DEPRESSION AND PSYCHOLOGICAL DISTRESS AS RISK FACTORS FOR STROKE AND WORSE STROKE RECOVERY: CLINICAL IMPLICATIONS AND THERAPEUTIC OPTIONS

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Disclosure: No potential conflict of interest.
Received: 07.02.14 **Accepted:** 09.05.14
Citation: EMJ Neurol. 2014;1:53-58.

ABSTRACT

Stroke and depression have a strong bidirectional association: on the one hand, depression and psychosocial distress are well known risk factors for stroke; on the other hand, stroke is known to be a strong risk factor for depression. In the first 2 years after a stroke approximately one-third of patients suffer from a post-stroke depression (PSD). PSD aggravates the burden of physical, psychological, and social disability after stroke, and hinders patient participation in rehabilitation. PSD is associated with a poorer outcome and increased mortality. For the treatment of PSD, selective serotonin reuptake inhibitors (SSRIs) were recommended. Interestingly, SSRIs also have positive effects on motor recovery in stroke patients even without depression, but may increase vascular risk.

Keywords: Depression, stroke, psychosocial stress, selective serotonin reuptake inhibitor (SSRI), prevention.

INTRODUCTION

Each year approximately 16 million people worldwide suffer a first ischaemic stroke. About one-third of these people remain disabled.[1] In addition to the well-established risk factors, various studies and meta-analyses during the last years have demonstrated that both depression and psychosocial distress were both independent risk factors for ischaemic stroke. During the first 2 years after stroke, up to 30% of patients developed depression, known as post-stroke depression (PSD). PSD aggravates the burden of physical, psychological, and social disability after a stroke and hinders patient participation in rehabilitation. In these patients, selective serotonin reuptake inhibitors (SSRIs) were recommended. However, less is known about whether the treatment of depression leads towards a stroke risk reduction. Recent studies proved that treatment with SSRI in stroke patients with or without depression leads towards a better outcome. This paper overviews recent studies concerning the bidirectional association between risk of depression in stroke patients as well as depression and psychosocial distress as risk factors for stroke. Moreover, new treatment options in stroke patients and preventing strategies for PSD are described. For this review we searched the PubMed databases and screened references for the items: "stroke", "depression", "psychosocial distress", and "selective serotonin reuptake inhibitor". Only reviews, original articles, and meta-analyses published in English were included.

DEPRESSION, PSYCHOSOCIAL DISTRESS, AND STROKE

Depression is a Risk Factor for Stroke

Depression is known to increase the risk of stroke.[2] Data from the Framingham Heart Study analysing 4,120 patients demonstrated that the risk of stroke

in patients younger than 65 years was 4.2-fold higher in persons with depressive symptoms, even after adjustment for education and other risk factors; in participants older than 65 years this association could not be detected. A large meta-analysis of 17 studies with >200,000 patients determined the association between stroke risk and depression.[3] After adjustment for various risk factors the relative risk of stroke was 1.43 (95% CI: 1.17-1.54), without a significant sex difference. Another systematic review and meta-analysis included 28 prospective cohort studies with a follow-up between 2 and 29 years and described an overall hazard ratio (HR) of 1.45 (95% CI: 1.29-1.63) for total stroke in depressive patients.[4] Jackson et al.[5] recently observed a >2-fold higher risk (odds ratio (OR): 2.41, 95% CI: 1.78-3.27) of stroke in women between the age of 47 and 52 years without a history of stroke during a follow-up of 3 years. After adjustment for several risk factors such as socioeconomic status, lifestyle, and physiological factors the OR was 1.94 (95% CI: 1.37-2.74).

Chronic Psychosocial Stress and Stroke Risk

Surtees and colleagues[6] found in 20,627 stroke-free participants, aged 41-80 years, that increased psychological distress is associated with elevated stroke risk. Episodic major depressive disorder was not associated with incident stroke in this study. A large population-based trial in Sweden analysed chronic psychosocial stress and long-term outcome, cardiovascular morbidity, and mortality in middle-aged men.[7] The OR for cardiovascular events in patients with chronic psychosocial stress was 1.27 (95% CI: 1.15-1.39). Even after adjustment for various risk factors, the difference remained statistically significant. The highest risk was found for fatal stroke in men with an OR of 2.04 (95% CI: 1.07-3.88). According to the results of the INTERSTROKE study[8] both depression and psychosocial distress are risk factors for stroke. This international multicentre study performed in 22 countries defined psychological distress as at least several periods of general stress at work or at home in the past year. Egido et al.[9] observed a gender-independent increased stroke risk in stroke patients with stressful habits and type A behaviour. Henderson et al.[10] analysed the risk of stroke mortality and incident stroke in relation to psychological distress in a population-based cohort in Chicago, including 4,120 persons with a medium age of 77 years and a follow-up of about 6 years. Four psychosocial indicators (depressive symptoms, perceived stress, neuroticism, and life satisfaction) measured psychological distress. The authors found a strong association between psychological distress and stroke mortality even after adjustment for stroke risk factors. Distress was strongly associated with haemorrhagic strokes (HR: 1.0, 95% CI: 1.28-2.25) but not with ischaemic stroke.

Incidence of PSD

The incidence of PSD varies between 25-36%.[11] A recent study analysed the prevalence, incidence, and predictors of depression in a cohort of stroke patients older than 75 years up to 10 years after stroke.[12] The main finding of this hospital-based cohort of survivors of first or recurrent ischaemic stroke was a remaining high prevalence of depression up to 10 years. Moreover, the baseline geriatric depression score was the main predicting factor for depressive symptoms after stroke at all time points. Cognitive impairment was a significant univariate predictor of depression up to 4 years of follow-up. In the first year after stroke, previous stroke and number of vascular risk factors were also predictors for depression. Ayerbe et al.[13] analysed the incidence of PSD in patients registered in the South London Stroke Register between 1995 and 2009 (n=4022 at registration) during a follow-up of 15 years. The authors found a cumulative incidence of 55% and prevalence ranging from 29-39% in their population. Interestingly most episodes of depression started within a year after stroke. Overall, 33% occur within the first 3 months after stroke and none 10 years after stroke. Main predictors for depression in this population were disability, pre-stroke depression, cognitive impairment, stroke severity, and anxiety. A recently published systematic review found that the most frequently cited risk factors were sex (female), history of depression, stroke severity, functional impairments, level of independence, and family/social support.[14]

Prevention of PSD

In the literature, different strategies were discussed to prevent PSD. Palomäki et al.[15] studied the effect of 60 mg mianserin or placebo in a double-blind controlled study for 1 year after acute ischaemic stroke in 100 consecutive patients. They did not find that early initiation of antidepressant therapy is able to prevent PSD. However, the rate of depressive patients was low in the study population, which might have affected the results.

Robinson et al.[16] described that the use of escitalopram or problem-solving therapy resulted in a significantly lower incidence of depression over 12 months of treatment compared with placebo in non-depressed patients with recent stroke. In an intention-to-treat analysis, problem-solving therapy did not achieve significant results over placebo. Rasmussen et al.[17] tested the effect of sertraline in the prevention of PSD. 137 non-depressed patients after experiencing an acute ischaemic stroke were randomly assigned to 12 months of double-blind treatment with either sertraline (n=70) or placebo (n=67). Sertraline was significantly better than placebo. Only 10% of the sertraline-treated patients developed depression, compared to 30% of the placebo group. Another study described the efficiency of fluoxetine in prevention of PSD.[18] The use of duloxetine leads towards a reduction of PSD.[19] In addition, duloxetine is associated with a more rapid rehabilitation from stroke, and was associated with better cognitive function and quality of life (QoL). In conclusion, the prophylactic use of duloxetine not only decreased the incidence of PSD, but also promoted rehabilitation, cognitive function, and QoL. A recent population-based study analysed the effect of stroke rehabilitation within 3 months after stroke on PSD incidence.[20] Over a 10-year follow-up period, 5.8% of the patients with rehabilitation and 8.7% in the control group without rehabilitation developed PSD. Rehabilitation significantly reduced the risk of PSD after 3 months with a HR of 0.57 (95% CI: 0.45-0.73). Recently, Lawrence et al.[21] reviewed the benefit of mindfulness-based intervention after stroke and transient ischaemic attack in 160 participants. The results demonstrated a trend towards the benefit of this intervention in the improvement of psychosocial outcomes.

Outcome of Patients with PSD

PSD is associated with poorer functional outcome.[22] Moreover, the rehabilitation efficacy and the activity of daily living were reduced in depressed patients.[23] Besides advanced motor function disabilities, depressed stroke patients are more likely to be cognitively impaired.[24] Studies have shown that PSD increases the mortality rate at 1 year following a stroke.[25] Some trials observed that depression increases the risk of first and recurrent stroke by 45% to 80%.[26,27] In a systematic review and meta-analysis including 13 studies and more than 59,000 patients, the OR for mortality after stroke was 1.22 (95% CI: 1.02-1.47) in depressive stroke patients.[28] In studies with a follow-up shorter than 2 years, no significant association between death and depression after stroke was found. In studies with >5 years of follow-up a trend was detected. Studies with a duration between 2 and 5 years after stroke reached statistical significance. A multi-centre prospective cohort study in China including 2,306 patients with acute stroke showed a 49% increase in OR of recurrent stroke at 1 year in patients with PSD, compared to patients without PSD following a stroke (OR: 1.49, 95% CI: 1.03–2.15). There was no significant correlation between anti-depressant drugs and the risk of recurrent stroke at 1 year following a stroke (OR: 1.96, 95% CI: 0.95–4.04).[29,30]

SSRI in Stroke Patients

A systematic Cochrane review found that antidepressant medications are effective in treating PSD.[31] Today, SSRIs are the recommended pharmacotherapy of PSD due to their favourable tolerability profile. However, antidepressive medication in elderly stroke patients might increase the risk of haemorrhagic or ischaemic stroke due to an interaction with antiplatelet agents.[32-35] A recent meta-analysis found that the use of SSRI was associated with a 1.48-fold increased risk of ischaemic stroke and a 1.3-fold increased risk of haemorrhagic strokes.[36] Mortensen et al.[37] studied the association between post-stroke SSRI use and outcome in a nationwide prospective score-matched follow-up study. Patients treated with SSRI had a lower risk of myocardial infarction (MI) and recurrent stroke. For the combined endpoint stroke and MI, the difference in both groups was significant with a HR of 0.77 (95% CI: 0.62-0.96). SSRI use after stroke was associated with increased mortality, which might reflect a combination of uncontrolled confounding by interaction owing to the underlying depression and an increased bleeding risk.[37] According to the results of a large meta-analysis of 52 studies using SSRI in stroke, participants receiving SSRI were more likely to have gastrointestinal side-effects, seizures, and bleedings.[30]

Improvement of Motor Function with SSRI

A small study including eight stroke patients demonstrated that a single dose of fluoxetine is able to improve motor performance.[38] A few other small studies using SSRI in stroke patients suggested that this drug might have positive effects.[39-41] Functional magnetic resonance imaging (MRI) revealed an activation of the ipsilesional

Table 1: Overview of prospective placebo-controlled studies analysing the motor recovery in patients after ischaemic stroke using selective serotonin-reuptake inhibitors.

Drug and treatment	Number of patients	Time of inclusion after stroke	Main results
Fluoxetine 20 mg per day and maprotiline[47]	48	1-6 months	10.7% improvement in HSS score
Fluoxetine 20 mg per day[38]	8	15-30 days	20-30% finger tapping improvement
Citalopram 40 mg per day[40]	8	>6 months	11.4% improvement in nine-hole peg test
Citalopram 10 mg for 30 days[39]	20	Not reported	38.8% improvement of NIHSS score
Fluoxetine 20 mg per day for 90 days[42]	118	5-10 days after stroke	Improvement of FMMS scores

HSS: Hemispheric Stroke Scale; NIHSS: National Institutes of Health Stroke Scale; FMMS: Fugl-Meyer motor scale score.

Table 2: Standardised mean difference (SMD) and 95% confidence interval (CI) in the disability score after treatment with selective serotonin-reuptake inhibitors (SSRIs) in different randomised controlled trials including 1,343 stroke patients (according to Mead et al.[44]).

	Number of patients with SSRI	Number of patients in the control group	SMD and 95% CI
Fluoxetine	394	339	0.68 (0.31-1.06)
Sertraline	65	65	1.38 (0.99-1.76)
Citalopram	108	104	1.07 (-0.26-2.39)
Paroxetine	149	144	1.31 (0.67-1.95)
Total	691	652	0.91 (0.60-1.22)

insular and lateral motor cortex 5 hours after application of 20 mg fluoxetine.[38] According to these positive results, a double-blind placebo-controlled trial in patients with ischaemic stroke with haemiparesis or haemiplegia was initiated in nine stroke centres in France.[42] 118 patients were randomly assigned to 20 mg fluoxetine or placebo and the motor recovery in these patients was compared using the Fugl-Meyer motor scale score (FMMS). The FMMS improved significantly after 3 months in the fluoxetine group (mean: 34 points, 95% CI: 29.7-38.4) versus 24.3 points (95% CI: 19.9-28.7, p=0.003; Table 1). The main adverse events in the fluoxetine and placebo groups were hyponatraemia, transient digestive disorders including nausea, diarrhoea, and abdominal pain, hepatic enzyme disorders, psychiatric disorders, insomnia, and partial seizure.[42] In conclusion, fluoxetine significantly improves motor function in stroke patients without depression after 3 months, and occurrence of depression was lower in the fluoxetine group. Another multicentre, randomised, placebo-controlled trial found that 10 mg escitalopram per day prevents the development of PSD and was associated with improved short and long-term memory recovery.[16] Experimental studies described a neurogenic and neuroprotective effect of SSRI.[43] Recently, a meta-analysis of all published and non-published randomised controlled trials with SSRI (52 studies and 4,059 patients) given within the first year after stroke to determine the effect on dependency, disability, and other clinical outcomes was performed by Mead et al.[44] The age of the patients

ranged from 55-77 years. The effect of treatment with SSRI versus placebo was greater in trials recruiting people with depression compared to people without depression at randomisation. In this meta-analysis SSRIs were effective in treatment of stroke patients even without depression (Table 2).

CLINICAL IMPLICATIONS

The lifetime incidence of depression is about 16% in the general population.[45] For the treatment of depression, SSRIs were recommended as first-line treatment. However, the use of these drugs might increase the risk of ischaemic and haemorrhagic stroke. On the other hand, depression and psychosocial stress were independent predictors for ischaemic stroke. Moreover, about one-third of stroke patients developed a PSD, which implicates worse outcome and an increased risk for stroke recurrence. Therefore a systematic screening for depression after stroke should be performed after stroke onset. Due to the reduced length of hospital stay after stroke, the diagnosis of depression might be complicated. Man-van Ginkel et al.[46] established a PSD prediction scale, which could help to identify stroke patients with a high risk of PSD. Other predictors for PSD were extent of stroke-related disability, pre-stroke depression, cognitive impairment, stroke severity, and anxiety.

Recently, a large amount of studies described a better clinical and functional outcome after stoke using SSRIs even in non-depressed patients. However, the evidence available in different studies does not provide a clear picture regarding the treatment of PSD and the efficacy and safety of SSRIs. Therefore, more placebo-controlled studies, including SSRIs but also non-medical therapies for PSD and functional outcome, are necessary. Moreover, potential side-effects such as increased bleeding risk, cardiac complications, and an increased risk of seizures should be taken into account.

REFERENCES

1. Strong K et al. Preventing stroke: saving lives around the world. Lancet Neurol. 2007;6:182–7.
2. Salaycik KJ et al. Depressive symptoms and risk of stroke: the Framingham Study. Stroke. 2007;38: 16–21.
3. Dong JY et al. Depression and risk of stroke: a meta-analysis of prospective studies. Stroke. 2012;43:32–7.
4. Pan A et al. Depression and risk of stroke morbidity and mortality: a meta-analysis and systematic review. JAMA. 2011;306:1241–9.
5. Jackson CA, Mishra GD. Depression and risk of stroke in midaged women: a prospective longitudinal study. Stroke. 2013;44:1555–60.
6. Surtees PG et al. Psychological distress, major depressive disorder, and risk of stroke. Neurology. 2008;70: 788–94.
7. Ohlin B et al. Chronic psychosocial stress predicts long-term cardiovascular morbidity and mortality in middle-aged men. Eur Heart J. 2004;25:867–73.
8. O'Donnell MJ et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet. 2010;376:112–23.
9. Egido JA et al. Is psycho-physical stress a risk factor for stroke? A case-control study. J Neurol Neurosurg Psychiatry. 2012;83(11):1104-10.
10. Henderson KM et al. Psychosocial distress and stroke risk in older adults. Stroke. 2013;44:367–72.
11. Hackett ML et al. Frequency of depression after stroke: a systematic review of observational studies. Stroke. 2005;36:1330–40.
12. Allan LM et al. Long-term incidence of depression and predictors of depressive symptoms in older stroke survivors. Br J Psychiatry. 2013;203: 453–60.
13. Ayerbe L et al. The natural history of depression up to 15 years after stroke: the South London Stroke Register. Stroke. 2013;44:1105–10.
14. De Ryck A et al. Risk factors for poststroke depression: identification of inconsistencies based on a systematic review. J Geriatr Psychiatry Neurol. 2014. [Epub ahead of print].
15. Palomäki H 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 Psychiatr. 1999;66:490–4.
16. Robinson RG et al. Escitalopram and problem-solving therapy for prevention of poststroke depression: a randomized controlled trial. JAMA. 2008;299: 2391–400.
17. Rasmussen A et al. A double-blind, placebo-controlled study of sertraline in the prevention of depression in stroke patients. Psychosomatics. 2003;44: 216–21.
18. Yi ZM et al. Fluoxetine for the prophylaxis of poststroke depression in patients with stroke: a meta-analysis. Int J Clin Pract. 2010;64:1310–7.
19. Zhang LS et al. Prophylactic effects of duloxetine on post-stroke depression symptoms: an open single-blind trial. Eur Neurol. 2013;69:336–43.
20. Hou W-H et al. Effects of stroke rehabilitation on incidence of poststroke depression: a population-based cohort study. J Clin Psychiatry. 2013;74:e859–66.
21. Lawrence M et al. A systematic review of the benefits of mindfulness-based interventions following transient ischemic attack and stroke. Int J Stroke. 2013;8:465–74.
22. Pohjasvaara T et al. Depression is an independent predictor of poor long-term functional outcome post-stroke. Eur J Neurol. 2001;8:315–9.
23. Gillen R et al. Screening for depression in stroke: relationship to rehabilitation efficiency. J Stroke Cerebrovasc Dis. 1999;8:300–6.
24. Serrano S et al. Frequency of cognitive impairment without dementia in patients with stroke: a two-year follow-up study. Stroke. 2007;38:105–10.
25. House A et al. Mortality at 12 and 24 months after stroke may be associated with depressive symptoms at 1 month. Stroke. 2001;32:696–701.

26. Wassertheil-Smoller S et al. Depression and cardiovascular sequelae in postmenopausal women. The Women's Health Initiative (WHI). Arch Intern Med. 2004;164:289–98.

27. Peters R et al. Association of depression with subsequent mortality, cardiovascular morbidity and incident dementia in people aged 80 and over and suffering from hypertension. Data from the Hypertension in the Very Elderly Trial (HYVET). Age Ageing. 2010;39:439–45.

28. Bartoli F et al. Depression after stroke and risk of mortality: a systematic review and meta-analysis. Stroke Res Treat. 2013;2013:862978.

29. Zhang WN et al. A prospective study of the incidence and correlated factors of post-stroke depression in China. PLoS One. 2013;8:e78981.

30. Yuan HW et al. Poststroke depression and risk of recurrent stroke at 1 year in a Chinese cohort study. PLoS One. 2011;7:e46906.

31. Hackett ML et al. Interventions for treating depression after stroke. Cochrane Database Syst Rev. 2008;(4):CD003437.

32. Smoller JW et al. Antidepressant use and risk of incident cardiovascular morbidity and mortality among postmenopausal women in the Women's Health Initiative study. Arch Intern Med. 2009;169:2128–39.

33. Coupland C et al. Antidepressant use and risk of adverse outcomes in older people: population based cohort study. BMJ. 2011;343:d4551.

34. Wu CS et al. Association of cerebrovascular events with antidepressant use: a case-crossover study. Am J Psychiatry. 2011;168:511–21.

35. Douglas I et al. The use of antidepressants and the risk of haemorrhagic stroke: a nested case control study. Br J Clin Pharmacol. 2011;71:116–20.

36. Shin D et al. Use of selective serotonin reuptake inhibitors and risk of stroke: a systematic review and meta-analysis. J Neurol. 2014;261:686–95.

37. Mortensen JK et al. Post stroke use of selective serotonin reuptake inhibitors and clinical outcome among patients with ischemic stroke: a nationwide propensity score-matched follow-up study. Stroke. 2013;44:420–6.

38. Pariente J et al. Fluoxetine modulates motor performance and cerebral activation of patients recovering from stroke. Ann Neurol. 2001;50:718–29.

39. Acler M et al. A double blind placebo RCT to investigate the effects of serotonergic modulation on brain excitability and motor recovery in stroke patients. J Neurol. 2009;256:1152–8.

40. Zittel S et al. Citalopram improves dexterity in chronic stroke patients. Neurorehabil Neural Repair. 2008;22: 311–4.

41. Gerdelat-Mas A et al. Chronic administration of selective serotonin reuptake inhibitor (SSRI) paroxetine modulates human motor cortex excitability in healthy subjects. Neuroimage. 2005;27:314–22.

42. Chollet F et al. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial. Lancet Neurol. 2011;10(2):123-30.

43. Shin TK et al. Fluoxetine and sertraline attenuate postischemic brain injury in mice. Korean J Physiol Pharmacol. 2009;13:257–63.

44. Mead GE et al. Selective serotonin reuptake inhibitors for stroke recovery: a systematic review and meta-analysis. Stroke. 2013;44:844–50.

45. Kessler RC et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA. 2003;289:3095–105.

46. de Man-van Ginkel JM et al. In-hospital risk prediction for post-stroke depression: development and validation of the post-stroke depression prediction scale. Stroke. 2013;44:2441–5.

47. Dam M et al. Effects of fluoxetine and maprotiline on functional recovery in poststroke hemiplegic patients undergoing rehabilitation therapy. Stroke. 1996;27:1211–4.