Chapter 3
Depression After Stroke

Sergio E. Starkstein, Simone Brockman, and Brad Hayhow

Abstract Poststroke depression (PSD) is among the most common neuropsychiatric sequelae of stroke. Cross-sectional studies have demonstrated that about one-third of patients develop depression during the acute stage after stroke and more than 50 % suffer depression at some later point. PSD is strongly associated with negative outcomes, such as increased length of hospital stay, increased severity of neurological and functional deficits, more severe cognitive deficits, worse quality of life, and increased mortality. Randomized controlled trials have demonstrated the efficacy of nortriptyline, citalopram, and reboxetine to treat PSD. Recent studies also suggest that prophylactic treatment with antidepressants may significantly decrease the incidence of PSD, although more research in this area is needed.

Keywords Poststroke depression • Cognition • Mortality • Prevention • Treatment • Physical impairment

Introduction

Depression is one of the most frequent psychiatric complications after stroke. Cross-sectional studies have reported that about 20 % of patients suffer from major depression after an acute stroke and an additional 20 % develop minor

S.E. Starkstein (✉)
School of Psychiatry and Clinical Neurosciences,
University of Western Australia, Crawley, WA 6009, Australia

Fremantle Hospital, T-7, Fremantle, WA 6959, Australia
e-mail: sergio.starkstein@uwa.edu.au

S. Brockman • B. Hayhow
School of Psychiatry and Clinical Neurosciences,
University of Western Australia, Crawley, WA 6009, Australia

J.M. Ferro (ed.), *Neuropsychiatric Symptoms of Cerebrovascular Diseases*,
Neuropsychiatric Symptoms of Neurological Disease,
DOI 10.1007/978-1-4471-2428-3_3, © Springer-Verlag London 2013

depression [1]. Poststroke depression (PSD) has a negative impact on functional recovery and is associated with more severe cognitive deficits, poor quality of life, and higher mortality [1]. This chapter will first discuss current conceptual limitations in the diagnosis of depression after stroke. It will then address the prevalence, natural course, clinical correlates, and treatment and prevention of PSD.

Diagnosis of PSD

One of the most challenging problems in neuropsychiatry is how to diagnose depression when the symptoms of the neurological illness overlap with those of the affective disorder. Stroke patients frequently complain of insomnia, loss of appetite, poor concentration, loss of libido, and poor energy, which are all commonly identified through assessment with generic depression scales.

Four strategies have been proposed to minimize the overlap dilemma. In the "inclusive approach," symptoms of depression are counted as present regardless of whether they may be related to physical illness [2]. In the "exclusive approach," symptoms are removed from the diagnostic criteria whenever there is a potential overlap between depression and the neurological condition [3]. In the "substitutive approach," somatic symptoms of depression are replaced with psychological symptoms [4]. Finally, in the "etiological approach," symptoms of depression are included only when the examiner considers the symptoms not to be related to the neurological disorder [5].

In recent years several studies have been conducted to determine the specificity of depressive symptoms in stroke. Paradiso and coworkers [6] followed a group of acute stroke patients for 2 years and found that suicide ideation, ideas of reference, and pathological guilt were the only depressive symptoms not to be significantly more frequent in patients with DSM-IV major depression vs. those with no depression at 3 months poststroke. They also found 100 % sensitivity of standard DSM-IV criteria for major depression during the acute stroke period and 96 % sensitivity at the 2-year follow-up. Cumming and coworkers [7] carried out a factor analysis of 10 depressive symptoms in depressed and nondepressed stroke patients and found no significant differences between PSD and primary major depression for either psychological or somatic symptoms of depression. Based on these and previous findings, Robinson and Spalletta [8] suggested that no modification of the DSM-IV criteria for major depression is needed for the diagnosis of PSD. Nevertheless, future studies should further examine the validity of these criteria, specifically on stroke patients that are difficult to assess with current techniques (e.g., patients with aphasia or dementia).

Prevalence of PSD

Most studies assessing patients in acute settings reported a frequency of major depression of about 20 %, while another 20 % had minor depression [1]. For patients living in the community, the frequency of major depression was reported to be of

about 14 %, with 9 % for minor depression [1]. Robinson [1] suggested that this difference may be explained by more severe strokes among patients cared for in hospital settings as compared to patients living in the community.

Natural Course of PSD

There are few prospective studies of patients with untreated PSD with a relatively long follow-up. Robinson's studies found that about 50 % of patients with acute major depression remained depressed 6 months later, with the frequency dropping to 11 % 12 months poststroke, and none at the 24-month follow-up [9]. On the other hand, patients with minor depression seem to have a more chronic course, with about 50 % showing major or minor depression throughout the 2-year follow-up period [9]. Astrom and coworkers [10] reported a frequency of major depression of 30 % at 3 months poststroke. One year later, 60 % of them were nondepressed, while the remaining 40 % continued to be depressed.

The mechanism underlying the variability in the duration of depression remains poorly understood. In a small study that compared six depressed patients who spontaneously recovered from depression 6 months poststroke and ten depressed patients who did not recover, the main finding was that the non-recovered group had a higher frequency of cortical lesions and more severe in-hospital impairment in activities of daily living than the recovered group [11].

In conclusion, if left untreated, PSD is a long-lasting mood disorder, and duration may be influenced by lesion location and severity of acute impairments.

Clinical Correlates of PSD

Relationship to Lesion Variables

Pioneering studies by Robinson's group [1] showed a significant association between the frequencies of PSD and left frontal lesions. Starkstein and coworkers [12] later found this association to be true for both cortical and subcortical strokes in anterior regions of the left hemisphere. Another important finding from Robinson's studies [1] was a significant correlation between the distance of the lesion from the frontal pole and depression scores (i.e., the closer the lesion to the frontal pole, the higher the depression score). Later studies by other investigators produced heterogeneous results, ranging from replication of Robinson's findings [10, 13, 14] to no association between PSD and lesion variables [15]. Potential reasons for these discrepancies have been extensively discussed [1] and include differences in the time since stroke, demographic factors, recruitment bias, and source of patients (e.g., acute stroke units, rehabilitation services, patients living in the community). Time since stroke was identified as the main confounder by Shimoda and Robinson [16]. They reported that

the frequency of depression 2 weeks after stroke was significantly higher for patients with left vs. right hemisphere strokes, but there were no significant between-group differences in the frequency of depression at 3–6 months and 1–2 years after stroke. A meta-analysis that only included patients assessed up to 2 months after stroke found a significant association between left anterior lesions and depression (OR = 2.29, 95 % CI = 1.6–3.4, $p < 0.001$) [17]. Bhogal and coworkers [13] reported that the association between PSD and lesion location is influenced by source of patients (inpatients vs. individuals living in the community) and by time since stroke.

Relationship to Physical Impairment

A significant association between PSD and both physical and functional deficits has been consistently demonstrated, but this association is a complex one. Several studies showed that while PSD is a significant predictor of poorer recovery, more severe functional and physical impairments in the acute stage are strong predictors of depression [1].

Parikh and coworkers [18] and Pohjasvaara and coworkers [19] reported that depression at baseline predicts poor long-term functional and physical outcome. Donnellan and coworkers [20] recently examined the impact of depression on stroke outcomes. After controlling for relevant confounders, they found acute PSD was significantly associated with increased functional disability and poorer quality of life at 1 month poststroke. A review by Hackett and Anderson [21] found that 9 of 11 studies assessing physical and functional impairments in PSD demonstrated that greater functional and physical disability was associated with a greater frequency of depression.

Narushima and Robinson [22] reported that 34 patients (with or without depression) who received a 12-week treatment within the first 30 days after stroke with either fluoxetine (up to 40 mg/day) or nortriptyline (up to 100 mg/day) showed a greater recovery on activities of daily living than 28 patients receiving the same medications but who started treatment at 140 days poststroke. This finding suggests that early treatment with antidepressant drugs, even in the absence of depression, may have a positive impact upon functional recovery. These preliminary findings should be confirmed in large-scale randomized controlled trials (RCTs).

Relationship with Cognitive Impairment

A significant association between PSD and more severe cognitive impairment has been consistently demonstrated in both hospital and community settings. Robinson and coworkers [23] were the first to demonstrate significantly lower scores on the Mini Mental State Examination (MMSE) for patients with major depression as compared to nondepressed patients. These findings were later replicated by Spalletta and coworkers [24], Downhill and Robinson [25], and Morris and coworkers [26]. To

control for lesion variables, Starkstein and coworkers [27] matched 11 patients with PSD with 11 nondepressed stroke patients for lesion location and volume. They replicated the finding of significantly lower MMSE scores for patients with major depression as compared to lesion-matched nondepressed individuals. Bolla-Wilson and coworkers [28] assessed a series of patients with an acute stroke using a comprehensive neuropsychological battery. They found that patients with PSD and left hemisphere lesions had significantly more severe deficits on temporal orientation, language, and executive functions than nondepressed patients with left hemisphere strokes. On the other hand, there were no significant differences on any cognitive domain between patients with right hemisphere strokes with or without depression.

The question now arises as to whether antidepressant treatment may have a beneficial effect upon cognition in PSD. Kimura and coworkers [29] reported that 24 patients with PSD who responded to treatment with nortriptyline had a greater improvement on MMSE scores than nonresponders ($N=23$). This improvement in cognition was reported to last for 2 years or more, even after the antidepressant was ceased [30] suggesting that antidepressant medication may improve cognitive deficits among patients with PSD.

Relationship to Mortality

Several studies have demonstrated an increase in both short-term (1–2 years poststroke) and long-term (5–10 years) mortality in patients with PSD. Morris and coworkers [31] reported that patients with PSD were 3.4 times more likely to have died during 10 years of follow-up than nondepressed patients. House and coworkers [32] reported that patients scoring 1 or more points on the depression subscale of the General Health Questionnaire had a mortality rate 2.4 times greater than patients who scored zero. In a retrospective study, Williams and coworkers [33] replicated the finding of greater mortality 6 years poststroke for patients with depression as compared to nondepressed patients. Jorge and coworkers examined mortality data 9 years after 104 acute stroke patients were randomly assigned to receive treatment with nortriptyline, fluoxetine, or placebo. The main finding was that 67 % of patients who were given full-dose antidepressants were alive at follow-up, as compared to only 35 % of placebo-treated patients. This suggests that treatment with antidepressants within the first 6 months after stroke is associated with increased survival of stroke victims with or without depression.

Treatment of Poststroke Depression

Given the poor prognosis of patients with PSD, it is not surprising that several RCTs have been conducted to investigate both the treatment and prevention of PSD. We will now discuss the most relevant RCTs and meta-analyses, including both pharmacological and psychosocial interventions.

Pharmacological Treatments

Antidepressants

The first randomized controlled trial (RCT) of antidepressants in PSD was carried out by Lipsey and coworkers [34] who used nortriptyline for 6 weeks with doses increasing from 25 to 100 mg/day. The main finding was greater efficacy of the nortriptyline over placebo. Side effects from the nortriptyline group were delirium, drowsiness, confusion, and agitation in three patients which were severe enough to require discontinuation. Since this seminal study, a number of RCTs have been reported, most of them using selective serotonin reuptake inhibitors (SSRIs). Andersen and coworkers [35] examined the efficacy of citalopram (10–20 mg/day) in a 6-week RCT that included 59 completers. The main finding was a significant reduction on the HAM-D in the citalopram group as compared to the placebo group, with only minor side effects in the active treatment group.

Robinson and coworkers [36] carried out the only RCT to compare the efficacy of a tricyclic drug (nortriptyline) against an SSRI (fluoxetine) and placebo. This was a 12-week study, and patients with contraindications to the use of fluoxetine (intracerebral hemorrhage) or nortriptyline (cardiac conduction abnormalities, cardiac arrhythmia, narrow-angle glaucoma, sedation, or orthostatic hypotension) were excluded. Patients in the fluoxetine group were started on 10 mg/day for the first 3 weeks, and the dose was increased up to 40 mg/day. Patients on nortriptyline were started on 25 mg/day for the first week, and the dose was increased up to 100 mg/day. The main finding was that patients on nortriptyline showed a significantly greater decrease on HAM-D scores as compared to patients on fluoxetine or placebo (Fig. 3.1). On the other hand, there were no significant differences between the fluoxetine and the placebo groups. Based on these findings, Robinson and coworkers recommended a slow increase of nortriptyline, with a goal of achieving a serum concentration between 50 and 150 ng/mL.

The only RCT to use a norepinephrine reuptake inhibitor was conducted by Rampello and coworkers [37] who assessed the efficacy of reboxetine among patients with PSD and psychomotor retardation. Patients on reboxetine (4 mg/day) showed a significant decline on depression scores as compared to patients on placebo over the 16-week trial.

The efficacy of antidepressants was examined in two meta-analyses. Chen and coworkers [38] identified 16 relevant RCTs: 12 assessed SSRIs, 2 assessed tricyclics, and the remaining trials assessed other compounds. There was a significantly greater improvement in depression with active treatment as compared to placebo (pooled response rates of 65 and 44 %, respectively). Positive effects were observed after 3–4 weeks of treatment, and longer duration of treatment was associated with a greater response. Based on this important finding, the time-dependent effect of antidepressants in PSD should be further studied, and maintenance treatment should be perhaps recommended. Hackett and coworkers [39] conducted a meta-analysis that included seven RCTs of antidepressants: 4 RCTs used SSRIs (fluoxetine,

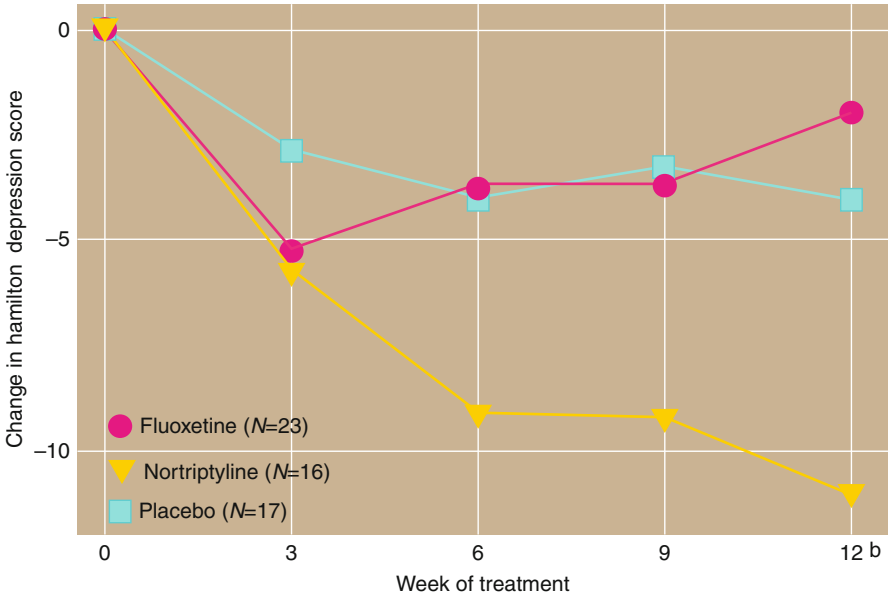


Fig. 3.1 Change in depression scores for depressed poststroke patients entered in a study comparing fluoxetine, nortriptyline, and placebo. Significant time-by-treatment interaction ($F = 3.45$, df = 8, 212, $p = 0.004$). Significantly greater change in patients treated with nortriptyline than in those taking fluoxetine or placebo (post hoc tests with Duncan's statistic, $p < 0.05$) [36] (Reprinted with permission)

sertraline, and citalopram), one RCT used a tricyclic compound (nortriptyline), and 2 RCTs assessed other antidepressants (aniracetam and trazodone). The main finding was that antidepressants were not associated with overall benefit as compared to placebo, but there was a significant effect in favor of active treatment on response rates and reduction in depression scores. Nevertheless, outcomes were quite heterogeneous, and active treatment was associated with increased frequency of adverse events.

Psychostimulants

Psychostimulants were mostly assessed in open-label studies using dextroamphetamine and methylphenidate and generally reported good efficacy of these compounds in treating PSD [40, 41]. However, the only RCT carried out to date failed to demonstrate significant treatment efficacy [42].

Several important limitations of RCTs for PSD should be noted. First, the recruitment periods of different studies ranged from that the acute stroke period to months or years after the stroke. Patients have also been recruited from different sources, such as acute stroke units, rehabilitation settings, or from the community. Second, some studies have excluded patients with a pre-stroke history of depression, while

other studies have included patients regardless of a previous positive psychiatric history. Third, the diagnosis of depression has been heterogeneous, ranging from scoring above a specific cutoff point on a depression scale to using more appropriate standardized diagnostic criteria for major depression. Finally, duration of treatment has ranged from 4 to 8 weeks, and primary outcome measures have varied from full remission (i.e., no longer meeting the criteria for depression), response (a reduction of 50 % or more on the baseline depression score), or a significant reduction in depression scores.

Non-pharmacological Treatments

Psychosocial Interventions

Few studies have examined the efficacy of psychosocial interventions as a treatment for PSD. Lincoln and coworkers [43] showed cognitive-behavioral treatment to be no more effective than a placebo treatment. One meta-analysis examined the efficacy of psychotherapy for PSD and showed no significant effects for active treatment [39]. Nevertheless, a recent RCT of a care management intervention (Activate-Initiate-Monitor intervention) showed that care management of PSD resulted in greater remission of depression and reduction of depressive symptoms than usual care alone [44]. Positive results were also found with the use of an integrated case model of depression treatment and a physical exercise program [45]. Treatment took place in the home three times a week for a total of 36 sessions and was supervised by a physical or occupational therapist. One limitation of this study is that there was no formal psychiatric interview to ascertain a diagnosis of PSD. Nevertheless, these findings suggest that adding patient activation and telephone-based treatment monitoring may enhance the efficacy of antidepressants to treat PSD.

Repetitive Transcranial Magnetic Stimulation (rTMS)

Two RCTs examined the efficacy of rTMS in PSD. The first study included 20 patients who received 10 sessions of rTMS or sham stimulation on the left dorsolateral prefrontal cortex [46]. Patients receiving active treatment showed a significant reduction of depressive symptoms as compared to sham treatment. The treatment was well tolerated, with only mild side effects in both groups. The second study [47] included 18 patients who were randomly assigned to low-frequency (1 Hz), high-frequency (10 Hz), or sham stimulation. The main finding was that high-frequency rTMS resulted in a significant decrease in depression scores as compared to sham treatment. Future studies are needed to further examine the efficacy and safety of rTMS for PSD.

Electroconvulsive Therapy (ECT)

There are no RCTs of ECT in PSD, but retrospective studies suggest that elderly individuals with stroke and depression may show moderate or marked improvement after ECT without further neurological complications except for prolonged postictal confusion and amnesia [48]. ECT could become a useful alternative for patients refractory to antidepressants or psychotherapy, but the efficacy and safety of ECT should be examined in appropriate RCTs.

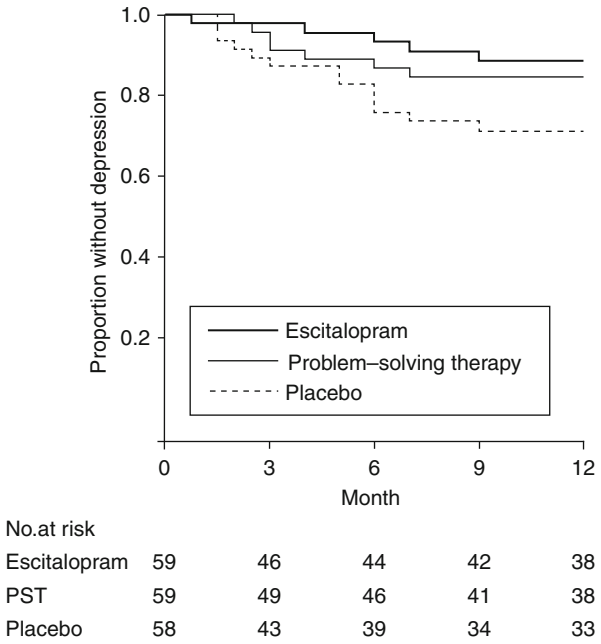
Prevention of Poststroke Depression

Given that PSD is associated with greater functional impairment, more severe cognitive deficits, and higher mortality, prevention is of great relevance. Both pharmacological and psychotherapeutic interventions have been explored in preventing PSD, with variable success.

Pharmacological Interventions

The first prevention study was carried out by Palomaki and coworkers [49], who compared the efficacy of mianserin (60 mg/day) against placebo during a 12-month period in a sample of 100 acute stroke patients. The authors found no significant differences between active treatment and placebo in preventing PSD. Rasmussen and coworkers [50] have examined the efficacy of sertraline (mean dose 63 mg/day) to prevent PSD in a series of 137 acute stroke patients who received acute treatment or placebo during 12 months. About 8 % of patients on sertraline developed depression as compared to 22 % of patients on placebo. Treatment with sertraline was well tolerated, and side effects were minor. On the other hand, using sertraline 50 mg/day, Almeida and coworkers [51] were unable to find significant efficacy for the active treatment. However, the study was methodologically limited given the short follow-up period (3 months only), and the study may have lacked power to detect significant differences between sertraline and placebo.

More recently, Robinson and coworkers [52] conducted a multicenter RCT that included 176 nondepressed patients within 3 months after stroke who were followed for 12 months. Patients were randomized to escitalopram, a non-blinded problem-solving therapy, or placebo. The main finding was that both active treatments were superior to placebo in preventing PSD. In another study, Robinson's group reported that nortriptyline treatment increased the vulnerability to depression after its discontinuation, suggesting that patients may develop tolerance to this antidepressant [53]. Finally, Jorge and coworkers [54] reported that a 12-week trial with nortriptyline (25–100 mg/day) or fluoxetine (10–40 mg/day) may significantly decrease the



No.at risk					
Escitalopram	59	46	44	42	38
PST	59	49	46	41	38
Placebo	58	43	39	34	33

Fig. 3.2 Risk comparison of depression onset for patients receiving escitalopram, problem-solving therapy (PST), or placebo over 1 year [52] (Reprinted with permission)

9-year mortality as compared to depressed or nondepressed stroke patients treated with placebo (Fig. 3.2).

Yi and coworkers [55] carried out a meta-analysis on the efficacy of fluoxetine for the prophylaxis of PSD. The analysis included six studies and the main finding was a significant reduction of PSD, increased recovery on neurological function, and improved independence on activities of daily living. On the other hand, there were no significant differences between the fluoxetine and placebo groups on depression scores at the end of the studies. There were no differences on side effects between patients on fluoxetine or placebo, although nausea, insomnia, and seizures were more frequent in the fluoxetine group. Of note, reductions in the incidence of PSD were related to onset of fluoxetine administration, with patients receiving fluoxetine 1 week after the stroke showing the best results. Side effects in the different trials were minimal, and the analysis of adverse events suggests a high risk-benefit ratio in favor of antidepressants.

Anderson and coworkers conducted a Cochrane review to examine whether pharmacological interventions can prevent PSD [56]. They included data from 10 RCTs, and main outcome measures of which were the presence of major depression or dysthymia or scoring above specific cutoff points for depressive disorder on specific depression rating scales. They reported no consistent evidence that antidepressant treatment prevents PSD, although the overall rate of depression was lower among patients treated with antidepressants. The negative finding may be explained by major differences between studies, such as time from stroke to onset of antidepressant intake, and the use of different drugs (fluoxetine, sertraline,

trazodone, piracetam, maprotiline, mianserin, nortriptyline, indeloxazine, and methylphenidate). Furthermore, treatment duration varied from 2 weeks to 12 months, and outcome measures differed between studies.

In conclusion, it is still unclear whether all stroke patients should receive prophylactic treatment with antidepressants. Ramasubbu [57] discussed several limitations to implement generic treatment, consequent to the fact that 50 % of stroke patients may never develop depression. For instance, patients and their families may not accept antidepressant treatment in the absence of depression, and clinicians may be reluctant to prescribe these medications due to concerns about side effects and potential drug interactions.

Psychosocial Interventions

Anderson's and coworkers Cochrane review [56] also assessed the efficacy of psychotherapy to prevent PSD. They included four RCTs and quasi-RCTs comparing different types of psychotherapy against standard care. Psychotherapeutic interventions consisted of problem-solving therapy, motivational interviewing, and multidisciplinary home-based therapy targeting psychosocial stressors. The main finding was a significant improvement on psychological distress after psychotherapy, but there were no significant differences on depression outcome. More evidence is required before a definite recommendation about using psychotherapy to prevent PSD is made.

Conclusion

PSD is a frequent finding after stroke and is significantly associated with negative physical, functional, and cognitive outcomes. RCTs have demonstrated the efficacy of nortriptyline and citalopram to treat PSD, but patients should be adequately selected to avoid severe side effects. Psychosocial interventions may also have efficacy for PSD and could enhance the effect of antidepressants. Prevention of PSD with antidepressants is still a debated issue, and future studies should identify the population of stroke patients that may significantly benefit from this intervention.

References

1. Robinson RG. The clinical neuropsychiatry of stroke. 2nd ed. Cambridge: Cambridge University Press; 2006.
2. Rifkin A, Reardon G, Siris S, Karagji B, Kim YS, Hackstaff L, et al. Trimipramine in physical illness with depression. J Clin Psychiatry. 1985;46(2 Pt 2):4–8.

3. Bukberg J, Penman D, Holland JC. Depression in hospitalized cancer patients. Psychosom Med. 1984;46(3):199–212.
4. Endicott J. Measurement of depression in patients with cancer. Cancer. 1984;53(10 Suppl):2243–9.
5. Rapp SR, Vrana S. Substituting nonsomatic for somatic symptoms in the diagnosis of depression in elderly male medical patients. Am J Psychiatry. 1989;146(9):1197–200.
6. Paradiso S, Ohkubo T, Robinson RG. Vegetative and psychological symptoms associated with depressed mood over the first two years after stroke. Int J Psychiatry Med. 1997;27(2):137–57.
7. Cumming TB, Churilov L, Skoog I, Blomstrand C, Linden T. Little evidence for different phenomenology in poststroke depression. Acta Psychiatr Scand. 2010;121(6):424–30.
8. Spalletta G, Robinson RG. How should depression be diagnosed in patients with stroke? Acta Psychiatr Scand. 2010;121(6):401–3.
9. Robinson RG, Spalletta G. Poststroke depression: a review. Can J Psychiatry. 2010;55(6):341–9.
10. Astrom M, Adolfsson R, Asplund K. Major depression in stroke patients. A 3-year longitudinal study. Stroke. 1993;24(7):976–82.
11. Starkstein SE, Robinson RG, Price TR. Comparison of spontaneously recovered versus nonrecovered patients with poststroke depression. Stroke. 1988;19(12):1491–6.
12. Starkstein SE, Robinson RG, Price TR. Comparison of cortical and subcortical lesions in the production of poststroke mood disorders. Brain. 1987;110(Pt 4):1045–59.
13. Bhogal SK, Teasell R, Foley N, Speechley M. Lesion location and poststroke depression: systematic review of the methodological limitations in the literature. Stroke. 2004;35(3):794–802.
14. Morris PL, Robinson RG, Raphael B, Hopwood MJ. Lesion location and poststroke depression. J Neuropsychiatry Clin Neurosci. 1996;8(4):399–403.
15. Carson AJ, MacHale S, Allen K, Lawrie SM, Dennis M, House A, et al. Depression after stroke and lesion location: a systematic review. Lancet. 2000;356(9224):122–6.
16. Shimoda K, Robinson RG. The relationship between poststroke depression and lesion location in long-term follow-up. Biol Psychiatry. 1999;45(2):187–92.
17. Narushima K, Kosier JT, Robinson RG. A reappraisal of poststroke depression, intra- and inter-hemispheric lesion location using meta-analysis. J Neuropsychiatry Clin Neurosci. 2003;15(4):422–30.
18. Parikh RM, Robinson RG, Lipsey JR, Starkstein SE, Fedoroff JP, Price TR. The impact of poststroke depression on recovery in activities of daily living over a 2-year follow-up. Arch Neurol. 1990;47(7):785–9.
19. Pohjasvaara T, Vataja R, Leppavuori A, Kaste M, Erkinjuntti T. Depression is an independent predictor of poor long-term functional outcome post-stroke. Eur J Neurol. 2001;8(4):315–9.
20. Donnellan C, Hickey A, Hevey D, O'Neill D. Effect of mood symptoms on recovery one year after stroke. Int J Geriatr Psychiatry. 2010;25(12):1288–95.
21. Hackett ML, Anderson CS. Predictors of depression after stroke: a systematic review of observational studies. Stroke. 2005;36(10):2296–301.
22. Narushima K, Robinson RG. The effect of early versus late antidepressant treatment on physical impairment associated with poststroke depression: is there a time-related therapeutic window? J Nerv Ment Dis. 2003;191(10):645–52.
23. Robinson RG, Bolla-Wilson K, Kaplan E, Lipsey JR, Price TR. Depression influences intellectual impairment in stroke patients. Br J Psychiatry. 1986;148:541–7.
24. Spalletta G, Guida G, De Angelis D, Caltagirone C. Predictors of cognitive level and depression severity are different in patients with left and right hemispheric stroke within the first year of illness. J Neurol. 2002;249(11):1541–51.
25. Downhill Jr JE, Robinson RG. Longitudinal assessment of depression and cognitive impairment following stroke. J Nerv Ment Dis. 1994;182(8):425–31.
26. Morris PL, Robinson RG, Raphael B. Prevalence and course of depressive disorders in hospitalized stroke patients. Int J Psychiatry Med. 1990;20(4):349–64.

27. Starkstein SE, Robinson RG, Price TR. Comparison of patients with and without poststroke major depression matched for size and location of lesion. Arch Gen Psychiatry. 1988;45(3):247–52.
28. Bolla-Wilson K, Robinson RG, Starkstein SE, Boston J, Price TR. Lateralization of dementia of depression in stroke patients. Am J Psychiatry. 1989;146(5):627–34.
29. Kimura M, Robinson RG, Kosier JT. Treatment of cognitive impairment after poststroke depression : a double-blind treatment trial. Stroke. 2000;31:1482–6.
30. Narushima K, Chan KL, Kosier JT, Robinson RG. Does cognitive recovery after treatment of poststroke depression last? A 2-year follow-up of cognitive function associated with post-stroke depression. Am J Psychiatry. 2003;160(6):1157–62.
31. Morris PL, Robinson RG, Samuels J. Depression, introversion and mortality following stroke. Aust N Z J Psychiatry. 1993;27(3):443–9.
32. House A, Knapp P, Bamford J, Vail A. Mortality at 12 and 24 months after stroke may be associated with depressive symptoms at 1 month. Stroke. 2001;32(3):696–701.
33. Williams LS, Ghose SS, Swindle RW. Depression and other mental health diagnoses increase mortality risk after ischemic stroke. Am J Psychiatry. 2004;161(6):1090–5.
34. Lipsey JR, Robinson RG, Pearlson GD, Rao K, Price TR. Nortriptyline treatment of post-stroke depression: a double-blind study. Lancet. 1984;1(8372):297–300.
35. Andersen G, Vestergaard K, Lauritzen L. Effective treatment of poststroke depression with the selective serotonin reuptake inhibitor citalopram. Stroke. 1994;25(6):1099–104.
36. Robinson RG, Schultz SK, Castillo C, Kopel T, Kosier JT, Newman RM, et al. Nortriptyline versus fluoxetine in the treatment of depression and in short-term recovery after stroke: a placebo-controlled, double-blind study. Am J Psychiatry. 2000;157(3):351–9.
37. Rampello L, Alvano A, Chiechio S, Raffaele R, Vecchio I, Malaguarnera M. An evaluation of efficacy and safety of reboxetine in elderly patients affected by “retarded” post-stroke depression. A random, placebo-controlled study. Arch Gerontol Geriatr. 2005;40(3):275–85.
38. Chen Y, Guo JJ, Zhan S, Patel NC. Treatment effects of antidepressants in patients with post-stroke depression: a meta-analysis. Ann Pharmacother. 2006;40(12):2115–22.
39. Hackett ML, Anderson CS, House AO. Interventions for treating depression after stroke. Cochrane Database Syst Rev. 2004;3:1–48.
40. Masand P, Murray GB, Pickett P. Psychostimulants in post-stroke depression. J Neuropsychiatry Clin Neurosci. 1991;3(1):23–7.
41. Lazarus LW, Moberg PJ, Langsley PR, Lingam VR. Methylphenidate and nortriptyline in the treatment of poststroke depression: a retrospective comparison. Arch Phys Med Rehabil. 1994;75(4):403–6.
42. Grade C, Redford B, Chrostowski J, Toussaint L, Blackwell B. Methylphenidate in early post-stroke recovery: a double-blind, placebo-controlled study. Arch Phys Med Rehabil. 1998; 79(9):1047–50.
43. Lincoln NB, Flannaghan T. Cognitive behavioral psychotherapy for depression following stroke: a randomized controlled trial. Stroke. 2003;34(1):111–5.
44. Williams LS, Kroenke K, Bakas T, Plue LD, Brizendine E, Tu W, et al. Care management of poststroke depression: a randomized, controlled trial. Stroke. 2007;38(3):998–1003.
45. Joubert J, Joubert L, Reid C, Barton D, Cumming T, Mitchell P, et al. The positive effect of integrated care on depressive symptoms in stroke survivors. Cerebrovas Dis. 199;26(2).
46. Jorge RE, Robinson RG, Tateno A, Narushima K, Acion L, Moser D, et al. Repetitive transcranial magnetic stimulation as treatment of poststroke depression: a preliminary study. Biol Psychiatry. 2004;55(4):398–405.
47. Kim D-Y, Lim J-Y, Kang EK, You DS, Oh M-K, Oh B-M, et al. Effect of transcranial direct current stimulation on motor recovery in patients with subacute stroke. Am J Phys Med Rehabil. 2010;89(11):879–86.
48. Murray GB, Shea V, Conn DK. Electroconvulsive therapy for poststroke depression. J Clin Psychiatry. 1986;47(5):258–60.
49. Palomaki H, Kaste M, Berg A, Lonnqvist R, Lonnqvist J, Lehtihalmes M, et al. Prevention of poststroke depression: 1 year randomised placebo controlled double blind trial of mianserin with 6 month follow up after therapy. J Neurol Neurosurg Psychiatry. 1999;66(4):490–4.

50. Rasmussen A, Lunde M, Poulsen DL, Sorensen K, Qvitzau S, Bech P. A double-blind, placebo-controlled study of sertraline in the prevention of depression in stroke patients. Psychosomatics. 2003;44(3):216–21.
51. Almeida OP, Waterreus A, Hankey GJ. Preventing depression after stroke: results from a randomized placebo-controlled trial. J Clin Psychiatry. 2006;67(7):1104–9.
52. Robinson RG, Jorge R, Moser D, Acion L, Solodkin A, Small SL, et al. Escitalopram and problem-solving therapy for prevention of poststroke depression: a randomized controlled trial. JAMA. 2008;28:2391–400.
53. Narushima K, Kosier JT, Robinson RG. Preventing poststroke depression: a 12-week double-blind randomized treatment trial and 21-month follow-up. J Nerv Ment Dis. 2002; 190(5):296–303.
54. Jorge RE, Robinson RG, Arndt S, Starkstein S. Mortality and poststroke depression: a placebo-controlled trial of antidepressants. Am J Psychiatry. 2003;160(10):1823–9.
55. Yi ZM, Liu F, Zhai SD. Fluoxetine for the prophylaxis of poststroke depression in patients with stroke: a meta-analysis. Int J Clin Pract. 2010;64(9):1310–7.
56. Anderson CS, Hackett ML, House A. Interventions for preventing depression after stroke. Cochrane Database Syst Rev. 2004;2:1–55.
57. Ramasubbu R. Therapy for prevention of post-stroke depression. Expert Opin Pharmacother. 2011;12(14):2177–87.