all the studies mentioned, patients with myocardial infarctions were excluded. Furthermore, those with cardiac arrhythmias, heart block, urinary outlet obstructions and narrow-angle glaucoma are advised against the use of heterocyclic antidepressants and, indeed, the use of amine medications (including imipramine, amitriptyline, nortriptyline or desipramine) has been linked to adverse
cardiovascular, anticholinergic and antihistamine effects (Kumar 1999). Steffens et al. (2008) demonstrated a significant association between use of tricyclic antidepressants and worsening of white matter lesions (OR = 1.77, 95% CI 1.07 to 2.94). Although the use of SSRI therapy was also associated with an increased risk for progression of white matter lesions, the effect was not significant.

The relatively high incidence of side effects associated with heterocyclic antidepressants, especially in elderly patients, must be taken into account when deciding on their use. Despite the risk profile associated with this class of medications, tricyclic antidepressants have been reported to be used commonly for the treatment of depression in the elderly. In a large collaborative study of aging (Brown et al. 1995), tricyclic antidepressants accounted for over 90% of the antidepressant medications used by study participants.

**Conclusions Regarding Heterocyclic Antidepressants**

*There is level 1a evidence that heterocyclic antidepressants may improve depression post stroke. Side effects in elderly patients mean that these medications should be used with caution in that population.*

**Heterocyclic antidepressants may improve post-stroke depression.**

### 18.7.2 Selective Serotonin Reuptake Inhibitors (SSRIs)

Selective serotonin-reuptake inhibitors selectively block serotonin-reuptake rather than blocking both serotonin and norepinephrine reuptake. They are commonly used to treat depression and have been studied in the treatment of post-stroke depression. Studies examining the use of SSRIs in the treatment of PSD are summarized in Table 18.7.2.1.

**Table 18.7.2.1 Summary of Studies Evaluating Selective Serotonin Reuptake Inhibitors 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>Intervention</th>
<th>Main Outcome(s) Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fruehwald et al.</strong>, (2003)</td>
<td>RCT (9)</td>
<td>N\textsubscript{Start}=54 N\textsubscript{End}=40</td>
<td>E: Fluoxetine (20mg/d) C: Placebo</td>
<td>• HAMD (Follow-up) (+) • BDI (Follow-up) (+) • HAMD (Post-treatment) (-) • BDI (Post-treatment) (-)</td>
</tr>
<tr>
<td><strong>Murray et al.</strong>, (2005)</td>
<td>RCT (9)</td>
<td>N\textsubscript{Start}=123 N\textsubscript{End}=69</td>
<td>E: Sertraline (50-100 mg/d) C: Placebo</td>
<td>• Emotional Distress Scale (at 6wk only) (+) • VAS (at 26wk only) (+) • MADRS (-)</td>
</tr>
<tr>
<td><strong>Andersen et al.</strong>, (1994)</td>
<td>RCT (8)</td>
<td>N\textsubscript{Start}=66 N\textsubscript{End}=59</td>
<td>E: Citalopram (10-20mg/d) C: Placebo</td>
<td>• HAMD (+) • Melancholia Scale (+)</td>
</tr>
<tr>
<td><strong>Robinson et al.</strong>, (2000)</td>
<td>RCT (8)</td>
<td>N\textsubscript{Start}=104 N\textsubscript{End}=83</td>
<td>E1: Fluoxetine (10-40mg/d) E2: Nortriptyline (25-100mg/d) C: Placebo</td>
<td>• HAMA (+) • HAMD (+) • FIM (+) • John Hopkins Functional Inventory (+) • MMSE (-) • Social Function Exam (-)</td>
</tr>
</tbody>
</table>
Discussion

Three of the randomized controlled trials summarized above demonstrated positive results favouring the treatment of serotonin reuptake inhibitors while two studies demonstrated no evidence for its therapeutic effects (Table 18.7.2.1). A single randomized controlled study demonstrated benefits to quality of life associated with treatment but no improvement in assessments of depression.

Although the drug’s effect in the Fruehwald et al. (2003) study was not evident at the first assessment, it should be noted that patients were included at 2 weeks post-stroke and the many therapeutic efforts that take place during the acute phase of stroke rehabilitation may facilitate spontaneous recovery from depression. However, the advantages of treatment with fluoxetine were observed at 12 and 18 weeks after treatment initiation. Response to treatment was reported to be quicker than for the heterocyclic drugs, taking effect 3 weeks into the treatment. Furthermore, side effects were found to be mild and transient and significantly less severe than those associated with the heterocyclic drugs. However, Robinson et al. (2000) noted that there was no significant difference between fluoxetine and placebo. Robinson et al. (2000) also observed fluoxetine-induced significant weight loss in the elderly patients studied.

In order to assess the overall effect of the administration of SSRIs on post stroke depression when compared with a placebo, we carried out a pooled analysis based on the frequency of response to treatment. With the exception of the study by Choi-Kwon et al. (2006), all studies provided a definition of response to treatment (Table 18.7.2.2) and corresponding data reflecting number of “responders”.

Table 18.7.2.2 Criteria used to define response to treatment

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Definition of Response to Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andersen et al. (1994)</td>
<td>( \geq 50% ) decrease in baseline Hamilton Rating Scale for Depression (HAMD) score</td>
</tr>
<tr>
<td>Robinson et al. (2000)</td>
<td>( \geq 50% ) decrease in baseline HAMD score</td>
</tr>
<tr>
<td>Wiart et al. (2000)</td>
<td>( \geq 50% ) decrease in baseline MADRS score</td>
</tr>
<tr>
<td>Fruehwald et al. (2003)</td>
<td>HAMD score &lt;13 at long-term follow-up</td>
</tr>
<tr>
<td>Murray et al. (2005)</td>
<td>( \geq 50% ) decrease in baseline MADRS score</td>
</tr>
</tbody>
</table>

Some recent studies have examined the potential risks associated with the use of antidepressants in older individuals (Coupland et al. 2011; Wu et al. 2011). Both demonstrated increased risk for such adverse outcomes as stroke/TIA and mortality associated with use of antidepressant medication.
Coupland et al. (2011) identified a large cohort (n=65,746) of individuals with depression between the ages of 65 and 100. In general, use of antidepressant medications were associated with significantly increased risk for a variety of adverse outcomes including all-cause mortality, attempted suicide/self-harm, falls, fractures and upper GI bleeding when compared to when antidepressants were not being used. The pattern of association with adverse outcomes varied with the class of drug examined. Overall, use of SSRIs was associated with the greatest risk for falls (HR=1.66, 95%CI 1.58-1.73) and hyponatraemia (HR=1.52, 95% CI 1.33-1.75) when compared to no use. Absolute risk for all-cause mortality was 10.61% for individuals taking SSRIs vs. 7.04% for individuals taking no antidepressants. It should be noted that although approximately 10% of identified records were for individuals with previous stroke, there were no analyses reported that examined this subgroup specifically. Rather, analyses were adjusted for the presence of previous stroke as a confounding factor.

In a retrospective study conducted in the United States, Ried et al. (2011) demonstrated that treatment with an SSRI antidepressant prior to stroke only was associated with an increased risk for mortality following stroke (HR=3.12, 95% CI 1.6 to 6.09). However, SSRI treatment for depression both before and after the stroke was found to be protective for mortality when compared to no post-stroke treatment (HR=0.31, 95% CI 0.11-0.86).

Conclusions Regarding Selective Serotonin Reuptake Inhibitors

Based on the results of meta-analysis, there is level 1a evidence that selective serotonin reuptake inhibitors are effective in the treatment of post-stroke depression. Further placebo studies should be conducted using a blinded administrator and an optimal treatment duration in order to address methodological differences across current studies.

Selective Serotonin Reuptake Inhibitors (SSRIs) may be effective in the treatment of post-stroke depression. Further study is required.

18.7.2.1 Adjunctive Light Therapy

Administration of bright light has been demonstrated to be effective, not only for the treatment of seasonal affective disorder, but also for non-seasonal depression. In a recently updated Cochrane review, Tuunainen et al. (2004) identified 20 studies (49 reports) examining the use of bright light vs. inactive placebo as a treatment for non-seasonal depression. Overall, the treatment response was greater in bright light conditions than in control treatment groups, particularly in studies considered high quality. The majority of studies examined the use of light therapy in combination with drug treatment (14 of 20 studies). Evaluation of these studies alone revealed a significant effect in favour of bright light vs. control (SMD=-0.25, 95% CI -0.47 to -0.02). It should be noted that reporting quality was considered to be generally poor; studies were short, underpowered and did not report outcomes with sufficient detail (2004). The authors conclude that bright light therapy, administered during the first week of treatment, offers promising antidepressant efficacy.

Studies examining the use of adjunctive light therapy in the treatment of PSD are summarized in Table 18.7.2.1.1.

Table 18.7.2.1.1 Summary of Studies Evaluating Adjunctive Light Therapy in the Treatment of Post-Stroke Depression
Conclusions regarding adjunctive light therapy

Based on the results of a recent meta-analysis, there is level 1a evidence that the use of bright light therapy in conjunction with SSRI antidepressants is an effective treatment for non-seasonal depression, in general.

There is level 1b evidence that adjunctive bright light therapy may be more effective than moderate intensity light therapy in the treatment of post-stroke depression. Further research is required to examine timing, duration and optimal intensity.

Light therapy may be an effective adjunct to treatment with SSRI antidepressants.

18.7.3 Selective Noradrenaline Reuptake Inhibitors (NARI)

Selective noradrenaline reuptake inhibitors are a class of antidepressants that function to inhibit noradrenaline reuptake. Patients suffering from depression characterized by lethargy, slowness to initiate action and displaying “anergia, hypokinesis and hypomimia” are said to be suffering from a retarded depression (Rampello et al. 2005). Antidepressant treatment with SSRIs may be more appropriate to treatment of anxious depression, characterized by anxiety, insomnia, hostility, restlessness and trepidation. NRIs are proposed as an alternative to SSRIs for individuals experiencing retarded depression (Rampello et al., 2005). A single RCT has examined the effectiveness of the NARI, reboxetine, in the treatment of this specific form of post-stroke depression (Table 18.7.3.1).

Table 18.7.3.1 Summary of Studies Evaluating Reboxetine 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>Intervention</th>
<th>Main Outcome(s) Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rampello et al. (2005)</td>
<td>RCT (8)</td>
<td>(N_{\text{start}}=31), (N_{\text{end}}=31)</td>
<td>E: Reboxetine (4mg, 2/d) C: Placebo</td>
<td>• HAMD (+) • BDI (+)</td>
</tr>
</tbody>
</table>

- Indicates non-statistically significant differences between treatment groups
+ Indicates statistically significant differences between treatment groups

Discussion

Treatment with reboxetine, a NARI, was associated with improvement in “retarded” depression over a 16-week course of treatment. During that time, no serious side effects were reported and no patients in the treatment condition withdrew from the study (Rampello et al. 2005). However, further study is non-statistically significant differences between treatment groups
+ Indicates statistically significant differences between treatment groups

Discussion

Treatment with reboxetine, a NARI, was associated with improvement in “retarded” depression over a 16-week course of treatment. During that time, no serious side effects were reported and no patients in the treatment condition withdrew from the study (Rampello et al. 2005). However, further study is needed to determine the optimal duration and intensity of treatment.
required to assess the safety effectiveness of long-term treatment with reboxetine.

**Conclusions Regarding Selective Noradrenaline Reuptake Inhibitors**

*There is level 1b evidence that Reboxetine, a noradrenaline reuptake inhibitor, is effective in reducing retarded post-stroke depression.*

*Reboxetine may be an effective treatment for “retarded” post-stroke depression characterized by lethargy and slowness to initiate action.*

**18.7.4 Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs)**

Venlafaxine and duloxetine are antidepressants characterized by the inhibition of the reuptake of serotonin, norepinephrine and, to a lesser extent, dopamine (Staab & Evans 2000). The use of venlafaxine in the treatment of geriatric depression has been examined in several randomized controlled trials and open label studies. Results of these trials have supported the safety and efficacy of venlafaxine within this population (Staab & Evans 2000). Studies examining the use of this drug within the stroke population are summarized in Table 18.7.4.1.

**Table 18.7.4.1 Summary of Studies Evaluating Venlafaxin and Duloxetine in the Treatment of Post-Stroke Depression**

<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>Zhang et al. (2013)</td>
<td>RCT (7)</td>
<td>E: Duloxetine (30-90mg/d)</td>
<td>• HAMD (at 4wk, 12wk and 24wk) (+)</td>
</tr>
<tr>
<td></td>
<td>NStart=118</td>
<td>C: No medication</td>
<td>• MMSE (at 12wk and 24wk) (+)</td>
</tr>
<tr>
<td></td>
<td>NEnd=97</td>
<td></td>
<td>• NIHSS (at 12wk and 24wk) (+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Chinese ADL Scale (at 12wk and 24wk) (+)</td>
</tr>
</tbody>
</table>

- Indicates non-statistically significant differences between treatment groups

+ Indicates statistically significant differences between treatment groups

**Discussion**

Although venlafaxine has been demonstrated to be safe and effective when used in the treatment of geriatric depression, there is little evidence to support the use of this drug in individuals with PSD. In one RCT, duloxetine was shown to be an effective prophylactic in reducing the incidence of minor and major depression among individuals with ischemic stroke. Although the studies summarized in Table 18.7.4.1 (examining venlafaxine) reported positive results, both were small studies of single-group design. Larger controlled trials are required.

**Conclusions Regarding Venlafaxin and Duloxetine**

*There is level 1b evidence that duloxetine may improve depression symptoms post-stroke.*

*There is level 4 evidence that venlafaxine may be an effective treatment for post-stroke depression.*

*More evidence is required to determine the efficacy of venlafaxine and duloxetine for post-stroke depression.*
18.7.5 Gamma Aminobutyric Acid Compounds (GABA)
Nefiracetam is a novel cyclic gamma aminobutyric acid compound (GABA) with documented effects on neurotransmission, regional blood flow and glucose utilization. Use of nefiracetam for the treatment of post-stroke depression has been studied in a single randomized controlled trial (Table 18.7.5.1).

18.7.5.1 Summary of Studies Evaluating Nefiracetam in the Treatment of Post-Stroke Depression

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Intervention</th>
<th>Main Outcome(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robinson et al. (2008a)</td>
<td>E1: Nefiracetam (600mg, 2/d) E2: Nefiracetam (900mg, 2/d) C: Placebo</td>
<td>• HAMD (-) • BDI (-) • FIM (-) • MMSE (-) • NIHSS (-)</td>
</tr>
</tbody>
</table>

- Indicates non-statistically significant differences between treatment groups
+ Indicates statistically significant differences between treatment groups

Conclusions Regarding Nefiracetam

There is level 1b evidence that the GABA compound nefiracetam may not be more effective than placebo in the treatment of post-stroke depression.

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

18.7.6 Psychostimulants
Methylphenidate, presently approved for treating attention-deficit disorders, has been used in the treatment of depression in the elderly as an alternative to tricyclics or other antidepressants. The states of the depressed elderly is often described as suffering a “lack of interest and emotional involvement in one’s surroundings” and this has been attributed to patients described as “rehabilitation failures secondary to poor cooperation and motivation,” (Johnson et al. 1992). Psychostimulants such as methylphenidate usually are effective in treating this state of apathy. Several studies suggest that use of psychostimulants in the treatment of post-stroke depression may be an effective treatment. Methylphenidate has its effects in the cortical and subcortical areas of the brain and thus is thought to heighten mood by affecting several neurotransmitter systems, in particular the noradrenergic system. In addition, it blocks the reuptake of serotonin and norepinephrine and has dopaminergic activity. Therefore, it is thought that methylphenidate may affect post-stroke depression by correcting the depletion of biogenic amines caused by stroke and to relieve apathy (Johnson et al. 1992). Individual studies are summarized in Table 18.7.6.1.

Table 18.7.6.1 Summary of Studies Evaluating Psychostimulants in the Treatment of Post-Stroke Depression

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Intervention</th>
<th>Main Outcome(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade et al. (1998)</td>
<td>E: Methylphenidate (5-30mg/d)</td>
<td>• ZDS (+)</td>
</tr>
</tbody>
</table>
RCT (7)  
N_{Start}=21  
N_{End}=19  
<table>
<thead>
<tr>
<th>C: Placebo</th>
<th>HAMD (+)</th>
<th>MMSE (-)</th>
<th>Fugl-Meyer Scale (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lazarus et al. (1994)</td>
<td>E: Methylphenidate (10mg/d)</td>
<td>DSM-III R Diagnosis of Depression (-)</td>
<td>DSM-III R Diagnosis of Depression (patients who improved only) (+)</td>
</tr>
</tbody>
</table>

- Indicates non-statistically significant differences between treatment groups  
+ Indicates statistically significant differences between treatment groups

**Discussion**

Six studies examining the efficacy of psychostimulants for post-stroke depression were identified. One study was a retrospective single group intervention study, two were retrospective cohort studies, two were single group intervention studies and one was a randomized controlled trial. Methylphenidate has been observed to have an early onset of action within 2 to 10 days of treatment onset whereas tricyclic antidepressants onset usually does not begin until 2 to 4 weeks after treatment has begun. The fast action of methylphenidate is of particular interest given patients are treated for a limited amount of time in a rehabilitation setting. It must be used with caution in individuals with cardiovascular disorders.

**Conclusions Regarding Psychostimulants**

*There is level 1b evidence that methylphenidate is more effective than placebo in improving both symptoms of depression and functional recovery. Methylphenidate (a psychostimulant) has an earlier onset of action than traditional antidepressants.*

**18.7.7 Melatonin Agonist**

Valdoxan is a melatonin receptor agonist and an antagonist of 5-HT<sub>2c</sub> serotonin receptors. This synergistic effect results in increased dopamine and noradrenaline release; however, no effect on monoamines has been observed. In a meta-analysis, Valdoxan at a dose 25-50mg was found to decrease depression symptomatology by 2 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 post stroke depression (Bogolepova et al. 2011). The study found improvement in HDS and HADS depressive and anxiety symptoms post treatment and at follow up.

**Conclusions Regarding Melatonin Agonist**

*There is limited level 4 evidence that valdoxan, a melatonin agonist, may be effective in management of PSD.*

More studies are needed to determine the effect of valdoxan, a melatonin agonist, on post-stroke depression.
18.7.8 Statins
Most often, cholesterol levels are identified as risk factors for heart and arterial disease. Alternatively, some studies suggest that total cholesterol concentrations may be associated with a risk of developing depressive symptoms. However, other studies have found this association to be non-significant (Aijanseppa et al. 2002; Blazer et al. 2002; Kim et al. 2006; Kim & Myint 2004; Morgan et al. 1993).

Table 18.7.8.1 Summary of Studies Evaluating Statins in the Treatment of Post-Stroke Depression

<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>Kim et al. (2014)</td>
<td>Cohort No Score NStart=423 NEnd=288</td>
<td>E: Statins C: No medication prescribed</td>
<td>• HADS Depression (+) • HAMD (+)</td>
</tr>
</tbody>
</table>

- Indicates non-statistically significant differences between treatment groups
+ Indicates statistically significant differences between treatment groups

Discussion
In a recent prospective study, Kim et al. (2014) investigated the effect of various statins on depression and anxiety scores in stroke individuals. Results demonstrate a significant interaction of time and group regarding both anxiety and depression scores in depressed individuals treated with statins but not in those not receiving statins. Although this study provides evidence towards the effectiveness of statins at reducing depression and anxiety scores, the authors acknowledge that the follow-up evaluation was only conducted once in one year after stroke and therefore, compliance to the drug was unknown during the intervention period. Furthermore, other non-pharmacological treatments were not recorded or considered in the analysis. Further randomized controlled studies are thus 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 improve post-stroke depression and anxiety.

More studies are needed to determine the effect of statins on post-stroke depression and anxiety.

18.7.9 Alternative Medicine
Given general concerns regarding potential side effects from the use of antidepressants, individuals with depression may choose to self-medicate, often with herbal products (Davidson & Zhang 2008). Unfortunately, there is little evidence from controlled trials evaluating the use of these preparations for the treatment of depression.

The Chinese herbal preparation, Free and Easy Wanderer Plus (FEWP) is one such alternative medicine. FEWP is a combination of 11 herbal drugs and is used for the treatment of mood disorders. A recent randomized controlled trial of individuals with unipolar and bipolar depression demonstrated that
treatment with a standardized preparation of FEWP was associated with greater improvement in greater reduction of depressive symptoms and higher clinical response rates (≥50% reduction in HAMD scores) when compared to the placebo condition (Zhang et al. 2007). The use of this alternative, herbal medicine has also been examined in a group of individuals with post-stroke depression (Table 18.7.9.1).

Table 18.7.9.1 Summary of Studies Evaluating Herbal Medicine in the Treatment of Post-Stroke Depression

<table>
<thead>
<tr>
<th>Author, Year Study Design (PEDro Score) Sample Size</th>
<th>Intervention</th>
<th>Main Outcome(s) Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li et al. (2008) RCT (8) NStart=150 NEnd=146</td>
<td>E1: Free and Easy Wanderer Plus E2: Fluoxetine (20-40mg/d) C: Placebo</td>
<td>• HAMD (+) • Barthel Index (+)</td>
</tr>
</tbody>
</table>

- Indicates non-statistically significant differences between treatment groups
+ Indicates statistically significant differences between treatment groups

Discussion
In the sole study identified to date, treatment with FEWP appeared to be as effective as fluoxetine when used in the treatment of post-stroke depression within the first 6 weeks of a stroke event. In addition, FEWP appeared to have an effect on both the experience of depressive symptomatology and the recovery of physical function sooner than fluoxetine (Zhang et al. 2007).

However, it should be noted that relatively little is known about the specific effects of each of the components in FEWP and how each of them might interact with other medications commonly prescribed to stroke patients (Davidson & Zhang 2008). Further research is required.

Conclusions Regarding Herbal Medicine

*There is level 1b evidence that treatment with the herbal preparation, Free and Easy Wanderer Plus (FEWP), may be as effective as fluoxetine in the treatment of post-stroke depression.*

*The herbal medicine Free and Easy Wanderer Plus (FEWP) may be effective in the treatment of PSD. Further research is required.*

18.7.10 Care Management
A single randomized controlled trial has assessed the impact of a care management intervention on the effectiveness of treatment (including pharmacologic intervention) for PSD (Table 18.7.10.1).

Table 18.7.10.1 Summary of Studies Evaluating Care Management in the Treatment for Post-Stroke Depression

<table>
<thead>
<tr>
<th>Author, Year Study Design (PEDro Score) Sample Size</th>
<th>Intervention</th>
<th>Main Outcome(s) Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Williams et al. (2007) RCT (8) NStart=188</td>
<td>E: AIM intervention (activation, initiating medication, monitoring treatment) C: Usual care</td>
<td>• HAMD (+)</td>
</tr>
</tbody>
</table>
Discussion
The care management intervention implemented by Williams et al. (2007) was associated with significant improvement in depressive symptomatology over the course of 12 weeks. This significant improvement was particularly notable in that 56% of individuals in the control or usual care condition also received treatment with antidepressants and an equal number of contacts as the intervention group.

Conclusions Regarding Care Management

There is level 1b evidence that an active care management program including patient education and ongoing monitoring may enhance effectiveness of pharmacologic treatment for post stroke depression.

Active care management in conjunction with antidepressant therapy may improve response to treatment; however, more research is needed.

18.8 Impact of Pharmacologic Treatment of PSD on Rehabilitation Outcomes

18.8.1 Functional Recovery Associated with Pharmacologic Treatment of Post-Stroke Depression
As established earlier, depression has a negative impact on function and cognitive recovery and thus the appearance of post-stroke depression is believed to adversely affect the rate of recovery and rehabilitation of stroke survivors. A secondary analysis of data collected as part of the Activate-Initiate-Monitor (AIM) Study demonstrated that individuals who reported improvement of depressive symptomatology were more likely to be independent at 12 weeks post-stroke than those who did not improve over the same period of time (p=0.012) (Schmid et al. 2011).

<table>
<thead>
<tr>
<th>Author, Year Study Design (PEDro Score) Sample Size</th>
<th>Intervention</th>
<th>Main Outcome(s) Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chollet et al. (2011) RCT (9) NStart=118 NEnd=113</td>
<td>E: Fluoxetine (20mg/d) C: Placebo</td>
<td>• Symptoms of depression over 90d (+) • Fugl-Meyer Motor Scale (FMMS) (+)</td>
</tr>
<tr>
<td>Lipsey et al. (1984) RCT (8) NStart=39 NEnd=34</td>
<td>E: Nortriptyline (20-100mg/d) C: Placebo</td>
<td>• HAMD (+) • Zung Self-Rating Depression Scale (+) • Present State Examination (+)</td>
</tr>
<tr>
<td>Robinson et al. (2000) RCT (8) NStart=104</td>
<td>E1: Nortriptyline (25-100mg/d) E2: Fluoxetine (10-40mg/d) C: Placebo</td>
<td>• HAMA (+) • HAMD (+) • FIM (+)</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>N Start</td>
</tr>
<tr>
<td>--------------------------</td>
<td>--------</td>
<td>---------</td>
</tr>
<tr>
<td>Wiart et al. (2000)</td>
<td>RCT (8)</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gonzalez-Torrescillas et al. (1995)</td>
<td>RCT (7)</td>
<td>130</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dam et al. (1996)</td>
<td>RCT (7)</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemerinski et al. (2001)</td>
<td>RCT (7)</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reding et al. (1986)</td>
<td>RCT (6)</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miyai &amp; Reding (1998)</td>
<td>RCT (6)</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mikami et al. (2011)</td>
<td>RCT (6)</td>
<td>104</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raffaele et al. (1996)</td>
<td>RCT (5)</td>
<td>22</td>
</tr>
<tr>
<td>Narushima et al. (2003)</td>
<td>Cohort</td>
<td>251</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilge et al. (2008)</td>
<td>PCT</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Indicates non-statistically significant differences between treatment groups
+ Indicates statistically significant differences between treatment groups

**Discussion**

Saxena et al. (2007) examined both depressive symptoms and functional variables in a group of 141 stroke patients. Linear regression analysis demonstrated that greater change in BI scores from rehabilitation
admission to 6 months was associated with better mood status at baseline and greater improvement in depressive symptoms (p=0.02 and p<0.001, respectively). Other significant predictors of functional recovery included baseline neurological status, neurological improvement, baseline functional status and age. The authors concluded that improvement in depressive symptomatology may accelerate functional recovery, but the level of function achieved is determined by neurological and cognitive factors.

A non-RCT study by Gainotti et al. (2001) demonstrated that treatment with fluoxetine was associated with an improvement in functional recovery in addition to recovery from depression; a finding which is supported by Gonzalez-Torrecillas et al. (1995), Dam et al. (1996), Miyai and Reding (1998), and Narushima et al. (2003) (see Table 18.8.1.1). A multi-unit study carried out in France by Chollet et al. (2011) also parallels these findings and further indicated that treatment with fluoxetine significantly improved motor function (p=0.003) when compared to the placebo group. Conversely, the study also reported several adverse events associated with the use of fluoxetine and the placebo treatment during the course of the study: hyponatraemia, transient digestive disorders including nausea, diarrhoea, abdominal pain hepatic enzyme disorders, psychiatric disorders, insomnia, and partial seizure.

Although several studies also documented the effectiveness of treatment with nortriptyline in terms of physical function, Miyai and Reding (1998) noted that trazodone and fluoxetine improved self-care function and depression after stroke while nortriptyline improved depression but not self-care.

Serotonergic antidepressants need to be investigated further for possible efficacy in promoting functional recovery in stroke patients undergoing rehabilitation (Dam et al. 1996; Gainotti et al. 2001; Miyai & Reding 1998). In addition, the effect of timing of treatment on recovery of ADLs requires further investigation. While the majority of studies examine the effectiveness of treatment initiated more than one month post stroke, the studies of Narushima et al. (2003) and Gonzalez-Torrecillas et al. (1995) focused on treatment beginning in the first month following the stroke event.

Gonzalez-Torrecillas et al. (1995), in an open label study, demonstrated that early treatment, initiated within 4 weeks of the index event, was associated with significant improvements in physical, cognitive and neurological function by the end of the 6-week treatment period. Similarly, Narushima et al. (2003) reported a significantly greater improvement in physical function over the active treatment period (12 weeks) for patients with early treatment initiation (within 4 weeks of stroke) when compared to those patients whose treatment started later. In addition, during a “naturalistic” period of observation, patients with late onset of treatment experienced a gradual deterioration in function between 12 and 24 months post stroke while patients in the early treatment group continued to improve slowly over the same period of time. These significant between group differences were not attributable to time since stroke. Logistic regression controlling for treatment type, initial diagnosis, presence/absence of motor impairment, past psychiatric history and continued use of medication past the end of the treatment phase demonstrated a significant effect of early versus late treatment on FIM scores at 12 – 24 months (Narushima et al. 2003).

Bilge et al. (2008) investigated the effects of Citalopram and found that depression scores improved significantly at 3 months (p=0.00) but not at 6 months in non-depressed individuals receiving treatment compared to non-treated non-depressed individuals. Functional recovery improved in both groups during the 6 month follow-up period suggesting that citalopram may have a beneficial effect on physical disabilities. Although this study provides important evidence for the effect of citalopram on post-stroke depression, the authors also acknowledge the limitation of not including a placebo group in the analysis to eliminate potential bias. Therefore, future RCTs with larger sample sizes and appropriate control groups are needed.
Conclusions Regarding Stroke Recovery After Treatment With Antidepressant Medications

There is level 1a evidence that treatment with Nortriptyline may improve post-stroke depression. There is also limited evidence to suggest that an improvement in post-stroke anxiety and functional recovery but not cognitive functioning may follow after treatment with Nortriptyline.

There is level 1a evidence that treatment with Fluoxetine may improve depression symptoms and independent functioning but not cognitive functioning. Findings for the effect of Fluoxetine on functional recovery are conflicting.

There is level 1a evidence that Trazodone treatment may not improve post-stroke depression.

There is level 1b evidence that Maprotiline may improve depressive symptoms, motor and independence functioning.

There is level 1b evidence that Desipramine may not improve depression or motor recovery post-stroke.

There is limited level 2 evidence that Citalopram may improve depression symptomology and functional recovery.

Treatments with Nortriptyline may improve post-stroke depression and functional recovery. Limited evidence also suggests that Maprotiline and Citalopram have a similar effect as Nortriptyline.

Fluoxetine, Trazodone, or Desipramine may not be associated with improved post-stroke depressive symptoms.

18.8.2 Mortality and Pharmacologic Treatment of Post-stroke Depression

In 1993, Morris et al. (1993) reported that stroke patients suffering from post-stroke depression were 3.4 times more likely to have died by 9-year follow-up than stroke patients without depression. Given the link between post-stroke depression and mortality (see section 18.5.4), the effect of treatment on mortality has been evaluated.

One randomized controlled trial evaluating the effect of antidepressant treatment on post-stroke mortality was identified (See Table 19.8.2.1).

Table 18.8.2.1 Summary of Studies Evaluating Mortality and Pharmacologic Treatment of Post-Stroke Depression

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design (PEDro Score)</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Main Outcome(s) Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jorge et al. (2003)</td>
<td>RCT (7)</td>
<td>N_{start}=104  N_{end}=81</td>
<td>E1: Nortriptyline (25-100mg/d)  E2: Fluoxetine (10-40mg/d)  C: Placebo</td>
<td>• Mortality rate (+)</td>
</tr>
</tbody>
</table>

*Indicates non-statistically significant differences between treatment groups*
Discussion
Early treatment with antidepressants, even for a relatively short period, may have a prolonged, protective effect on mortality rates following stroke (Jorge et al. 2003). Furthermore, the association between antidepressant treatment and improved survival was demonstrated not only in patients who were depressed at the time of study enrolment, but also in those who were not. The authors speculate that the use of antidepressant medications following stroke may alter pathophysiological mechanisms associated with mortality or with the development of later depression. In a recent case series, Ayerbe et al. (2014b) showed that use of SSRIs prior to a stroke incident was not significantly associated with increased mortality rates however, use of SSRIs after stroke onset showed a significant increase in mortality at 5 year follow-up.

In a retrospective study conducted in the United States, Ried et al. (2011) demonstrated that treatment with an SSRI antidepressant prior to stroke only was associated with an increased risk for mortality following stroke (HR=3.12, 95% CI 1.6 to 6.09). However, SSRI treatment for depression both before and after the stroke was found to be protective for mortality when compared to no treatment during the first year post-stroke (HR=0.31, 95% CI 0.11-0.86) as was SSRI treatment only after stroke (HR=0.57, 95%CI 0.25-1.32), although the post-stroke treatment effect did not reach statistical significance. After 7 years post stroke, SSRI use was again associated with increased mortality risk. Diagnosis of depression following stroke was, of course, associated with a significant increase in risk for mortality (HR=1.87, 95% CI 1.24-2.82).

In a recent nationwide study, Mortensen et al. (2014) found that the use of SSRIs was associated with a reduced risk of myocardial infarction or recurrent ischemic stroke (HR=0.77, 95% CI 0.62 to 0.96). Conversely, higher risk of overall major bleeding (HR=1.33, 95% CI 1.14 to 1.55) was found in SSRI users in addition to a non-significant increase in the risk of intracranial bleedings (HR=1.14, 95% CI 0.62 to 2.12). Although an increased risk of mortality was related to the use of SSRIs (HR=1.13, 95% CI 1.00 to 1.28) the relationship did not reach significance. The authors further speculate that this effect may have been driven by the increased risk of bleeding associated with the use of SSRIs (HR=1.89, 95% CI 0.97 to 3.66).

Conclusions Regarding Mortality and Pharmacologic Treatment of Post-Stroke Depression

There is level 1b evidence that early treatment with antidepressants (Nortriptyline or Fluoxetine) post stroke is associated with improved long-term survival. Further research is required.

Treatment with antidepressants following stroke may improve long-term survival; however, additional studies are warranted.

18.9 Non-Pharmacologic Treatment of Post-Stroke Depression

18.9.1 Electroconvulsive Therapy
Electroconvulsive therapy (ECT) is an older treatment for major depression that has traditionally been considered effective (Janicak et al. 2002).

Discussion
Two retrospective studies (Currier et al. 1992; Murray et al. 1986) suggest that ECT is a relatively safe and effective treatment for post-stroke depression, although Currier et al. reported that patients were at risk for relapse following ECT despite good initial responses and maintenance therapy with antidepressant medications (Currier et al. 1992).

In a recent case report, ECT was provided after a series of pharmacological interventions were deemed unsuccessful in a patient experiencing post-stroke depression. ECT was tolerated well without any complications and revealed a clinical improvement in overall mood and the resolution of suicidal ideations. The authors note however, that the benefits/risks of ECT must be weighed prior to moving forward with the procedure, with a heavy emphasis on the patient’s clinical presentation (Harmandayan et al. 2012).

Currently, there are no prospective controlled clinical trials evaluating the use of ECT in post-stroke patients.

Conclusions Regarding Electroconvulsive Therapy

*There is limited level 3 evidence that electroconvulsive therapy may be an effective treatment for short term depressive symptoms without worsening existing neurological deficits. Further studies are required.*

*There is insufficient evidence to evaluate the use of electroconvulsive therapy as a treatment for post-stroke depression.*

18.9.2 Repetitive Transcranial Magnetic Stimulation

Recent randomized controlled trials have demonstrated antidepressant effects associated with repetitive transcranial magnetic stimulation (rTMS) in populations of patients suffering from major depression (Grunhaus et al. 2003; Janicak et al. 2002; Loo et al. 2003). Treatment effects comparable to those associated with ECT have been reported (Grunhaus et al. 2003; Janicak et al. 2002), although more modest results have been demonstrated among patients with resistant depression (Loo et al. 2003). Mild adverse effects were associated with rTMS.

Randomized controlled trials examining the possible efficacy of rTMS in the treatment of PSD are summarized in Table 18.9.2.1.

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design (PEDro Score)</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Main Outcome(s) Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kim et al. (2010)</strong></td>
<td>RCT (8)</td>
<td>N_Start=18 N_End=18</td>
<td>E1: Low-frequency Stimulation (1Hz) E2: High-frequency Stimulation (10Hz) C: Sham Stimulation</td>
<td>• BDI (+) • Modified Barthel Index (+) • Neuropsychological Battery (-)</td>
</tr>
<tr>
<td><strong>Jorge et al. (2004)</strong></td>
<td>RCT (7)</td>
<td>N_Start=20 N_End=20</td>
<td>E: Active Left Prefrontal TMS C: Sham TMS</td>
<td>• HAMD (+) • MMSE (-) • NIHSS (-)</td>
</tr>
</tbody>
</table>
- Indicates non-statistically significant differences between treatment groups
+ Indicates statistically significant differences between treatment groups

**Discussion**
Both RCTs identified above reported improvement in depressive symptomatology; however, participants in the Kim et al. (2010) trial had not been diagnosed with depression at study entry. As in previous studies, in non-stroke populations, rTMS appears to be well tolerated by patients and was associated with mild adverse effects only. Both studies are very small and while Jorge et al. include patients with PSD, they represent a select group in whom depression had proven resistant to pharmacotherapy (Jorge et al. 2004). A larger trial evaluating the efficacy of rTMS with citalopram maintenance therapy is currently underway (Jorge et al. 2004).

**Conclusions Regarding Repetitive Transcranial Magnetic Stimulation (rTMS)**

**There is level 1a evidence that rTMS may improve depressive symptomatology.**

**Use of repetitive transcranial magnetic stimulation (rTMS) is associated with reduced symptoms of post-stroke depression.**

**18.9.3 Cognitive Behavioural Therapy**
Cognitive behavioural therapy 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, cognitive behavioural therapy 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). Individual studies examining the use of cognitive behavioural therapy in the treatment of post-stroke depression are summarized in Table 18.9.3.1.

**Table 18.9.3.1 Summary of Studies Evaluating Cognitive Behavioural Therapy 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>Intervention</th>
<th>Main Outcome(s)</th>
</tr>
</thead>
</table>
| Humphreys et al. (2015) RCT (8) | NStart=105 NEnd=87          | E: Cognitive Behavioural Therapy C: Usual Care       | SADQH (-)  
Cost of intervention over 3mo (+)  
Cost of intervention over 12mo (-) |
| Lincoln et al. (2003) RCT (7) | NStart=123 NEnd=111         | E: Cognitive Behavioural Therapy C1: Attention placebo C2: Usual Care | BDI (-)  
Wakefield Depression Inventory (-)  
Extended Activities of Daily Living (-) |
| Chang et al. (2011) RCT (7) | NStart=77 NEnd=66          | E: Counselling and Conventional Care C: Conventional Care only | HAMD (+)  
HAMA (-)  
State Trait Anger Expression Inventory (STAXI) State Anger (+)  
STAXI Trait Anger (-) |
| Thomas et al. (2013) | E: Mood-elevating activities and Education | SADQ (+) |
RCT (7)  
N\text{Start}=105  
N\text{End}=89  
C: Usual Care  
- VAS Self-Esteem (+)  
- Nottingham Leisure Questionnaire (-)

| Johansson et al. (2012) | E: Mindfulness-based stress reduction  
C: Waitlist, no treatment  
- Mental Fatigue Scale (+)  
- Comprehensive Psychopathological Rating Scale (-) |
|---|---|

| Hoffmann et al. (2015) | E1: Coping Skills (Cognitive and behavioural exercises)  
E2: Self-Management (Problem-solving skills)  
C: Usual Care  
- HADS (+)  
- MADRS (-)  
- SAQoL (-)  
- SKQ (+)  
- NEADL (-)  
- MBI (-) |
|---|---|

- Indicates non-statistically significant differences between treatment groups  
+ Indicates statistically significant differences between treatment groups

Discussion
Humphreys et al. (2015) and Lincoln et al. (2003) investigated the effect of cognitive behavioral therapy (CBT) in post-stroke patients with depression and noted no significant difference between the CBT intervention and usual care with respect to improvements in depression scores. Similarly, Hoffmann et al. (2015) showed that although some improvement in depression was found, the MADRS outcome concluded no significant difference between CBT-based interventions and usual care. Conversely, Chang et al. (2011) provided a counselling-type of intervention similar to CBT to individuals with post-stroke depression and found that depression symptomology improved along with state anger compared to conventional care while anxiety was not affected.

Focusing CBT on mood-elevating activities was found to improve depression and self-esteem scores in aphasic patients with low mood (Thomas et al. 2013). This improvement was maintained at 3 months and at 6 months, suggesting that mood-elevating type CBT may be helpful for improving mood in patients with aphasia.

Mindfulness, a meditative type of practice in which the individuals bring into attention their state of being in the present moment, has been shown to have a positive effect on mental fatigue after a stroke (Johansson et al. 2012). Further studies are needed to determine if this intervention is also efficacious in individuals experiencing post-stroke depression.

Conclusions Regarding Cognitive Behavioural Therapy

There is level 1a evidence that cognitive behavioral therapy (CBT) may not be effective at improving post-stroke depression symptomology.

There is level 1b evidence that mood-based CBT may improve depression and self-esteem in post-stroke patients with aphasia.

There is level 1b evidence that mindfulness may help improve mental fatigue after a stroke.
Further research is required to determine if different forms of CBT and mindfulness may be advantageous at improving post-stroke depression.

### 18.9.3.1 Combined Therapy

Although psychotherapeutic interventions have been successfully used in the treatment of other forms of depression, there has been little evidence to support their use in the treatment of PSD (Hackett et al. 2008). Supplementation of antidepressant use with therapy intended to change behaviours associated with depression could result in a more effective intervention (Joubert et al. 2008). Several studies examining the use of antidepressant therapy in addition to a psychosocial behavioural intervention were identified (Table 18.9.3.1.1).

#### Table 18.9.3.1.1 Summary of Studies Evaluating Combined Therapy in the Treatment of Post-Stroke Depression

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design (PEDro Score)</th>
<th>Intervention</th>
<th>Main Outcome(s) Result</th>
</tr>
</thead>
</table>
| Mitchell et al. (2009) | RCT (7) | E: Psychosocial-Behavioural Intervention and Anti-Depressants  
C: Usual Care and Anti-Depressants | HAMD (+) |
| Sondergaard et al. (2006) | RCT (6) | E1: High-light intensity + Citalopram  
E2: Medium-light intensity + Citalopram | HAM-D6 (+) |
| Cao et al. (2013) | RCT (6) | E: Hyperbaric Oxygen Therapy (HBOT) with 2.5-5mg of Dexamethasone  
C: Deanxit (Depixol 0.5mg and Melitracen 10mg, 1-2/d) | HAMD (+)  
NIHSS (+) |
| Yan et al. (2015) | China | E1: Fluoxetine (20mg/d)  
E2: Hyperbaric Oxygen Therapy (HBOT)  
E3: HBOT and Fluoxetine (20mg/d) | HAMD (+)  
SSS (-) |

- Indicates non-statistically significant differences between treatment groups  
+ Indicates statistically significant differences between treatment groups

#### Discussion

Mitchell et al. (2009) found that when combining Psychosocial-Behavioral therapy with antidepressants, depression scores improved significantly relative to when the pharmacological treatment was provided alone. This effect was found immediately after the treatment and it was also maintained at 12 months after the intervention period ended.

Similarly, hyperbaric oxygen therapy in combination with antidepressants such as fluoxetine (Yan et al. 2015) and dexamethasone (Cao et al. 2013) were shown to improve depression scores however, the effect of the combination therapy remained inconclusive regarding its effect on neurological recovery.

Sondergaard et al. (2006) investigated the effect of varying intensity of light treatment and demonstrated that high-intensity light therapy combined with Citalopram showed no significant differences in the
depression scores when compared to medium-intensity light therapy combined with Citalopram at 2 weeks of treatment. However, at 4 weeks of treatment a significant difference between the two groups was found with the high-intensity light group performing significantly better (p<0.05) compared to the medium-intensity light therapy group on the depression questionnaire.

**Conclusions Regarding Combined Therapy**

*There is level 1b evidence that delivery of a brief psychosocial intervention in addition to antidepressant therapy may be more effective than antidepressant therapy alone in terms of depressive symptomatology, functional ability and social participation.*

*There is level 1a evidence that hyperbaric oxygen therapy with dexamethasone or fluoxetine may improve depressive symptoms post-stroke.*

*There is level 1b evidence that combination therapy of high-intensity light therapy and citalopram is superior over low-intensity light therapy with citalopram at improving post-stroke depression.*

**Psychosocial behavioural therapy may be used as an effective adjunct to treatment with antidepressants; however, further research is needed.**

*Hyperbaric oxygen therapy may improve post-stroke depression when combined with dexamethasone or fluoxetine.*

**18.9.4 Music Therapy**

The use of music therapy in the treatment of physical, cognitive, communicative, social and emotional rehabilitation has recently gained attention. Music therapy builds a relationship between the therapist and patients (or client) 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. Individual studies examining the effectiveness of music therapy are presented in Table 18.9.4.1.

**Table 18.9.4.1 Summary of Studies Evaluating Music Therapy in the Treatment of Post-Stroke Depression**

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design (PEDro Score)</th>
<th>Intervention</th>
<th>Main Outcome(s)</th>
</tr>
</thead>
</table>
| **Sarkamo et al.** (2008) | RCT (6) | E1: Music Therapy  
E2: Language Therapy  
C: Usual Care | • Profile of Moods Depression subscale (+) |
| | N<sub>Start</sub>=60  
N<sub>End</sub>=55 | | |
| **Jun et al.** (2013) | RCT (4) | E: Music-Movement Therapy  
C: Routine Care | • CES-D (-)  
• K-MBI (-)  
• ROM for shoulder during flexion (+)  
• ROM for elbow joint flexion (+) |
| | N<sub>Start</sub>=40  
N<sub>End</sub>=30 | | |
| **Purdie et al.** (1997) | PCT | E: Music Therapy  
C: Usual Care | • Emotional Stability (-)  
• Clarity of Thought (-)  
• Musical Behaviour (-) |
| | N<sub>Start</sub>=40 | | |
Discussion

Music therapy appears to provide a stimulating environment that may promote rehabilitation gains. In a small, randomized controlled trial, Sarkamo et al. (2008) demonstrated less self-reported depressive symptomatology associated with music listening and, in general, results associated with the provision of music therapy have seemed favourable. In a smaller study by Jun et al. (2013), providing music and encouraging the movement of patients in their wheelchairs did not seem to have a beneficial effect on depression symptoms however, it significantly improved upper limb range of motion (p<0.05) when compared to routine care.

In two prospective controlled studies, music therapy did not reveal significant improvements in mood or emotional behavior when compared to usual care as noted by Purdie et al. (1997) and Nayak et al. (2000). More research is needed to assess the possible role of music therapy in the treatment of post-stroke depression.

Conclusions Regarding Music Therapy

There is conflicting level 1b and level 2 evidence regarding the effect of music therapy on post-stroke depression.

There is level 1b evidence that music-movement therapy may not improve depression however, it may improve upper limb range of motion.

Table 18.9.1 Summary of Studies Evaluating Speech Therapy and Emotional Outcomes in Post-Stroke Depression

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design (PEDro Score)</th>
<th>Intervention</th>
<th>Main Outcome(s) Result</th>
</tr>
</thead>
</table>

18.9.5 Speech Therapy

The counselling role of speech therapists is thought to help patients, in particular aphasic patients, adapt to their communication disturbances and better express their needs that in return may alleviate emotional problems (Lincoln et al. 1985). Studies examining the impact of speech therapy on emotional outcomes are summarized in Table 18.9.5.1.
Table 18.9.6.1 Summary of Studies Evaluating the Impact of Physical Activity on Post-Stroke Depression

<table>
<thead>
<tr>
<th>Author, Year Study Design (PEDro Score)</th>
<th>Intervention</th>
<th>Main Outcome(s) Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lai et al. (2006) RCT (8) N_{Start}=100</td>
<td>E: Progressive, In-home Exercise Program C: Usual Care</td>
<td>GDS (+)</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>N Start</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>--------</td>
<td>---------</td>
</tr>
<tr>
<td>Mead et al. (2007)</td>
<td>RCT (8)</td>
<td>66</td>
</tr>
<tr>
<td>Van de Port et al. (2012)</td>
<td>RCT (8)</td>
<td>250</td>
</tr>
<tr>
<td>Linder et al. (2015)</td>
<td>RCT (8)</td>
<td>99</td>
</tr>
<tr>
<td>Lennon et al. (2008)</td>
<td>RCT (7)</td>
<td>48</td>
</tr>
<tr>
<td>Sims et al. (2009)</td>
<td>RCT (7)</td>
<td>45</td>
</tr>
<tr>
<td>Harrington et al. (2010)</td>
<td>RCT (7)</td>
<td>243</td>
</tr>
<tr>
<td>Immink et al. (2014)</td>
<td>RCT (7)</td>
<td>25</td>
</tr>
<tr>
<td>Topcuoglu et al. (2015)</td>
<td>RCT (6)</td>
<td>52</td>
</tr>
<tr>
<td>Brittle et al. (2009)</td>
<td>RCT (5)</td>
<td>56</td>
</tr>
<tr>
<td>Smith and Thompson (2008)</td>
<td>PCT</td>
<td>20</td>
</tr>
<tr>
<td>Stuart et al. (2009)</td>
<td>PCT</td>
<td>93</td>
</tr>
<tr>
<td>Baek et al. (2014)</td>
<td>PCT</td>
<td>40</td>
</tr>
<tr>
<td>McDonnell et al. (2014)</td>
<td>PCT</td>
<td>40</td>
</tr>
</tbody>
</table>
Cohort  
N_{start}=40  
N_{end}=40  
C: No Exercise Training  
• DASS Anxiety (-)  
• AQoL (+)  
Taricco et al. (2014)  
PCT  
N_{start}=229  
N_{end}=199  
E: Adapted Physical Activity and Therapeutic Patient Education with Caregivers and Families  
C: Usual Care  
• GDS (baseline) (+)  
• GDS (post-treatment) (-)

- Indicates non-statistically significant differences between treatment groups  
+ Indicates statistically significant differences between treatment group

Discussion

Based on the results of studies examining physical activity and depression in older individuals without stroke, the idea that exercise would have a positive impact on PSD seems reasonable. However, only Lai et al. (2006) and Topcuoglu et al. (2015) demonstrated positive improvements in depression scores following physical exercise when compared to usual care. The majority of RCTs showed no difference between different forms of exercise therapies and usual care regarding their effect on depression symptomology. Conflicting findings emerge from prospective controlled studies suggesting that exercise may be beneficial for reducing post-stroke depression. However, the results from the studies identified here seem less clear cut. The types and intensity of exercise vary between studies and the results appear inconsistent. Within group analyses seem generally positive, but for many studies, between groups comparisons are non-significant. It should also be noted that none of these interventions were evaluated as treatment for diagnosable depression; rather the effects of exercise interventions were evaluated in terms of the effect on symptoms of depression only. In addition, depression was evaluated as a secondary outcome only.

Conclusions Regarding Physical Activity

There is level 1a and limited level 2 evidence (one study) that various forms of exercise therapy may not improve depressive symptoms. However, level 2 evidence suggest otherwise.

Exercise training, whether progressive group programs, treadmill training or aerobic training, does not appear to be associated with a reduction in symptoms of depression post stroke. Further research is required.

18.9.7 Ecosystem Focused Therapy

The developers of ecosystem focused therapy have approached the treatment of post stroke depression from the point of view of stroke as a catastrophic event separates the individual from his or her usual skills and competencies (Alexopoulos et al. 2012). The family of the individual with stroke also experiences significant upheaval associated with the stroke event and so Ecosystem Focused Therapy (EFT) was designed to target both the individuals with stroke and his/her family members (Alexopoulos et al. 2012). A recent RCT examining the effectiveness of EFT in the treatment of PSD is summarized in Table 18.9.7.1.

Table 18.9.7.1 Summary of Studies Evaluating Ecosystem Focused Therapy in the Treatment Post-Stroke Depression
Alexopoulos et al. (2012)  
RCT (6)  
NStart=24  
NEnd=80  

| E: Ecosystem Focused Therapy  
C: Education Program.  
+ HAMD (-)  
+ World Health Organization Disability Assessment Schedule II (WHODAS-II) (+)  

- Indicates non-statistically significant differences between treatment groups  
+ Indicates statistically significant differences between treatment groups

Conclusions Regarding Ecosystem Focused Therapy

There is level 1b evidence that ecosystem focused therapy may not be more effective than education in reducing depressive symptoms post-stroke.

Ecosystem focused therapy may not be an effective treatment for post-stroke depression. Further research is required.

18.9.8 Acupuncture

Acupuncture was considered part of Complementary and Alternative Medicine however, it has quickly become integrated into mainstream biomedicine. A meta-analysis evaluating the benefits of acupuncture suggested that although no effect on motor recovery was found, disability and independent functioning may be improved (Sze et al. 2002). Thus far, few studies have investigated the potential of acupuncture on improving post-stroke depression. The studies are briefly summarized in table 18.9.8.1 below.

Table 19.9.8.1 Summary of Studies Evaluating Acupuncture in the Treatment of Post-Stroke Depression

<table>
<thead>
<tr>
<th>Author, Year Study Design (PEDro Score) Sample Size</th>
<th>Intervention</th>
<th>Main Outcome(s) Result</th>
</tr>
</thead>
</table>
| Wayne et al. (2005)  
RCT (9)  
NStart=33  
NEnd=24 | E: Acupuncture  
C: Sham | • CES-D (-)  
• Barthel Index (-)  
• NHP (+) |
| Man et al. (2014)  
RCT (8)  
NStart=43  
NEnd=33 | E: Dense cranial Acupuncture + SSRI body electro-acupuncture  
C: Non-invasive Cranial Acupuncture + SSRI body electro-acupuncture | • HAMD-17 (at 1wk only) (+)  
• HAMD-17 (at 2wk and 4wk) (-)  
• CGI-S (at 1wk and 4wk only) (+)  
• CGI-S (at 2wk) (-)  
• Barthel Index (at 4wk only) (+)  
• Barthel Index (at 1wk and 2wk) (-)  
• Adverse Events (-) |
| Youn et al. (2013)  
South Korea  
PCT  
NStart=28  
NEnd=28 | E1: Electro-Acupuncture (Patients with good motor function)  
E2: Electro-Acupuncture (Patients with poor motor function) | • BDI (+)  
• HAMD (+) |

Discussion
In one RCT, Wayne et al. (2005) found that acupuncture improved general neurological status however, no significant difference was found between acupuncture and sham treatment regarding depression scores or functional independence.

Man et al. (2014) used a different approach to acupuncture and delivered dense cranial acupuncture stimulation (DCEAS) in which electrical stimulation is delivered directly to acupoints on the forehead innervated by the trigeminal sensory pathway (Zhang 2015), in combination with SSRI body electro-acupuncture. The authors noted that although a significant improvement was found in depression scores at the first week of treatment, the improvements were not maintained at the 4 week treatment point. Interestingly, functional independence scores did not improve after the first week of treatment but showed a significant difference compared to the control group at 4 weeks.

In a small prospective controlled trial, electro-acupuncture was found to be advantageous at reducing depression symptoms in patients with relatively good conserved motor function compared to those with poor motor function (Jong-In et al. 2013).

**Conclusions Regarding Acupuncture**

*There is level 1b evidence that acupuncture may not improve post-stroke depression however, it may improve neurological status.*

*There is level 1b evidence that dense cranial acupuncture with SSRI body electro-acupuncture may improve post-stroke depression however, the effects are not maintained.*

*There is limited level 2 evidence that electro-acupuncture may help improve post-stroke depression.*

*More studies are needed to determine the effect of acupuncture on post-stroke depression.*

**18.9.9 Reiki Treatments**

Reiki is a form of energy healing that originated in Japan in the early 1900’s. Reiki is considered to be a form of alternative energy medicine. Life energy is thought to be transferred to patients when practitioners place their hands on or directly above the treatment areas. The mechanism through which Reiki may confer benefit have not been scientifically proven, since the existence of Ki, or life energy, is hypothetical (Borang 2001). During the treatment, the practitioner plays a passive role, whereby the practitioner’s body acts as a channel for the healing energy to flow through and into the client’s body (Shiflett et al. 2002).

**Table 18.9.9.1 Summary of Studies Evaluating Reiki Treatments in the Treatment of Post-Stroke Depression**

<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>Shiflett et al. (2002)</td>
<td>RCT (7) N_surr=50 N_int=44</td>
<td>E1: Reiki Therapy from Reiki Master E2: Reiki Therapy from Reiki Practitioner C1: Sham Reiki C2: No Treatment (Historical Controls)</td>
<td>• CES-D (-) • FIM (-)</td>
</tr>
</tbody>
</table>

*Indicates non-statistically significant differences between treatment groups*
Discussion
Thus far, only one RCT investigated the effect of Reiki Treatment on post-stroke depression. Shiflett et al. (2002) found that there was no significant difference between real Reiki treatment and sham Reiki treatment regarding their effect on depression or functional independence. More studies are therefore needed regarding this intervention and its effect on mood and post-stroke depression.

Conclusions Regarding Reiki Treatment

There is level 1b evidence that Reiki treatment may not improve functional recovery or depression symptomology post-stroke.

Although limited evidence suggests that Reiki treatments may not improve post-stroke depression, more studies are needed to investigate its effect.

18.9.9.1 Meridian Acupressure
Like acupuncture, Meridian acupressure is a form of traditional Chinese medicine based on the theory of ying/yang balance. It requires a technique using finger acupressure delivered to the Meridian points in qi flow of body (Shin et al. 2007; Sok & Kim 2005). Thus far, only one randomized controlled trial exists on the use of Meridian acupressure on depression as summarized below.

Table 18.9.9.1.1 Summary of Studies Evaluating Meridian Acupressure in the Treatment of Post-Stroke Depression

<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>Kang et al. (2009)</td>
<td>RCT (5) N&lt;sub&gt;ini&lt;/sub&gt;=56 N&lt;sub&gt;fin&lt;/sub&gt;=56</td>
<td>E: Meridian Acupressure C: Usual Care</td>
<td>• Beyer Six-Face Rating Scale (+) • ADL Scale (+)</td>
</tr>
</tbody>
</table>

Discussion
Kang et al. (2009) found significant improvements on hand edema, range of motion of the upper extremity, activities of daily living and depression outcomes which favoured the group receiving Meridian acupressure compared to those receiving usual care. Although this study provides positive findings, more studies are needed to provide stronger evidence for the use of Meridian acupressure on post-stroke depression and functional outcomes.

Conclusions Regarding Meridian Acupressure

There is limited level 2 evidence that meridian acupressure may improve depression and independent functioning.
More studies are needed to determine the effect of meridian acupressure on post-stroke depression.

18.9.10 Massage Therapy

Although pharmacological interventions have become the standard first line of defense for a large majority of mood related diseases, non-pharmacological treatments are beginning to gain popularity among the health care industry. Massage therapy is one type of non-pharmacological treatments which showed an improvement in self-esteem, body image, mood and anxiety levels when administered to patients in the intensive care unit (Dunn et al. 1995). Based on these promising findings, Mok & Woo (2004) attempted to determine the effect of slow-stroke back massage in stroke patients. Results suggest that pain and anxiety scores significantly decreased in the group receiving massage therapy compared to the control group. Furthermore, a significant decrease in heart rate, systolic and diastolic blood pressure was also noted.

Table 18.9.10.1 Summary of Studies Evaluating Massage Therapy 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>Intervention</th>
<th>Main Outcome(s) Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mok &amp; Woo (2004) RCT (5) NStart=118 NEnd=102</td>
<td>E: Slow-stroke Back Massage C: No Treatment</td>
<td>• STAI (+)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Indicates non-statistically significant differences between treatment groups
+ Indicates statistically significant differences between treatment groups

Conclusions Regarding Massage Therapy

*There is limited level 2 evidence that anxiety may be improved following massage therapy.*

More studies are needed to determine the effect of massage therapy on post-stroke anxiety.

18.9.11 Relaxation and Stroke Recovery

Relaxation therapy works by promoting a physical and psychological state antithetical to the stress response which has been associated with various levels of anxiety (Manzoni et al. 2008). In the elderly population and in those with physical complaints, relaxation therapy has been shown to reduce levels of anxiety (Manzoni et al. 2008). In stroke populations, only a few studies have been conducted. Kneebone et al. (2014) investigated the effects of autogenic relaxation in a pre-post study where participants were asked to silently repeat statements regarding the state of being of their hemiplegic limb such as “my right arm is very heavy”. Results reveal a significant reduction in self-reported tension. Marshall et al. (2014) delivered a different technique whereby aphasic post-stroke individuals received deep unilateral nostril breathing. This technique required the individuals to breathe in through one nostril and breathe out through the other. Unlike autogenic relaxation, unilateral nostril breathing did not improve anxiety and depression scores in the aphasic group relative to the non-aphasic group. Much is still unknown regarding the effect of relaxation therapy on mood post-stroke and thus, more studies are warranted.
<table>
<thead>
<tr>
<th>Author, Year Study Design (PEDro Score) Sample Size</th>
<th>Intervention</th>
<th>Main Outcome(s) Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marshall et al. (2014) PCT N\textsubscript{左}=11 N\textsubscript{右}=11</td>
<td>E1: Unilateral Nostril Breathing (Aphasic stroke patients) E2: Unilateral Nostril Breathing (Non-aphasic stroke patients)</td>
<td>• BAI (-) • BDI (-)</td>
</tr>
</tbody>
</table>

- Indicates non-statistically significant differences between treatment groups
+ Indicates statistically significant differences between treatment groups

Conclusions Regarding Relaxation Therapy

*There is limited level 2 evidence that relaxing unilateral nostril breathing may not improve anxiety or depressive symptoms in aphasic compared to non-aphasic individuals.*

More studies are needed to determine the effect of relaxing therapies on post-stroke anxiety and depression symptomology.

18.9.12 Art Therapy and Stroke Recovery

Combining various aspects from the fields of art and psychotherapy led to the creative method of expression known as art therapy. This technique has been shown to help stroke individuals achieve their specific goals and to improve their time management skills. Thus far, limited evidence exists regarding the effect of art therapy on post-stroke depression and mood disturbances. Ali et al. (2014) recently demonstrated in a pilot pre-post study that both depression and anxiety scores were reduced from baseline levels in post-stroke patients after art therapy. This study also revealed that participants found the intervention beneficial for their wellbeing. Future studies are therefore encouraged to explore the potential benefits of art therapy in a stroke populations.

Conclusions Regarding Art Therapy

*There is limited level 4 evidence that art therapy may improve anxiety or depressive symptoms post-stoke.*

More studies are needed to determine the effect of art therapy on post-stroke anxiety and depression.

18.10 Post-Stroke Emotionalism

Pathological crying or laughing following stroke has been given many different labels within the literature including emotional incontinence, emotional lability, pathological display of affect, pseudobulbar affect or emotionalism (Andersen et al. 1995a). While there appears to be no consensus regarding the most appropriate label or diagnostic criteria for this condition, many reports refer to the definition provided by House and colleagues as part of the Oxfordshire Community Stroke Project (House et al. 1989). 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”. While this
definition focuses on pathological crying, similar criteria were applied to pathological laughing (House et al. 1989). Patients who are severely affected may have as many as 100 episodes per day, each lasting from 1 – 10 minutes. Patients who are the least affected may present with excessive and/or inappropriate facial grimacing. In either case, individuals experiencing post-stroke emotionalism may withdraw from participation in normal social roles due to distress and fear of social embarrassment (Andersen 1995).

18.10.1 Prevalence and Natural History of Post-stroke Emotionalism

The reported frequency of emotionalism following stroke ranges from 11% (House et al. 1989) to 34% (J.S. Kim & Choi-Kwon 2000). However, this figure depends on both the criteria used to define emotionalism and the time elapsed since stroke onset. Kim and Choi-Kwon (2000) used criteria that differed from House et al. (1989) in that the patient and relatives had to agree that excessive and inappropriate laughing or crying had occurred on more than two occasions. Inappropriateness is not included in the House et al. criteria (House et al. 1989). 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 majority of participants in the House et al. (1989) and the Calvert et al. (1998) studies were able to identify provoking stimuli for their episodes of uncontrollable crying; in the House et al. (1989) study most were provoked by stimuli related to sadness and sentimentality. In a comparison of the two criteria, it was reported that use of the Kim and Choi-Kwon’s (2000) criteria resulted in a much higher frequency of reported emotionalism (17.9% in the first 3 months following stroke) than the use of the criteria proposed by House et al. (1989) (6.3%). Clearly, there is a need to develop a single set of criteria with which to diagnose post-stroke emotionalism.

Within the first few months of stroke onset, reported estimates of the frequency of emotionalism ranges from 12% (Langhorne et al. 2000) to 29.2% (Eccles et al. 1999). House et al. (1989) reported that most patients identified the onset of emotionalism as within the first 4 to 6 weeks following stroke. While the frequency and severity of crying episodes have been reported to improve over the course of the first year post stroke and some cases resolve spontaneously (Andersen 1997; House et al. 1989), the frequency of emotionalism at 12 months has been reported as 11% (Andersen 1995; House et al. 1989).

A significant association has been reported between post-stroke emotionalism and post-stroke depression (Calvert et al. 1998; House et al. 1989; Kim & Choi-Kwon 2000; MacHale et al. 1998) (Andersen et al.1995a), though most individuals with emotionalism do not have significant or diagnosable depression (Calvert et al. 1998; Kim & Choi-Kwon 2000). Patients experiencing post-stroke emotionalism may have more symptoms of psychological disorders or syndromes, in general, than those without emotionalism. Both Eccles et al. (1999) and Calvert et al. (1998) reported that the presence of emotionalism was associated with significantly greater emotional distress and a greater likelihood for the presence of other diagnosable psychiatric disorders. In both studies, it was suggested that post-stroke emotionalism could share common characteristics with post-traumatic stress disorder.

Conclusion Regarding Post-Stroke Emotionalism

In the first 6 months following stroke, post-stroke emotionalism affects approximately one-quarter of stroke survivors.
18.10.2 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 younger age (Calvert et al. 1998), the presence of cognitive impairment (Andersen et al. 1995b; House et al. 1989), female sex (Kim & Choi-Kwon 2000), ischemic stroke vs. haemorrhagic stroke (Kim & Choi-Kwon 2000), motor impairment (Andersen 1995b; Kim & Choi-Kwon 2000), functional ability (Andersen et al. 1995a), history of depression and cortical infarcts (Tang et al. 2004). Tang et al. (2004) also noted an association between emotionalism and younger age, previous TIA or stroke and stroke severity on univariate analysis. However, when entered into a multivariate regression model, only history of depression and the presence of cortical infarcts remained as significant independent predictors. Andersen et al. (1995) found no association between emotionalism and sex, age, history of depression or lesion location.

As is the case for post-stroke depression, studies have attempted to determine a relationship between lesion location and the development of emotionalism with similarly varied results. House et al. (1989) reported that emotionalism was associated with larger lesions and lesions located in the left frontal and temporal regions. This has been confirmed in studies by Andersen et al. (1995a) and MacHale et al. (1998); however, MacHale et al. (1998) also reported a significant association between emotionalism and lesions in the right cerebral hemisphere (p<0.01). Andersen et al. (1995a) reported that severe emotionalism was associated with the presence of large, bilateral pontine lesions while moderate emotionalism was associated with lesions of the basal ganglia or periventricular structures. Mild emotionalism was associated with the presence of large, unilateral subcortical lesions (Andersen 1995).

A more recent study by Kim et al. (2000) demonstrated that while lesion location was an important factor in the development of both post-stroke depression and post-stroke emotionalism, it was more strongly associated with depression (p<0.05). The authors reported that while lesions associated with emotionalism were distributed in a similar pattern to those associated with post-stroke depression, emotionalism was associated more closely with lesions occurring in the lenticulocapsular area. There was also a non-significant trend noted toward an association between pontine base, medial medulla and cerebellar lesions and post-stroke emotionalism (Kim & Choi-Kwon 2000). The study by Kim and Choi-Kwon (2000) also confirmed a significant association between the presence of emotionalism and anterior cortical lesions. It has been postulated that, given the pattern of association with lesion location, post-stroke emotionalism may be attributable to changes in neurochemical pathways or, more specifically, damage inflicted on the serotonergic system (Andersen 1997; Kim & Choi-Kwon 2000; Andersen et al. 1995a).

18.10.3 Treatment of Post-Stroke Emotionalism
There are relatively few published studies regarding effective treatment of post-stroke emotionalism. No reports of non-pharmacologic treatment could be located. Instead, treatment, in general, consists of administration of an antidepressant medication – most often a selective serotonin reuptake inhibitor (SSRI).
A Cochrane meta-analysis included 5 trials of antidepressant medication in the treatment of post-stroke emotionalism (Table 18.10.3.1) (House et al. 2004). Three trials assessed the effectiveness of SSRIs, while the remainder examined the effectiveness of tricyclic anti-depressants (TCAs). Although the authors did not pool results, due to the heterogeneity of assessment methods used in the included studies, House et al. (2004) did conclude that the use of antidepressants appeared to be associated with reductions in the frequency and severity of episodes of pathological crying. This effect was not specific to either class of medication used.

The present review identified 5 trials investigating the effectiveness of pharmacologic treatment of post-stroke emotionalism. Details of these studies are provided in Table 18.10.3.2.

Table 18.10.3.1 Studies included in Meta-analysis by House et al. (2004)

<table>
<thead>
<tr>
<th>Author</th>
<th>Antidepressant studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andersen et al. 1993</td>
<td>Citalopram (SSRI)</td>
</tr>
<tr>
<td>Robinson et al. 1993</td>
<td>Nortriptyline (TCA)</td>
</tr>
<tr>
<td>Brown et al. 1998</td>
<td>Fluoxetine (SSRI)</td>
</tr>
<tr>
<td>Burns et al. 1999</td>
<td>Sertraline (SSRI)</td>
</tr>
</tbody>
</table>

Table 18.10.3.2 Summary of 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)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown et al. (1998) RCT (8) NStart=20 NEnd=19</td>
<td>E: Fluoxetine (20 mg/d) C: Placebo</td>
<td>• Lawson &amp; MacLeod Rating Scale of Emotionalism (+) • Number of outbursts (+) • Side Effects (-)</td>
<td></td>
</tr>
<tr>
<td>Choi-Kwon et al. (2006) RCT (8) NStart=152 NEnd=125</td>
<td>E: Fluoxetine (20 mg/d) C: Placebo</td>
<td>• BDI (-) • VAS (+) • Emotional incontinence (crying) (+) • Emotional incontinence (laughing) (+) • Post-Stroke anger (+)</td>
<td></td>
</tr>
<tr>
<td>Choi-Kwon et al. (2008) RCT (8) NStart=158 NEnd=107</td>
<td>E: Fluoxetine (20 mg/d) C: Placebo</td>
<td>• SF-36 Mental Health (+) • SF-36 General Health (+) • SF-36 Social Function (+)</td>
<td></td>
</tr>
<tr>
<td>Robinson et al. (1993) RCT (7) NStart=82 NEnd=81</td>
<td>E: Nortriptyline (20-100mg/d) C1: Placebo C2: Rating Scale Reliability/Validity condition</td>
<td>• Pathological Laughter and Crying Scale (+) • HAMD (+)</td>
<td></td>
</tr>
<tr>
<td>Burns et al. (1999) RCT (7) NStart=28 NEnd=24</td>
<td>E: Sertraline (50mg/d) C: Placebo</td>
<td>• CIBIC (+) • Frequency of episodes of tearfulness (+) • Emotional lability (+)</td>
<td></td>
</tr>
<tr>
<td>Andersen et al. (1993) RCT (6) NStart=16 NEnd=13</td>
<td>E: Citalopram (10-20mg/d) C: Placebo</td>
<td>• Frequency of crying (+) • HAMD (+)</td>
<td></td>
</tr>
</tbody>
</table>

- Indicates non-statistically significant differences between treatment groups
+ Indicates statistically significant differences between treatment groups

Discussion
The results of 5 RCTs of “good” quality demonstrate a significant and positive effect on post-stroke emotionalism associated with treatment with an anti-depressant, whether an SSRI or TCA (Table 18.10.3.2).

In general, treatment appeared to be well-tolerated and was associated with a reduction in the frequency and severity of crying episodes while cessation of treatment was associated with a recurrence of outbursts. Certainly, the suggestion that treatment of post-stroke emotionalism with SSRIs is effective seems reasonable, particularly if emotionalism develops as a result of damage to serotonergic pathways (Andersen 1995, 1997; Kim & Choi-Kwon 2000).

However, as noted by House et al. (2004), study results should be interpreted with caution. Most studies, with the exception of Choi-Kwon et al. (2006) were quite small and used varying definitions for post-stroke emotionalism. There was considerable variation in the methods used to assess emotionalism; most studies relied upon a combination of interview-based and self-report data to determine frequency and severity of episodes or outbursts. A single study (Robinson et al. 2000) evaluated the measurement properties of a scale specific to the evaluation of pathological crying and laughing, but it was not used in subsequent studies.

Although there is a known relationship between depression and emotionalism, few studies attempted to control or adjust for the possible effects of depression on study outcomes. While Brown et al. (1998) and Burns et al. (1999) excluded patients with major depression, they included patients with minor depressive disorders. Similarly, Andersen et al. (1993) noted that no patients were diagnosed with major depression at baseline. Choi-Kwon et al. (2006) placed patients with post stroke depression, emotional incontinence and post-stroke anger proneness in groups for analysis; however, the groups do not appear to be mutually exclusive. Robinson et al. (1993) noted that a substantial proportion of study participants were experiencing major post stroke depression. The authors of this study did attempt to provide an analysis of the impact of depression on the improvement in emotionalism based on a subgroup analysis of 8 pairs of participants matched for depression scores. Within this small subgroup, treatment of emotionalism with nortriptyline was reported to be effective independent of depression (Robinson et al. 1993).

Duration of treatment and time since stroke also varied between studies. Given that the outbursts associated with post-stroke emotionalism tend to become less frequent and less severe over the first 12 months post stroke, further study is required to determine the optimal timing and duration of treatment.

**Conclusions Regarding the Treatment of Post-Stroke Emotionalism**

*There is level 1a evidence that antidepressants and SSRIs in particular may be an effective treatment for post-stroke emotionalism.*

**Antidepressants, and SSRI antidepressants in particular, may be effective in the treatment of post-stroke emotionalism. Further study is required to determine optimum timing and duration for treatment.**
18.11 Guidelines for Treatment of Post-Stroke Depression and Other Mood Symptoms

There are several sets of current rehabilitation guidelines that make recommendations for the assessment and treatment of mood disorders following stroke. In general, all acknowledge the importance of identification and diagnosis of depression. All recommend the use of standardized assessment and most indicate that a clinical interview conducted by an appropriate mental healthcare professional is required for diagnosis. Treatment, in the form of antidepressant medication (usually an SSRI), is recommended, though the details and possible duration of treatment are not clearly stated. The possible role of psychotherapy is acknowledged although there is little evidence of its effectiveness within this population. The most recent clinical guidelines are the “Canadian Best Practice Recommendations for Stroke Care” endorsed by the Canadian Stoke Network and the Heart and Stroke Foundation. These guidelines are found in Table 18.11.1.

Table 18.11.1 Canadian Best Practice Recommendations for Stroke Care

<table>
<thead>
<tr>
<th>Recommendations for Mood Disturbance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screening</strong></td>
</tr>
<tr>
<td>• All patients with stroke should be screened for depressive symptoms using a validated tool.</td>
</tr>
<tr>
<td>• Screening should include evaluation or risk factors for depression, particularly a history of depression.</td>
</tr>
<tr>
<td>• Screening should take place at various stages throughout the continuum of stroke care. Stages of care may include:</td>
</tr>
<tr>
<td>• During acute care stay</td>
</tr>
<tr>
<td>• Following hospital discharge from the emergency department or inpatient setting to an outpatient or community-based setting</td>
</tr>
<tr>
<td>• Throughout rehabilitation within inpatient/outpatient/home-based setting</td>
</tr>
<tr>
<td>• Periodically, following discharge to the community, during follow-up appointments and/or during period health assessments.</td>
</tr>
<tr>
<td><strong>Assessment</strong></td>
</tr>
<tr>
<td>• Patients identified as being at risk for depression during screening should be managed by a healthcare professional with expertise in diagnosis and management of depression in stroke patients. If required, a referral should be made to an appropriate mental health specialist.</td>
</tr>
<tr>
<td>• Further assessments by the mental health care professional may include:</td>
</tr>
<tr>
<td>• More in-depth interview for the purpose of assessment and diagnosis based on accepted diagnostic criteria</td>
</tr>
<tr>
<td>• Population-specific assessment measures</td>
</tr>
<tr>
<td>• Determination of appropriate course of treatment and individualized management plan</td>
</tr>
<tr>
<td>• Post-treatment assessment and follow-up as needed</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
</tr>
<tr>
<td><strong>A. Pharmacotherapy</strong></td>
</tr>
<tr>
<td>• Patients with mild depressive symptoms or those diagnosed with minor depression may initially be managed by “watchful waiting”.</td>
</tr>
<tr>
<td>• Pharmacological treatment should be considered/started if the depression is persistent and interferes with clinical goals, or worsens.</td>
</tr>
<tr>
<td>• Patients diagnosed with a depressive disorder following formal assessment should be considered for a trial of antidepressant medication.</td>
</tr>
<tr>
<td>• No one drug class has been found to be superior for PSD treatment. Side effect profiles, however suggest that some selective serotonin reuptake inhibitors may be favoured in this patient population.</td>
</tr>
<tr>
<td>• 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 interaction with other current medications and underlying disease conditions.</td>
</tr>
</tbody>
</table>
Response to treatment should be monitored regularly by a health professional with expertise in mental healthcare. 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 six months before slowly withdrawing the antidepressant.

- 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), and improved motivation to carry out daily activities.

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

B. Non-Pharmacological and Adjunct Therapy

- There is inadequate evidence at present to support the use of psychotherapy as monotherapy in the treatment of PSD.

- Treatment for PSD may also include psychotherapy as an adjunct in combination with antidepressants and/or longer term option to prevent relapse. This approach, while supported by evidence in other populations, requires more research in stroke populations.
  - Different options that have been explored in small studies have included cognitive behavioural therapy (CBT) and problem solving therapy, although the methodological details of the therapies have not been well described. These therapies could be considered where appropriate at the discretion of the mental health expert.

- Other approaches to adjunctive treatment of PSD that are emerging, but require more research, include other forms of Repetitive Transcranial Magnetic Stimulation (rTMs), CBT, physical exercise, and acupuncture

C. Other Mood Symptoms (Anxiety)

- Patients with marked anxiety should be offered psychotherapy.
  - Although evidence is limited in stroke patients, pharmacotherapy may be considered as an adjunct to psychotherapy

D. Post Stroke Emotional Incontinence (PSEI)

- In cases of severe, persistent or troublesome tearfulness, 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.

Prevention of Post Stroke Depression

- Although, emerging data on the use of pharmacotherapy as a preventive intervention for post stroke depression is encouraging, routine use of prophylactic antidepressants is not recommended in post-stroke patients, at this time.
  - Further research is required to define at risk patients, choice of antidepressant agents, optimal timing and duration of intervention.

- Non-pharmacological, talk-based interventions including problem-solving therapy and motivational interviewing may be used to enhance rehabilitation and prevent depression post stroke.

- Engaging patients in activities such as exercise or music therapy may also have a beneficial effect on mood post-stroke.

Ongoing Monitoring, Support and Education

- Patients 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.

- Patients and their caregivers should have their psychosocial and support needs assessed and reviewed on a regular basis (at least annually) as part of long-term stroke management by primary care practitioners and consulting specialists.

- For patients who experience some degree of communication challenge or deficits following stroke, appropriate strategies for screening of possible PSD should be implemented to ensure adequate assessment and access to appropriate treatment.

While the preferred mode of treatment is specified, there are no guidelines provided regarding how treatment plans should be developed, how or for how long treatment should be provided and what happens at the end of the course of treatment. The National Clinical Guidelines for Stroke (Party 2004) suggest that antidepressant treatment for PSD should begin only after a period of “watchful waiting” to determine if the depressive episode will become persistent. Following this, treatment may be initiated for
persistent episodes by an “appropriately trained and supervised practitioner.” Treatment should be kept under review and should continue for at least 6 months, if a good response is achieved. Persistent disorders causing distress or worsening disability “should be managed by or with advice from an experienced clinical psychologist or psychiatrist.”

In 2005, the British Society of Rehabilitation Medicine and the British Geriatrics Society in association with the Royal College of Physicians published concise guidelines for the use of antidepressant medication following “acquired brain injury” (Turner-Stokes & MacWalter 2005). The recommendations were intended for clinicians working with individuals who had sustained brain injury from any cause, including stroke, and include recommendations for screening and assessment issues to consider prior to the commencement of treatment, as well as suggestions for treatment planning, evaluation and withdrawal. A summary of the guidelines is provided in Table 18.11.2.

Table 18.11.2 Summarized Guidelines for the Use of Antidepressant Medication Following Brain Injury (British Society of Rehabilitation Medicine & the British Geriatric Society).

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Treatment</th>
<th>During Treatment</th>
<th>Referral for Formal Psychiatric Interview</th>
<th>Withdrawal from Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Recommend informal screening at each assessment point (e.g. ask patient about mood or ask family about behaviours that might suggest depression)</td>
<td>- Clinicians should observe patients carefully regarding impact of depression on function, social participation and QOL</td>
<td>- Patients should see doctor regularly during treatment (every 2 months) – any clinical deterioration should be investigated – particularly known side effects such as hyponatraemia, seizures, G1 bleeding, anti-cholinergic symptoms, sexual dysfunction, sedation, hallucinations, increased confusion, headache</td>
<td>- If depression is severe or resistant to treatment</td>
<td>- At end of treatment (generally 4 – 6 months), there should be a planned period of withdrawal taking place gradually over a period of 1 – 2 months</td>
</tr>
<tr>
<td>- If depression is suspected, proceed to more formal, detailed assessment (using validated measures, interview and/or observation)</td>
<td>- Clinicians should attempt to determine if other, simple, interventions might be appropriate to “boost the patient’s mood”</td>
<td>- Antidepressant medication should not be given with repeat prescription and no more than 2 months supply should be written.</td>
<td>- Past history of psychiatric disorder and/or use of antidepressant</td>
<td>- Prior to withdrawal, patient mood should be re-evaluated (using same measure as at baseline)</td>
</tr>
<tr>
<td></td>
<td>- Possible risks and contraindications for treatment should be considered carefully along with issues of informed consent and patient/family education</td>
<td></td>
<td>- Patient shows evidence of suicidal ideation or intent</td>
<td>- Patient/family should be warned re: possibility of rebound symptoms. For longer lasting relapse of depression, long-term treatment may be considered. Formal psychiatric advice should be sought.</td>
</tr>
</tbody>
</table>
Though the 2005 guidelines for use of antidepressants post brain injury do not include specific recommendations for a particular antidepressant agent, the authors suggest that SSRIs, while as effective as heterocyclic antidepressants, have fewer reported side effects.

**Conclusions Regarding Treatment Guidelines**

*Current guidelines recommend both screening and appropriate assessment of depression in patients with stroke. Treatment with an appropriate antidepressant is recommended for a period of approximately 6 months (given evidence of treatment effectiveness). Treatment (and subsequent withdrawal) should be monitored closely by an appropriately trained healthcare professional.*

*Guidelines for the treatment of post stroke depression recommend screening, assessment and treatment with an appropriate antidepressant for a period of approximately 6 months.*
Summary

1. At least one-third of stroke patients will experience depression. While the patterns of incidence and recovery change over time, for many individuals PSD may be persistent.

2. There is level 4 evidence that personality traits such as neuroticism and pessimism, and a passive coping style is significantly associated with the development of depression.

3. There is level 5 evidence that comorbidity of depression and anxiety occur in at least one-third of stroke patients and, despite recovery over time, are prevalent in one-fifth of patients after 5 years.

4. Commonly identified risk factors for depression include female gender, older age, a previous history of depression, functional limitations and cognitive impairment.

5. Prior treatment of depression and the need for assistance with activities of daily living may be the factors most predictive of risk of post stroke depression.

6. Younger age was found to be a commonly identified risk factor for developing multiple comorbid psychiatric concerns such as depression and anxiety, and psychological distress including anger, helplessness, emotional dyscontrol, and indifference.

7. The relationship between the site of the brain lesion and depression.

8. There remains a wide diversity of findings in studies looking at the relationships between stroke location and depression. Not all studies have confirmed this relationship and meta-analyses have failed to establish a definitive relationship between the site of the stroke and depression.

9. There is conflicting evidence regarding the hemispheric side of the lesion and rates of depression.

10. There is level 4 and level 5 evidence that left hemispheric strokes are more susceptible to developing depression.

11. There is level 5 evidence that right hemispheric strokes are more susceptible.

12. There is level 5 evidence suggesting mixed results with only one outcome measure out of five revealing a significant difference in levels of depression. There is level 5 evidence of a lack of an association between the hemispheric side of the lesion and depression.

13. There is level 5 evidence that strokes involving the basal ganglia are associated with the development of PSD.

14. There is level 5 evidence suggesting that patients with stroke experience greater levels of depression and mood disturbance than traumatic brain injury patients.

15. There is level 1a evidence from one meta-analysis that the PHQ-9 is an effective diagnostic tool for post-stroke depression as well as favourable findings for use of the CES-D and the HAM-D.

16. There is level 5 evidence that PSD is significantly different from a diagnosis of major depression and that a new tool for PSD, the Post-Stroke Depression Predict Scale (DePres), may be of use when detecting post-stroke depression.
17. There is level 5 evidence that the Hospital Anxiety and Depression Scale (HADS) demonstrates low sensitivity but mixed conclusions were drawn regarding specificity with one study reporting a low specificity score whilst the other reported a higher score.

18. There is level 3 evidence that depression may have a significant and negative impact on functional ability following stroke.

19. There is level 3 evidence that functional dependence is associated with greater levels of depression, illness comorbidity and cognitive deficits when compared to functional independence.

20. There is level 5 evidence that patients admitted to an inpatient stroke unit demonstrate significantly greater levels of apathy compared to patients living in the community.

21. There is level 3 evidence that decreased socialization outside of the home, inside the home, and in hobbies and interests lead to significant increases in depressive symptoms among stroke patients compared to age and gender-matched controls.

22. There is level 5 evidence that patients who socialise with friends, spend time with relatives and/or a partner, and participate in passive activities such as listening to music exhibit lower levels of depression while returning to work and/or playing sports was associated with higher levels of depression.

23. There is level 1a evidence that cognitive impairments can be improved with cognitive training interventions but these do not result in improvements for depression.

24. There is level 5 evidence that executive dysfunction and depression-executive dysfunction syndrome are both associated with older age.

25. There is level 1a evidence that cognitive impairments can be improved with cognitive training interventions but these do not result in improvements for depression.

26. There is level 5 evidence that executive dysfunction and depression-executive dysfunction syndrome are both associated with older age.

27. There is level 1a evidence that early initiation of antidepressant therapy, in non-depressed stroke patients is associated with reduced risk for the development of post-stroke depression. Further study is required to assess both duration of treatment and optimal timing for the initiation of therapy.

28. There is level 1a evidence that Fluoxetine is an effective pharmaceutical treatment for preventing PSD with level 1b evidence from one RCT that Fluoxetine can also improve functional disabilities.

29. There is level 1a evidence that Escitalopram can assist with improving mood among stroke patients with one RCT revealing a successful prevention of depression compared to problem-solving therapy and a placebo group, and another RCT revealing a prevention of apathy compared to a placebo.

30. There is mixed evidence regarding the efficacy of Sertraline with level 1b evidence it does not prevent depression any better than a placebo while other level 1b evidence reporting successful prevention of depression compared to placebo.
31. There is level 1b evidence that Milnacipran may be effective in preventing depression compared to a placebo.

32. There is level 2 evidence that Mirtazapine may be effective in preventing depression compared to not receiving pharmacological treatment.

33. There is level 1a evidence that ongoing individualized contact and support provided via various care provision models is associated with less deterioration of mood and/or mental health state following stroke.

34. There is level 1a evidence that outreach communication initiatives such as mailed postcards and letters to patients are ineffective in reducing depression however mixed evidence in regards to direct telephone calls with level 1b evidence that it is ineffective and level 2 evidence that weekly telephone appointments reduced depression scores.

35. There is level 1a evidence that motivational interviewing resulted in significant improvements in reducing depression compared to usual care.

36. There is level 1b evidence that outreach initiatives in the form of follow-up home visits from nurses resulted in significant improvements in depression and functioning compared to no contact or home visits.

37. There is level 2 evidence that assistance from a stroke family support service did not result in a significant improvement in depression compared to usual care.

38. There is level 2 evidence that goals and recommendations for general practitioners to manage risk factors and provide frequent appointments with patients did not reduce rates of depression significantly compared to usual care.

39. There is level 1b evidence that fish oil supplementation following stroke has no impact on mood.

40. There is level 1b evidence that B-vitamin therapy, administered over a long period, may be associated with reduction in long-term risk for depression. Further study is required.

41. There is level 1a evidence that heterocyclic antidepressants may improve depression post stroke. Side effects in elderly patients mean that these medications should be used with caution in that population.

42. There is level 1a evidence that selective serotonin reuptake inhibitors are effective in the treatment of post-stroke depression. Further placebo studies should be conducted using a blinded administrator and an optimal treatment duration in order to address methodological differences across current studies.

43. There is level 1a evidence that the use of bright light therapy in conjunction with SSRI antidepressants is an effective treatment for non-seasonal depression, in general.

44. There is level 1b evidence that adjunctive bright light therapy may be more effective than moderate intensity light therapy in the treatment of post-stroke depression. Further research is required to examine timing, duration and optimal intensity.
45. There is level 1b evidence that Reboxetine, a noradrenaline reuptake inhibitor, is effective in reducing retarded post-stroke depression.

46. There is level 1b evidence that duloxetine may improve depression symptoms post-stroke.

47. There is level 4 evidence that venlafaxine may be an effective treatment for post-stroke depression.

48. There is level 1b evidence that the GABA compound nefiracetam may not be more effective than placebo in the treatment of post-stroke depression.

49. There is level 1b evidence that methylphenidate is more effective than placebo in improving both symptoms of depression and functional recovery. Methylphenidate (a psychostimulant) has an earlier onset of action than traditional antidepressants.

50. There is limited level 4 evidence that valdoxan, a melatonin agonist, may be effective in management of PSD.

51. There is limited level 2 evidence that statins may improve post-stroke depression and anxiety.

52. There is level 1b evidence that treatment with the herbal preparation, Free and Easy Wanderer Plus (FEWP), may be as effective as fluoxetine in the treatment of post-stroke depression.

53. There is level 1b evidence that an active care management program including patient education and ongoing monitoring may enhance effectiveness of pharmacologic treatment for post stroke depression.

54. There is level 1a evidence that treatment with Nortriptyline may improve post-stroke depression. There is also limited evidence to suggest that an improvement in post-stroke anxiety and functional recovery but not cognitive functioning may follow after treatment with Nortriptyline.

55. There is level 1a evidence that treatment with Fluoxetine may improve depression symptoms and independent functioning but not cognitive functioning. Findings for the effect of Fluoxetine on functional recovery are conflicting.

56. There is level 1a evidence that Trazodone treatment may not improve post-stroke depression.

57. There is level 1b evidence that Maprotiline may improve depressive symptoms, motor and independence functioning.

58. There is level 1b evidence that Desipramine may not improve depression or motor recovery post-stroke.

59. There is limited level 2 evidence that Citalopram may improve depression symptomology and

60. There is level 1b evidence that early treatment with antidepressants (Nortriptyline or Fluoxetine) post stroke is associated with improved long-term survival. Further research is required.
61. There is limited level 3 evidence that electroconvulsive therapy may be an effective treatment for short term depressive symptoms without worsening existing neurological deficits. Further studies are required.

62. There is level 1a evidence that rTMS may improve depressive symptomatology.

63. There is level 1a evidence that cognitive behavioral therapy (CBT) may not be effective at improving post-stroke depression symptomology.

64. There is level 1b evidence that mood-based CBT may improve depression and self-esteem in post-stroke patients with aphasia.

65. There is level 1b evidence that mindfulness may help improve mental fatigue after a stroke.

66. There is level 1b evidence that delivery of a brief psychosocial intervention in addition to antidepressant therapy may be more effective than antidepressant therapy alone in terms of depressive symptomatology, functional ability and social participation.

67. There is level 1a evidence that hyperbaric oxygen therapy with dexamethasone or fluoxetine may improve depressive symptoms post-stroke.

68. There is level 1b evidence that combination therapy of high-intensity light therapy and citalopram is superior over low-intensity light therapy with citalopram at improving post-stroke depression.

69. There is conflicting level 1b and level 2 evidence regarding the effect of music therapy on post-stroke depression.

70. There is level 1b evidence that music-movement therapy may not improve depression however, it may improve upper limb range of motion.

71. There is level 1b evidence that speech therapy may not improve depression scores or overall psychological wellbeing.

72. There is level 1a and limited level 2 evidence (one study) that various forms of exercise therapy may not improve depressive symptoms. However, level 2 evidence suggest otherwise.

73. There is level 1b evidence that ecosystem focused therapy may not be more effective than education in reducing depressive symptoms post-stroke.

74. There is level 1b evidence that acupuncture may not improve post-stroke depression however, it may improve neurological status.

75. There is level 1b evidence that dense cranial acupuncture with SSRI body electro-acupuncture may improve post-stroke depression however, the effects are not maintained.

76. There is limited level 2 evidence that electro-acupuncture may help improve post-stroke depression.

77. There is level 1b evidence that Reiki treatment may not improve functional recovery or depression symptomology post-stroke.
78. There is limited level 2 evidence that meridian acupressure may improve depression and independent functioning.

79. There is limited level 2 evidence that anxiety may be improved following massage therapy.

80. There is limited level 2 evidence that relaxing unilateral nostril breathing may not improve anxiety or depressive symptoms in aphasic compared to non-aphasic individuals.

81. There is limited level 4 evidence that art therapy may improve anxiety or depressive symptoms post-stoke.

82. There is level 1a evidence that antidepressants and SSRI s in particular may be an effective treatment for post-stroke emotionalism.

83. Current guidelines recommend both screening and appropriate assessment of depression in patients with stroke. Treatment with an appropriate antidepressant is recommended for a period of approximately 6 months (given evidence of treatment effectiveness). Treatment (and subsequent withdrawal) should be monitored closely by an appropriately trained healthcare professional.
References


Appendix

**Acute Stroke**

1. There is level 1b evidence that individual computerized training programs may not improve depression and anxiety when compared to conventional treatment.

2. There is conflicting level 1b evidence for the effects of Sertraline on preventing post-stroke depression.

3. There is level 1a evidence that Fluoxetine may be effective at preventing post-stroke depression when compared to placebo.

4. There is level 1b evidence that Mianserin may not be an effective prevention treatment for post-stroke depression when compared to placebo.

5. There is level 1b evidence that Milnacipran may be superior to placebo at preventing depression.

6. There is level 2 evidence that Mirtazapine may prevent post-stroke depression when compared to no pharmacological treatment.

7. There is level 1a evidence that Escitalopram may be effective at preventing depression and apathy when compared to problem-solving therapy and placebo.

8. There is level 1a evidence that motivational interviewing compared with usual care improves mood.

9. There is level 1b and limited level 2 evidence that home-visits post-discharge may reduce depression and improve activities of daily living when compared to usual care. There is level 1b evidence that home visits for pre-discharge assessment reduces depression in the short term, but not long term, when compared to pre-discharge interviews in the hospital.

10. There is level 1b evidence that personalized postcards delivered to patients does not reduce depression or anxiety.

11. There is limited level 2 evidence that recommendations for management and goal oriented therapy from general practitioners may not improve depressive symptoms when compared to usual care.

12. There is level 2 evidence that information provided by support services in the community may not improve activities of daily living or reduce mood.

13. There is level 1b evidence that vitamin-B supplements may not be superior to placebo in regards to reducing depressive symptoms.

14. There is level 1b evidence that Fluoxetine reduces depression in the long-term, but not immediately post-treatment.

15. There is level 2 evidence that high intensity light therapy may be superior to moderate intensity light therapy at reducing depressive symptoms.

16. There is level 1b evidence that Nefiracetam may not be more effective than placebo at reducing depression.

17. There is level 1b evidence that Methylphenidate may reduce symptoms of post stroke depression.

18. There is level 1a evidence for Fluoxetine and level 1b evidence for Nortriptyline evoking an improvement in depressive symptoms when compared to placebo.

19. There is level 1b evidence that rTMS may reduce depressive symptoms; however the effect of frequency of rTMS on post-stroke depression needs further study.
20. There is level 1b evidence that cognitive behavioural therapy may not reduce depressive symptoms.

21. There is level 1b evidence that psychosocial behavioural interventions combined with antidepressants may reduce post-stroke depression.

22. There is level 1b evidence that high-intensity light therapy combined with Citalopram may improve depressive symptoms when compared to moderate-intensity light therapy with Citalopram.

23. There is level 1b evidence that hyperbaric oxygen therapy combined with Fluoxetine may be superior to therapy or Fluoxetine alone at reducing depression.

24. There is level 1b evidence that music therapy may be superior to language therapy at reducing depression.

25. There is level 2 evidence that speech therapy combined with orofacial therapy may reduce depressive symptoms and improve activities of daily living when compared to speech therapy alone.

26. There is level 1b evidence that dense cranial acupuncture may be superior to non-invasive cranial acupuncture at reducing short term depressive symptoms and functional independence; however, no long-term effects are observed.

27. There is level 2 evidence that meridian acupressure reduces depression and improve functional independence.

**Subacute Stroke**

1. There is level 1a evidence that Escitalopram may be effective at preventing depression and apathy when compared to problem-solving therapy and placebo.

2. There is level 1b evidence that vitamin-B supplements may not be superior to placebo in regards to reducing depressive symptoms.

3. There is level 1a evidence that Nortriptyline reduces depression and improves activities of daily living compared to Fluoxetine and placebo.

4. There is level 1b evidence that Fluoxetine reduces depression by follow-up at 45 days, but level 1b evidence suggests it may not be as effective as Nortriptyline at reducing depression.

5. There is level 1b evidence that Citalopram reduces depression compared.

6. There is level 1b evidence that Reboxetine may reduce post-stroke depression.

7. There is level 1b evidence that herbal preparation therapy called Free and Easy Wanderer Plus may be as effective as Fluoxetine at reducing depression.

8. There is level 1b evidence that the AIM intervention reduces depression.

9. There is level 1a evidence that Fluoxetine may reduce depressive symptoms. There is level 1b evidence that Nortriptyline may be superior to Fluoxetine at reducing depression.

10. There is level 1b and level 2 evidence that Trazodone may not reduce depression or improve activities of daily living.

11. There is level 1b evidence that there is no significant difference between Fluoxetine, Trazodone, and Desipramine at reducing depressive symptoms and improving functional independence.

12. There is level 1a evidence that counselling and coping skill management reduces depression.
13. There is level 1b evidence that hyperbaric oxygen therapy combined with Dexamethasone may be superior to Deanxit in regards to reducing depression.

14. There is level 2 evidence that speech therapy compared to routine therapy may not improve depression and anxiety.

15. There is level 1b evidence that home exercise programs may reduce depression; however, level 1b evidence suggests that robotic training devices with exercise programs may not.

16. There is level 1a evidence that strength, resistance training and circuit training may not be superior to standard therapy at reducing depressive symptoms.

17. There is level 1b evidence that ecosystem focused therapy may not be superior to an education based program at reducing depression.

18. There is level 1b evidence that Reiki therapy does not reduce symptoms of post stroke depression.

19. There is level 1b evidence that Nortriptyline reduces depression and emotionalism.

**Chronic Stroke**

1. There is level 1b evidence that multimodal support interventions with patient contact may not reduce depression.

2. There is level 1b evidence that omega-3 fish oil capsules may not improve mood.

3. There is level 1b evidence that Nortriptyline reduces depression.

4. There is level 1b evidence that Fluoxetine may not reduce post-stroke depression.

5. There is level 1b evidence that Sertraline improves emotional distress only in the short term, but has no effect on post stroke depression.

6. There is level 1b evidence that Nortriptyline reduces depressive symptoms however, level 1b evidence suggests that the same effect does not hold true for remitted depression.

7. There is level 1b evidence that rTMS may improve depression but not functional independence.

8. There is level 1b evidence that mindfulness based therapy may improve mental fatigue.

9. There is level 1b evidence that mood-elevating cognitive behavioural techniques may reduce depression and improve self-esteem.

10. There is level 1a evidence that exercise therapy may not be effective at reducing depressive symptoms.

11. There is level 1b evidence that aerobic rehabilitation paired with skill development classes may not reduce depressive symptoms.

12. There is level 1b evidence that acupuncture does not reduce symptoms of post stroke depression.

13. There is level 2 evidence that slow-stroke back massage may improve anxiety.

14. There is level 1a evidence that Fluoxetine improves emotionalism, mental health and socialism.

15. There is level 1b evidence that Sertraline improves post stroke emotionalism.

16. There is level 1b evidence that Citalopram improves post stroke emotionalism and reduces depression symptoms.