Post-Stroke Depression

Ricardo E. Jorge, MD, Department of Psychiatry, Roy J. and Lucille A. Carver College of Medicine, University of Iowa, Iowa City, IA, USA.

Robert G. Robinson, MD, Department of Psychiatry, Roy J. and Lucille A. Carver College of Medicine, University of Iowa, Iowa City, IA, USA.

Introduction

Post-stroke Depression (PSD) is among the most common neuropsychiatric disorders that occur after stroke. In the present review we analyze the prevalence and clinical course of depressive disorders following stroke and the specificity of Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition (DSM-IV) criteria for their diagnosis. We examine current knowledge of the mechanisms involved in the pathogenesis of PSD, as well as its relationship with physical and cognitive impairment and long-term mortality. Finally, we review the most relevant aspects of treatment and prevention of this condition.

Prevalence

The frequency of post-stroke depression depends upon whether it is assessed in clinical or community samples and whether patients are studied during the subacute post-stroke period or later, during its clinical course. PSD constitutes a difficult diagnosis, particularly because it occurs among patients with motivational, cognitive, and vegetative symptoms related to their neurological disorder and is therefore not associated with the depressed state. Discrepancies in the reported prevalence rates of PSD might be related to methodological differences. For instance, using arbitrary cut-off scores to categorize PSD will result in different prevalence estimates than those obtained through the more appropriate “gold standard” of structured interviews in combination with established diagnostic criteria. Overall, pooling the data of the most relevant studies, the mean prevalence in hospitalized acute stroke patients is 22% for major depression and 17% for minor depression. In outpatient populations, the mean prevalence was 23% for major depression and 35% for minor depression. In community samples the mean prevalence for major depression was 13% and minor depression was 10%.1-2

Diagnosis

The diagnosis of PSD may be difficult or impossible to establish in some groups of stroke patients. For instance, the presence of global aphasia and/or significant cognitive impairment may prohibit the reliable assessment of symptoms of depression.8 The DSM-IV-TR criteria for “mood disorders due to stroke” are applicable to the diagnosis of PSD. Criteria for depression due to stroke with major depressive-like episode require the presence of either depressed mood or loss of interest during two or more weeks following a stroke, accompanied by at least four of the following symptoms:

- decreased or increased appetite or weight
- insomnia or hypersomnia
- psychomotor agitation or retardation
- loss of energy
- feelings of worthlessness or inappropriate guilt
- loss of concentration
- recurrent suicidal ideation

Investigators of depression associated with physical illness have debated the most appropriate method for the diagnosis of depressive disorders when there is the possibility that some criterion symptoms (e.g., sleep or appetite disturbance) could result from the physical illness, the hospital environment, or even...
medication effects.\textsuperscript{10} Four approaches have been used to assess depression in the physically ill: 1) the “inclusive approach,” in which depressive diagnostic symptoms are counted regardless of whether they may be related to physical illness; 2) the “etiological approach,” in which a symptom is counted only if the diagnostician feels that it is not caused by the physical illness; 3) the “substitutive approach,” in which other psychological symptoms of depression replace the vegetative symptoms; and 4) the “exclusive approach,” in which symptoms are removed from the diagnostic criteria if they are not found to be more frequent in depressed than non-depressed patients.

We examined the utility of inclusive and exclusive approaches among 142 patients who were followed during the first two years following stroke. Compared to “gold standard” diagnoses based solely on the existence of five or more specific symptoms (i.e., symptoms that were significantly more common in depressed than non-depressed patients for the diagnosis of DSM-IV major depression), diagnoses based on unmodified symptoms had a sensitivity of 100\% and a specificity that ranged from 95–98\% during the two-year follow-up period.\textsuperscript{11} Thus, one could reasonably conclude that modifying DSM-IV-TR criteria because of the existence of cerebrovascular disease is unnecessary.

In addition, we have used the DSM-IV research diagnosis of minor depression (which requires the presence of more than two, but fewer than five major depressive symptoms, including either a depressed mood or loss of interest) to identify stroke patients with sub-syndromal forms of depression. Several studies have provided some validation for this diagnosis by identifying differences between major and minor depression in the frequency of past personal history of depression,\textsuperscript{12} the association with cognitive impairment,\textsuperscript{13,14} and association with lesion location.\textsuperscript{15} However, further studies are required to clarify the relationship between minor depression and long-term disability following stroke, as well as the specificity of this diagnosis among patients with severe stroke.

**Clinical Course**

The duration of PSD has been examined in several longitudinal studies. According to these studies, approximately two-thirds of depressive disorders with major depression features will remit within 12 months following stroke. However, Aström et al.\textsuperscript{16} reported that 30\% of patients with in-hospital major depression remained depressed at one-year follow-up, 25\% were depressed at two-year follow-up, and 20\% were still depressed at three years follow-up. Although a significant proportion of patients with minor depression will remit within three months after stroke, Robinson et al.,\textsuperscript{17} reported that only 30\% of patients with in-hospital minor depression were without a diagnosis of major or minor depression at two years follow-up.\textsuperscript{18} The previous data suggest that there is a group of patients with PSD who have a more chronic and/or relapsing course.

The genetic and environmental risk factors that are associated with a chronic course, the phenomenology of depression among these patients, brain structural correlates, as well as the characteristics of treatment response have not yet been elucidated completely.

**Figure 1: Impact of Post-Stroke Depression Recovery in Activities of Daily Living**

* A higher ADL score indicates greater impairment.

Source: With information from Parikh et al. 1990.\textsuperscript{40}

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**Anatomical Correlates**

Mood disorders might be conceptualized as resulting from the functional disruption of distributed networks that regulate mood, motivation, and emotion. It is reasonable to hypothesize—though difficult to establish—that strategic lesions along these networks could be associated with functional alterations that lead to PSD.

In one of the earliest studies that examined the relationship between PSD and lesion location, Robinson and colleagues found that 14 of 22 patients with left hemisphere lesions and no risk factors for depression (i.e., prior personal history, family history of mood disorders) suffered either major or minor depression while these disorders occurred in only two of 14 patients with right hemisphere lesions.\textsuperscript{19} The authors later compared 13 patients with PSD and predominantly left-sided lesions to a group of stroke patients without depression matched for age, sex, lesion size, and lesion location. The major finding was that subcortical atrophy (as evidenced by increased ventricular to brain ratios) was associated with the presence of PSD.\textsuperscript{20}

Although the association of depression with left hemisphere lesions has been replicated by other authors,\textsuperscript{21–23}
Numerous studies have not found lateralized effects.\textsuperscript{24,25}

There is also evidence that laterality effects are present only during the first two months following stroke.\textsuperscript{3} A significant inverse correlation between severity of depression and distance of the lesion from the frontal pole among 163 patients with left hemisphere stroke, but not among 106 patients with right hemisphere stroke, was demonstrated in one study.\textsuperscript{26} Moreover, a recent analysis of data from the Helsinki Stroke Aging Memory study concluded that among 70 patients with single ischemic stroke lesions, the brain infarcts involving frontal-subcortical circuits (especially larger lesions involving the left pallidum) predisposed stroke patients to depression.\textsuperscript{27}

**Post-Stroke Depression and Activities of Daily Living (ADL)**

One might wonder if depression is a normal emotional response to the physical and cognitive disabilities ensuing after stroke. Folstein et al. compared a group of stroke patients to patients with orthopaedic injuries and similar degree of impairment in activities of daily living (ADL). They found that approximately half of the stroke patients were depressed, compared with 10\% of orthopaedic patients who developed depression,\textsuperscript{28} suggesting that factors specific to brain injury are contributing to depression independent of the degree of functional impairment, and that the relationship between disability and depressive symptoms was more complex than originally presumed.

A significant correlation between the severity of depressive symptoms and severity of impairment in basic and instrumental activities of daily living (ADL) (e.g., the patients’ ability to dress and feed themselves, walk, find their way around, express needs, read and write, and keep their room in order) has been shown in several studies.\textsuperscript{4,5,29–38} However, the most relevant clinical question pertains to the effect of PSD on recovery in ADL.\textsuperscript{39–41} A prospective study that followed 63 stroke patients, 28 of whom suffered from PSD while the other 35 patients were depression-free, determined that the two groups were initially comparable in neurological and functional impairments and demographic features; however, the depressed group was significantly more impaired at two-year follow-up than the non-depressed group in both physical activities and language functions (Figure 1).\textsuperscript{40}

A logistic regression analysis showed that depression was a significant independent factor in ADL recovery even after other factors such as age, education, lesion volume, hours of rehabilitation therapy, and type of stroke were taken into account.

If post-stroke depression impairs recovery in ADL, recovery from post-stroke depression would be expected to improve recovery in ADL. Chemerinski et al.\textsuperscript{42} have shown that 21 depressed patients, whose mood improved between in-hospital evaluation and 3–6 months after stroke, had significantly greater recovery in ADL than 34 patients whose mood did not improve (Figure 2). The authors also examined the effect of antidepressant treatment with nortriptyline. At a dose of 100mg/day, the patients who responded to nortriptyline had significantly lower (i.e., less impaired) ADL scores at six or nine weeks of treatment compared to the 10 patients who failed to respond at the same time and dose.\textsuperscript{43}

**Post-Stroke Depression and Cognitive Impairment**

Cognitive impairment is one of the most common consequences of stroke. This may result from structural brain damage produced by the vascular lesion (e.g., Broca’s aphasia or hemispatial neglect) and/or from coexistent neurodegenerative processes that are associated with progressive intellectual decline. Longitudinal studies of stroke patients have demonstrated that cognitive impairment is a reliable predictor of poor functional recovery and increased long-term mortality rates.\textsuperscript{44–47} Whether PSD contributes to a greater degree of cognitive impairment than that expected from the extent and location of cerebrovascular lesions, or whether depression contributes to the neurodegenerative changes observed following stroke, constitute important questions that require further elucidation.

A study by Starkstein et al. that compared 13 patients who developed major depression within two years following stroke with 13 patients who didn’t, but who were matched for both size and location of lesion as the depressed group, found that the depressed group showed a significantly lower mean Mini-Mental State Examination (MMSE)\textsuperscript{48} score and higher frequency of abnormal MMSE.
scores (i.e., MMSE score of 23 or below). This finding suggested that PSD might produce cognitive impairment independent of the stroke lesion itself. Recently, other studies have delineated the characteristics of the neuropsychological deficits associated with PSD. Although preliminary, these studies demonstrated greater executive dysfunction among depressed stroke patients than in patients with comparable strokes who were non-depressed. These executive deficits might result from the disruption of neural circuits involving the dorsolateral region of the prefrontal cortex, thalamus, and caudate.

Several studies have linked PSD to delayed recovery from stroke-induced cognitive impairment for up to 24 months following the attack, while other investigators reported that improvement in mood with antidepressant treatment was not always associated with improvement in cognitive performance, suggesting that, at least in some patients, depressive symptoms need to be interpreted in the context of progressive dementia.

**Post-Stroke Depression and Mortality**

It has been demonstrated that patients with acute stroke and PSD have a much higher mortality at one year compared to non-depressed patients; one study concluded that early depression correlates with early death. Our group also examined this association among 103 acute stroke patients followed for 10 years. Although the in-hospital background characteristics were not significantly different between depressed and non-depressed patients, the mortality rate among patients with major or minor depression (i.e., 71% and 70%) was significantly higher than patients without depression (relative risk 3.4, 95% CI 1.4-8.4, P=0.007).

Many hypotheses can be proposed to explain the increased risk of dying observed among patients with post-stroke depression. Depressed patients might not comply with treatment recommendations such as medications or health-promoting behaviours. Depressive disorders might be associated with abnormal activation of central stress-related circuits involving the prefrontal cortex, amygdala, hypothalamus-pituitary-adrenal axis, and noradrenergic brainstem nuclei. The medical consequences of these changes are widespread and include development of hypertension, endothelial injury, and progressive atherosclerosis. Alterations in autonomic nervous system activity, as demonstrated by reduced heart rate variability (HRV), have been observed in depressed patients in comparison with non-depressed groups, possibly predisposing to ventricular arrhythmias. Moreover, cardiovascular disease and major depression have been associated with increased serotonin-mediated platelet activation, activation of coagulation factors, and increased thrombus formation.

The ability of antidepressant therapy to modify pathological mechanisms initiated by depression was studied in 104 patients who were randomly assigned to receive a 12-week double blind course of nortriptyline, fluoxetine, or placebo early in the recovery period following stroke. There were no intergroup differences in severity of stroke, cognitive or activities of daily living impairment, coexistent medical conditions, or concurrent medications. Of the 104 patients, 50 (48.1 %) had died. Of 53 patients who were given full-dose antidepressants, 36 were alive at follow-up, compared with only 10 out of 28 placebo-treated patients (P=0.005) (Figure 3). Thus, the most striking finding was that patients who had received active antidepressant treatment were more likely to survive compared with those patients who did not receive it regardless of whether they were initially depressed. The beneficial effect of antidepressants remained significant after controlling for age, stroke type, coexistent medical illness, and the occurrence of a depressive disorder with a relapsing course. Moreover, mortality rates attributable to cardiovascular illness or recurrent stroke were significantly more frequent in patients who did not receive adequate treatment with antidepressants.

Antidepressants may have different effects at different points in the clinical course of stroke patients. We have observed that even a relatively short course of antidepressants early after an index stroke has a protective effect on long-term mortality. It might be speculated that neurotrophic and neuroplastic changes associated with antidepressant treatment could produce long-lasting changes in cortical and hypothalamic networks mediating stress responses.
On the other hand, continuation of treatment with antidepressants for prolonged periods may normalize platelet function and progression of atherosclerosis, as well as reverse the autonomic changes that make patients prone to severe cardiac arrhythmias.

Among the 58 patients who were followed for two years at our site, 36 received antidepressants during the first 12 weeks of the study. Of these 36 patients, 17 were continued on therapeutic doses of antidepressants for approximately 12 months (Mean=11.6, SD = 5.9 months). At nine years follow-up, 15 of 17 patients (88.2%) who received continuation treatment with antidepressants were alive compared with 10 of 19 patients (52.6%) who received only 12 weeks of antidepressant treatment (Fisher Exact Test = 0.02).58

Another important question is how could antidepressants prolong survival in patients who were initially non-depressed? The most obvious answer is that early antidepressant treatment could modify the pathophysiological mechanisms associated with increased mortality independently of their effect on other behavioural measures. The fact that fluoxetine was not effective in treating acute post-stroke depression,59 but was just as effective as nortriptyline in protecting against long-term mortality, is consistent with this hypothesis. Furthermore, early antidepressant treatment could prevent the occurrence of delay-onset depression or modify its pathophysiological correlates in order to provide for a better outcome.

Treatment of Post-Stroke Depression

There are currently five double-blind placebo controlled studies that have examined the efficacy of antidepressant medication in PSD.

In a controlled study by Reding et al.,61 seven PSD patients with an abnormal Dexamethasone Suppression Test (DST) treated with trazodone had a significantly greater improvement in activities of daily living at 2–3 months following stroke measured using the Barthel ADL scale, compared to nine comparable patients treated with placebo.

Andersen et al.1 assessed the efficacy and tolerability of the selective serotonin reuptake inhibitor antidepressant citalopram in a controlled study of 66 patients with stroke. The HAM-D and the Melancholia Scale (MES) were significantly better at both three and six weeks after starting treatment among patients who received citalopram compared to patients given placebo.

Robinson et al. recently compared nortriptyline and fluoxetine in the treatment of depression using an entirely different socioeconomic population than their original study.57,59 A total of 104 patients with acute stroke were randomized to receive either nortriptyline, fluoxetine, or placebo over 12 weeks of treatment. Patients treated with nortriptyline (25mg week one, 50mg week two, 75mg weeks 3–6, and 100mg weeks 7–12) had a significantly greater decline in HDRS scores than either fluoxetine (10mg weeks 1–3, 20mg weeks 4–6, 30mg weeks 7–9, and 40mg weeks 10–12) or placebo treated patients at 12 weeks of treatment (F= 3.73, df=2,53; P=<0.031) (Figure 4). The response rate for nortriptyline was 77% for patients who completed the study while the response rate for fluoxetine was 14% (Fisher Exact Test, P=<0.0018).

Side effects frequently observed in the fluoxetine-treated group were gastrointestinal side effects, insomnia, and headache. In addition, fluoxetine led to an average 14-pound weight loss over 12 weeks that was not seen with other treatments.

On the whole, there is a proportion of patients with PSD who are refractory to treatment with antidepressants, either alone or in combination therapy. Electroconvulsive Therapy (ECT) constitutes an alternative for these refractory patients. However, although effective in uncontrolled trials, ECT may produce or aggravate cognitive dysfunction in stroke patients, and involves general anesthesia and usually hospitalization.61 Magnetic Stimulation (rTMS) might be a safe and effective alternative in these refractory cases. We conducted a randomized parallel double-blind study of active vs. sham left prefrontal rTMS in patients with refractory PSD.62 After discontinuing antidepressants, patients were randomly assigned to receive 10 sessions of active (10 Hz, 110% of the motor threshold, 20 trains of five-second duration) or sham left prefrontal rTMS. When compared with sham stimulation, 10 sessions of active rTMS of the left dorsolateral prefrontal cortex were associated with a significant reduction of depressive symptoms. These preliminary findings
suggest that rTMS may be an effective and safe treatment alternative for patients with refractory depression and cerebrovascular disease.

Prevention of Post-Stroke Depression

Stroke patients without depression might benefit from prophylactic interventions to prevent the onset of depression. Because prior studies have shown that 40% of initially non-depressed patients will develop a depressive disorder, early antidepressant treatment might improve physical and cognitive outcomes, reduce the frequency of cardiovascular complications, and prolong survival.

Rassmussen et al. examined the prophylactic effect of antidepressants among 137 non-depressed stroke patients who were randomly assigned to receive either sertraline (mean dose = 63mg) or placebo during a 12-month follow-up period. The authors found that the frequency of depression was significantly lower in the treated group.63

References