Review article

Post stroke depression: clinics, etiopathogenesis and therapeutics

VINICIUS SOUSA PIETRA PEDROSO1,2, LEONARDO CRUZ DE SOUZA1,2, ANDRE R. BRUNONI1, ANTONIO LUCIO TEIXEIRA1,2

1 Interdisciplinary Laboratory of Medical Investigation, School of Medicine, Federal University of Minas Gerais (UFMG), Belo Horizonte, MG, Brazil.
2 Neuroscience Branch, Interdisciplinary Laboratory of Medical Investigation, School of Medicine, UFMG, Belo Horizonte, MG, Brazil.

Received: 9/5/2014 – Accepted: 1/19/2015
DOI: 10.1590/0101-60830000000041

Abstract

Background: Stroke is a major cause of morbidity and mortality worldwide. Neuropsychiatric disorders are often associated with stroke and, among them, depression is the most prevalent. Post-stroke Depression (PSD) is related to disability, failure in returning to work, impairment in interpersonal functioning and mortality. Its etiopathogenesis is still uncertain, as well as its treatment. In Brazil, there are few data on the impact of PSD. Objective: This work is dedicated to conduct a comprehensive review of the concept of PSD, its pathophysiology, morbidity and treatment. Methods: PubMed, Medline and Lilacs searches of relevant terms yielded 3,265 papers in the last 10 years. We selected original studies and reviews that addressed the aspects mentioned above. Results: We present the history of the notion of PSD and describe its epidemiology, looking to highlight Brazilian studies. Diagnostic criteria and clinical presentation were detailed, with emphasis on cognitive aspects. The four main pathophysiological theories proposed to PSD are presented and we discuss the various treatment strategies, involving psychopharmacologic options, brain stimulation techniques and psychotherapy. Discussion: This work provides comprehensive information on PSD, of great utility for clinical practice and research in this topic.

Keywords: Stroke, cerebrovascular diseases, depression, post-stroke depression, vascular depression.

Introduction

Stroke is a major cause of death and disability worldwide1. In the United States (US), there are approximately 610,000 new cases each year1. In Brazil, epidemiologic data are scarce. The available information allows stating that stroke is the main cause of death in the country, accounting for approximately 100,000 deaths annually2. Nevertheless, over the last decades there has been a global trend of decrease in stroke mortality. This is probably due to the improvement in acute stroke management and to preventive measures, such as arterial hypertension treatment. In Brazil, there is also a decrease in stroke mortality, but restricted to the South and Southeast regions3. Currently, an estimated 5 million stroke survivors live in the US4. In Brazil, where the highest stroke death rates in Latin America are found, it is estimated that stroke survivors achieve at least half of that sum3. As the management of acute stroke continues to improve, the number of survivors will increase even more and, since it often results in major changes in the patient’s life, factors associated with morbidity have received increased attention.

Stroke is frequently associated with psychiatric symptoms such as depression1,2, anxiety and apathy4. The psychiatric complications of stroke, although recognized for more than a century, have never received the attention that has been devoted to other stroke complications, such as motor impairment, language problems, or cognitive deficits5. Depression is the most common neuropsychiatric condition experienced after stroke1. More than a hundred years ago, Adolf Meyer postulated that depression should be the consequence of the combined effects of brain injury, affecting mainly the left frontal lobe as well as other lobar convexities, and psychosocial vulnerability, such as past psychiatric history. In the beginning of the XX century, Eugen Bleuler noted that after stroke “melancholic moods lasting for months and sometimes longer appear frequently”. Further in this direction, in 1962, after assessing 100 elderly patients with depression, Post remarked that the association of brain ischemia with a first episode of depressive disorder was so common that the causes of atherosclerotic disease and depression should be “etiologically linked”. However, although the association of depression with stroke has been clinically recognized for several decades, only in the past 25 years systematic studies have been conducted, with emerging evidence that depression after a stroke is associated with increased disability, increased cognitive impairment and, ultimately, worse rehabilitation outcomes and increased mortality5,6.

This review aimed to gather information on available epidemiological, pathophysiological, clinical and therapeutic aspects of post-stroke depression (PSD), their impacts in patient’s recovery and, when possible, to contextualize them to the Brazilian scenario.

Methods

We conducted a narrative review of the literature through Lilacs, Medline and PubMed electronic databases, using the keywords “stroke”, “cerebrovascular diseases”, “depression” and “post-stroke depression”. When indicated, other bibliographies were consulted from the reference lists of these articles. The search was restricted to articles published in English and Portuguese, in the last ten years. After this step, the titles and abstracts of all articles found were read in order to identify studies that addressed the theme and purpose of this review.

Results

Historical perspective

Isolated studies with patients affected by PSD started to appear in the 1960s4. Most of these works adopted a perspective of “empathic understanding”. In other words, these researchers explained PSD as a natural and understandable emotional reaction of the individual to a decrease in self-esteem produced by the combination of a life-threatening injury, the associated physical and intellectual disability, and the resulting loss of independence. Adopting such psychological perspective, Guido Gainotti’s group, from the Catholic University of Rome, Italy, conducted the first systematic study of neuropsychiatric symptoms in patients with stroke or other brain injuries4. His works can be considered one of the main representatives of the idea that the depressive syndromes associated with stroke may not be “true”...
depressions, but a completely different category from Major Depressive Disorder (MDD) that would be associated with the patients’ adjustment to changes in their living conditions\textsuperscript{4,5}.

In 1977, however, Folstein et al. conducted a study comparing the prevalence of mood disorders in patients with stroke or orthopedic problems which all presented comparable functional disability\textsuperscript{5}. They observed that patients with stroke exhibited a far greater frequency of depression than orthopedic patients, and concluded that mood disorders would be a complication of stroke that was linked not only to the degree of functional disability. This seminal study led to the development of a biological explanation for PSD, whereby brain changes would lead to depressive symptoms. This line of reasoning was primarily developed in the 1980's by Robert Robinson's group, from the University of Iowa, in opposition to the psychological perspective\textsuperscript{4,11}. These opposing perspectives have led to many of the continuing controversies and uncertainties about emotional disorders following stroke.

**Epidemiology**

Since the first systematic studies, depression (major and minor) has been regarded as the most common neuropsychiatric disorder after stroke, with an estimated prevalence ranging from 18 to 60%\textsuperscript{3}. According to DSM-V, MDD corresponds to the presence of at least four accessory symptoms, besides depressed mood or anhedonia. Minor Depressive Episode is a DMS-IV research diagnosis characterized by two to four depressive symptoms, including depressed mood or anhedonia\textsuperscript{4}. DSM-V incorporated this syndrome into the category Other Specified Depressive Disorders: Depressive Episode with insufficient symptoms.

The prevalence of PSD among hospitalized patients in the acute phase is around 22% for major depression and 17% for minor depression. In outpatient samples (from 3 months to 10 years after stroke), it is around 23% for major depression and 35% for minor depression, while community samples exhibit mean prevalence rates of 13% and 10%, respectively\textsuperscript{4}. A recent meta-analysis showed that the prevalence of depression at any time after stroke was 29%\textsuperscript{4}.

A cohort of 4,022 patients followed for 15 years showed the dynamic history of PSD\textsuperscript{4}. The peak prevalence of MDD occurs 3 to 6 months after the stroke. Most subjects had MDD remission one year after stroke, however showing persistent subsyndromal depressive symptoms and/or short lasting depressive episodes. Also according to Robinson, MDD often subside without complete remission one year after the index event\textsuperscript{4}.

In Brazil, there are few data on the epidemiology of PSD. A study conducted in Fortaleza, which investigated the quality of life (QoL) of individuals from two to six years post-stroke, reported a 40% prevalence of depressive symptoms (predominantly mild to moderate)\textsuperscript{9}. The presence of depressive symptoms was the most important factor in reducing QoL. Similarly, de Souza et al. evaluated patients with Chagas disease and stroke, and found that QoL was more influenced by depressive symptoms than neurological disability\textsuperscript{11}. Carod-Artal et al. also demonstrated that depression, disability and motor deficits were the main determinants of health-related QoL in patients with stroke, and depression was the strongest predictor of reduced QoL, especially among women\textsuperscript{11}. Table 1 presents Brazilian studies that reported the frequency of PSD.

**Diagnosis and clinical picture**

The DSM-V criteria for the diagnosis of PSD match those for Depressive Disorder Due to a Medical Condition\textsuperscript{4,5}. Stroke is one of the few conditions listed in the former DSM-IV and the current DSM-V as “directly” causing depression; therefore PSD is diagnosed differently from depression following, for instance, a myocardial infarction or a hip fracture, and can be named as Depressive Disorder Due to Stroke. One of the following specifiers should be added to the diagnosis: “with depressive features”, if full criteria are not met for a major depressive episode; “with major depressive-like episode”, if full criteria are met for a major depressive episode (except for criterion C); and “with mixed features”, if symptoms of mania or hypomania are also present but do not predominate in the clinical picture.

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>City (state)</th>
<th>n</th>
<th>Setting</th>
<th>Time after stroke</th>
<th>Instrument</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simis, Nitini (2006)\textsuperscript{12}</td>
<td>Sorocaba (SP)</td>
<td>93</td>
<td>H</td>
<td>2 weeks</td>
<td>HAM-D</td>
<td>59,1\textsuperscript{1}</td>
</tr>
<tr>
<td>Carod-Artal et al. (2009)\textsuperscript{9}</td>
<td>Brasilia (DF)</td>
<td>260\textsuperscript{*}</td>
<td>O</td>
<td>20.7 months (mean)</td>
<td>HADS</td>
<td>20,0\textsuperscript{0} (F; 25.0; M: 15.4)</td>
</tr>
<tr>
<td>Terroni et al. (2009)\textsuperscript{10}</td>
<td>Sao Paulo (SP)</td>
<td>73</td>
<td>H/O</td>
<td>1 week – 4 months</td>
<td>HAM-D</td>
<td>28,8\textsuperscript{0}</td>
</tr>
<tr>
<td>Froes et al. (2011)\textsuperscript{11}</td>
<td>Fortaleza (CE)</td>
<td>64</td>
<td>RP</td>
<td>&lt; 2 years: 9.4% 2-6 years: 50% &gt; 7 years: 40.7%</td>
<td>BDI</td>
<td>40,0\textsuperscript{0}</td>
</tr>
<tr>
<td>Scheffer et al. (2011)\textsuperscript{11}</td>
<td>Porto Alegre (RS)</td>
<td>19\textsuperscript{*}</td>
<td>O</td>
<td>9 – 27 months</td>
<td>BDI</td>
<td>33,3\textsuperscript{0}</td>
</tr>
<tr>
<td>Rangel et al. (2013)\textsuperscript{11}</td>
<td>Maceio (AL)</td>
<td>139\textsuperscript{*}</td>
<td>RP</td>
<td>3 – 316 months</td>
<td>BDI</td>
<td>49,7\textsuperscript{1}</td>
</tr>
</tbody>
</table>

BDI: Beck Depression Inventory; F: Female gender; H: Hospital sample; HADS: Hospital Anxiety and Depression Scale; HAM-D: Hamilton Depression Scale; M: Male gender; O: Outpatient sample; RP: Rehabilitation Program sample.

\* The study included patients with hemorraghic stroke (Ischemic stroke: Carod-Artal et al.: 87.7%, Scheffer et al. 84.2%; Rangel et al.: 83.5%).

\textsuperscript{0} Prevalence; \textsuperscript{1} Incidence in 4 months.

PSD should be distinguished from post-stroke demoralization, which can be understood as a type of adjustment disorder. Several authors have attempted to differentiate depression and demoralization\textsuperscript{11,17}. This distinction may seem even more complicated when considering the concept of PSD adopted by the psychological perspective described above. Overall, demoralization is related to feelings of incompetence and loss of self-control after repeated failures, whereas depression is marked by anhedonia and decreased motivation. Shader observed that individuals with demoralization may respond favorably to positive stimuli and relief of stressors, while patients with depression cannot get rid of their negative mood state, regardless of environmental changes\textsuperscript{17}. Once the presence of demoralization is recognized, the clinician should work with the patient in order to promote a sense of ability, mastery and return of hope. Encouragement, support and education are essential.

According to Spalletta and Robinson\textsuperscript{14}, although it seems likely that some forms of PSD may be, in part, sustained by reaction to disability, the attempt to differentiate between “reactive” (i.e. demoralization) and “endogenous” forms of depression ceased many years ago because no clear etiopathogenetic or phenomenological distinction has ever been shown to distinguish between them and a mixture of these two forms is present in almost all patients with a diagnosis of depression.

Fedoroff et al. assessed the suitability of the diagnostic criteria for MDD in the diagnosis of PSD\textsuperscript{19}. They observed that, except for early-morning awakening, all symptoms of depression were more frequent in the stroke patients with depressed mood than in the euthymic ones. Cumming et al. also conducted an investigation to determine whether the phenomenology of depression after stroke was different from the phenomenology of depression with no known medical cause\textsuperscript{19}. They noted that there were no major differences between the symptom profiles of both groups, except that stroke patients were less likely to report anhedonia than controls. Interestingly stroke patients
were no more likely than controls to report somatic complaints over psychological symptoms. However, some authors point to clinical differences between patients with PSD and those with MDD. Compared to these, stroke patients would have more cognitive impairment, mood fluctuations, psychomotor retardation, anxiety and vegetative and somatic symptoms. Gainotti et al. identified depressed mood, anhedonia and suicidal thoughts as more prevalent in non-stroke depressive patients than in patients with PSD. In Brazil, Terroni et al. point out the relevance of fatigue symptoms and reduction of general interests in the diagnosis of PSD.

Despite these controversies, there is no evidence that the diagnosis of depression after stroke is less valid than the diagnosis of depression in non-stroke populations. Since there are no specific biological markers, the diagnosis is based on clinical findings, and this task can become very difficult in the presence of severe cognitive deficits, especially language disorders.

Cognitive impairment in PSD

Cognitive deficits are commonly observed in depressed patients. Executive functions, including concept formation, planning, cognitive control, initiation and psychomotor speed, have been regularly shown to be impaired in depression. Short term and working memory are disturbed in depression, as assessed either by the digit span test or by the digit ordering test. Objective memory deficit is regularly demonstrated in depressed patients, characterized by lower immediate recall performance in both verbal and visual memory tests, but with a normal cued recall and recognition. This pattern is typically described as a retrieval memory disorder, rather than a storage dysfunction. Language and visuospatial abilities are generally preserved in depression.

A series of papers has specifically investigated cognitive disorders in PSD. Post-stroke depression affects problem solving, verbal and visual memory, language, visuospatial processes, attention and psychomotor speed. Moreover, the degree of cognitive impairment is associated with the severity of depressive symptoms.

In a cohort of 143 patients who were followed up to 10 months after a stroke, Nys et al. found that cognitive impairment at baseline independently predicted long-term depressive symptoms. Moreover, they found that cognitive deficits were related to worse quality of life. Among all cognitive deficits, the QoL was mostly affected by visuospatial and visuo-constructive disorders, while unilateral neglect at baseline assessment was the greatest risk factor for depressive symptoms after 6 months.

Taken together, these data suggest that cognitive deficits may account for PSD and, on the other hand, the degree of depression impacts on cognitive performance. Patients with PSD should undergo a formal neuropsychological evaluation, and therapeutic rehabilitation program adapted according to the cognitive profile of the patient.

Pathophysiology

The polarity between the biological and the psychological perspectives may have hampered the development of a comprehensive approach to PSD prevention and treatment. Table 2 presents the main arguments of each school.

Among the major biological theories on the pathophysiology of PSD, four main hypotheses can be listed: lesion location, biogenic amines, inflammatory cytokines and gene polymorphism hypotheses.

The lesion location hypothesis was formulated by Robinson based on the observation that depression severity was associated with lesions in the left frontal lobe, and that this association was stronger in the first 6 months after stroke. However, this finding has not been consistently replicated by other authors. Carson et al., in a meta-analysis of 35 studies, observed that the risk for developing depression was not associated with lesion location. Other authors proposed that strategic or specific location of the ischemic damage might play a role in the development of PSD. Neuroimaging studies found the hippocampus, basal ganglia and frontal areas to be associated with PSD. Although the debate is still open, the correlations between affected areas and depressive symptoms seem to be weak.

The biogenic amines theory can be understood as a pathophysi-ological sophistication of the lesion location hypothesis. It was first proposed by Robinson and Bloom. They postulated that ischemic lesions might interrupt the biogenic amine-containing axons ascending from the brainstem nuclei to the cerebral cortex, thus decreasing the release of serotonin (5-HT) and norepinephrine (NE).

<table>
<thead>
<tr>
<th>Biological causation</th>
<th>Psychological causation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence</td>
<td>Evidence</td>
</tr>
<tr>
<td><strong>For</strong></td>
<td><strong>Against</strong></td>
</tr>
<tr>
<td>Higher frequency of depression in stroke versus other similarly disabling medical illness</td>
<td>Finding not consistently replicated Temporal relationship between psychological stressors (e.g. bereavement) and depression</td>
</tr>
<tr>
<td>Temporal relationship between stroke and onset of depression</td>
<td>Finding not consistently replicated</td>
</tr>
<tr>
<td>Specific lesions associated with PSD</td>
<td>PSD symptom profile is not specific and may be a form of “functional” depression</td>
</tr>
<tr>
<td>PSD may occur in the context of silent infarcts</td>
<td>Temporal relationship between psychological stressors (e.g. bereavement) and depression</td>
</tr>
<tr>
<td>Risk factors unrelated with stroke</td>
<td>Risk factors unrelated with stroke predicts occurrence of depression (e.g. family history of depression)</td>
</tr>
<tr>
<td>Disability severity is the most consistent risk factor for PSD and psychosocial factors become increasingly important in later onset PSD</td>
<td>“Functional” depression may have biological underpinnings</td>
</tr>
</tbody>
</table>

| Lesion location theory. PSD may be related to the location of the lesions, disturbing specific areas of the brain (e.g. left frontal lobes, hippocampus, basal ganglia) | Patients with stroke experience a traumatic event that undermines their physical and mental integrity, their autonomy and self-esteem as well as their social lives. Psychological coping mechanisms, as well as premorbid personality, are responsible for the development of PSD |
| Biogenic amines theory. PSD may be related to disruption of monoamines circuitry, through direct or indirect mechanisms | Explanatory theories |
| Inflammatory cytokines theory. PSD may be related to the production of “depressogenic” cytokines by the inflammatory response to ischemia | Genetic polymorphisms theory. PSD may be related to genetic predisposition, especially in the serotonergic system |

Table 2. Key features of the biological and psychological hypothesis of post stroke depression (PSD) etiopathogenesis
in the limbic structures of the frontal and temporal lobes as well as in the basal ganglia. According to this hypothesis, lesions located in the anterior portions of the frontal lobes could interrupt the ascending monoaminergic axonal bundles leading to depression. Indeed, the studies of Robinson suggested that anterior lesions, located close to the left frontal pole, would be associated with the development of depressive symptoms. Later it was suggested that dysfunction of cortico-striato-pallido-thalamic-cortical circuits predisposes to PSD, and that these loops could even be disrupted indirectly by secondary degeneration when not included in the primary ischemic lesion by means of anterograde or retrograde degeneration and vasogenic edema. This could explain, at least partly, the great variability described by anatomic-clinic-correlational studies. In addition, it was observed that in acute brain lesion, there is decreased monoamine synthesis because of enzyme inhibition during ischemia. Accordingly, significantly lower cerebrospinal fluid (CSF) concentrations of the 5-HT metabolite 5-hydroxy-indoleacetic acid were measured in PSD patients compared to non-depressed stroke survivors. Positron Emission Tomography (PET) findings on 5-HT1a receptor availability after stroke suggest that changes in 5-HT neurotransmission may occur in the early phase of stroke and can be modulated by treatment with Selective Serotonin Reuptake Inhibitors (SSRIs).

Based on the strong association of proinflammatory cytokines, such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), IL-6, IL-8 and IL-18, with ischemic brain injury and the evidence of the severity of psychiatric disease in certain subtypes of depression, Spalletta et al. proposed the inflammatory cytokine hypothesis for PSD. In the last two decades, increased blood and CSF concentrations of pro-inflammatory cytokines, including IL-1β, IL-6, Interferon-γ (IFNγ) and TNFα, acute phase proteins, such as C-reactive protein (CRP), and their receptors, chemokines, adhesion molecules and other inflammatory mediators, have been demonstrated in MDD subjects. The long-term exposure to cytokines may be associated with the onset of depression. The best studied example comprises patients receiving IFN-α to treat melanoma and hepatitis C virus infection. In experimental animals, the administration of cytokines, such as IL-6, or cytokine inducers, such as lipopolysaccharide (LPS), have been found to induce depressive-like behaviors. The inflammatory mediators seem to activate the widespread tryptophane depletion, increasing monoamine synthesis because of enzyme inhibition during ischemia. Accordingly, significantly lower cerebrospinal fluid (CSF) concentrations of the 5-HT metabolite 5-hydroxy-indoleacetic acid were measured in PSD patients 3 to 6 months after stroke, but this was not associated with BDNF gene Val66Met polymorphisms. Based on the theory of inflammatory cytokines, Kim et al. reported that the IL-4 + 33C/C and the IL-10 –1082A/A genotypes were associated with PSD. These studies rely on very small samples and need to be replicated consistently in larger populations.

It should be noted that, traditionally, most studies on the pathophysiology of PSD have focused on large vessel disease, without making an explicit mention of lacunes. However, paralleling this debate, the literature on “vascular depression” hypothesis is increasingly emphasizing the role of small vessel and microvascular chronic burden in triggering depressive episodes. According to this hypothesis, cerebrovascular disease could predispose, precipitate or perpetuate some geriatric depressive syndromes. Nevertheless, longitudinal studies in large community-based series of patients with PSD are needed to test the validity of this interesting proposal.

As the evidence supporting the different lines of biological explanations has not pointed to definite conclusions, the psychological school still maintains proposals of psychosocial mechanisms for the pathogenesis of PSD. For instance, Gainotti et al. found that the symptom profiles and anatomical-clinical correlates of major PSD were not different in the acute and more chronic stages. He argued that this finding was more consistent with a psychological than a neurobiological model of PSD. Lieberman et al. studied 516 hospitalized elderly patients, 221 after stroke and 295 after hip fracture. There were no differences in the symptoms of depression score between the two groups, contradicting the influential work of Folstein et al. Bozakas et al. performed a clinicopathological analysis of 95 consecutively autopsied elderly individuals who survived an initial stroke and were followed to record the occurrence of PSD. They observed that the severity of brain vessel arteriosclerosis and the frequency of brain vascular lesions were not significantly different between 21 cases with PSD and 74 cases without depression. No lesion pattern characterized the depression group. Thus, they suggested that psychological rather than neuropathological factors were the main determinants of PSD. In fact, patients who had a stroke experience a traumatic event that undermines their physical and mental integrity, their autonomy and self-esteem as well as their marital and professional lives. Psychological coping mechanisms, as well as premorbid personality, certainly play an important role in the development of PSD. However, these arguments are not sufficient to explain the emergence of depression after silent infarctions or in patients with anosognosia.

Ultimately, this polarity of thought appears unreasonable given the current understanding on the inseparable nature of somatic and psychiatric illness. PSD does not appear to be the result of “pure” biological versus psychological causes, but instead is multifactorial in origin and consistent with the biopsychosocial model of mental illness. At this time, more investigations are needed to clarify the relative contributions of both biological and psychosocial risk factors and their interactions to the development of poststroke psychopathology.
Many factors have been roughly associated with PSD, as can be seen in figure 1, such as previous history of psychiatric disorders, female gender, family history of depression, and cerebrovascular risk factors, among others. Of those, physical disability, stroke severity and cognitive impairment have been more consistently associated with PSD. Further, it has been suggested that patients who develop PSD just after a stroke have different risk factors than those who present a first episode later on. Accordingly, early PSD would be closely related to biological mechanisms, whereas PSD developed six months after a stroke would be related to psychosocial mechanisms. A better understanding of the influence of these risk factors on the course of PSD and treatment response will lead to better treatment and, possibly, primary prevention interventions.

**Treatment**

There is consensus that, if PSD is left untreated, it may exert negative impact on functional recovery. Longitudinal studies show that major and minor depressions are determinants of disability, failure in returning to work, impairment in interpersonal functioning and mortality. The relation between PSD and functional impairment is complex. Patients with PSD have significantly higher disability in ADLs than euthymic patients with comparable neurological deficits. PSD negatively impacts on the involvement in rehabilitation programs and is associated with more institutional care and increase in using of health services. These findings suggest a phenomenon of reciprocity, in which depression influences the recovery of ADLs and the impairment of ADLs influences the severity and duration of depression. Increased mortality is perhaps the ultimate validation of the importance of depression in the prognosis following stroke. PSD appears to be a significant risk factor for increased death as early as 1 year and as late as 7 years following stroke. The mechanism underlying increased death rates is an important issue, which has not been examined in depth. One study showed that PSD is associated with decreased heart rate variability (HRV). In this line, Tokgozooglu et al. reported that patients with decreased HRV, as a result of stroke lesions of the insular cortex, are at risk for sudden death, and Makikallio et al. found that decreased long-term HRV was the only multivariate predictor of death after adjusting for age. There are no guidelines for PSD treatment and the effectiveness of interventions is not well established. In a systematic review, Hackett et al. concluded that the use of antidepressants is associated with a small but significant beneficial effect. According to the meta-analysis conducted by Price et al., the use of antidepressants may be indicated on both major and minor depressive disorders, but there are no specific guidelines for the selection of drugs. The most studied drugs were tricyclic antidepressants, especially nortriptyline, and SSRIs, particularly fluoxetine, sertraline and citalopram. There were also studies evaluating the use of trazodone, venlafaxine, reboxetine, mirtazapine, milnacipran and methylphenidate.

Some authors recommend the use of Nortriptyline as the first line drug, based on the evidence that it has a better efficacy than any other antidepressant available. However, Nortriptyline may determine undesirable side effects and drug interactions, which can be problematic in a population at higher risk of cardiovascular disease. In this scenario, SSRIs are an interesting alternative. The use of antidepressants in the prevention of PSD is even more controversial. Isolated studies have shown benefits with nortriptyline, fluoxetine, sertraline, mirtazapine and methylphenidate. Nevertheless, a Cochrane systematic review found no significant effect of antidepressant use in the prevention of PSD.

One very interesting point is that antidepressants, especially SSRIs, have been associated with improvement of motor recovery and dependence after stroke even in patients without depression. Experimental studies reporting neurogenic and neuroprotective effects of SSRIs provide a plausible mechanism of action. The largest study conducted to date has been the “Fluoxetine in motor recovery of patients with acute ischaemic stroke” (FLAME) trial. It was a double-blind, placebo-controlled trial, in which 118 ischemic stroke patients with moderate to severe motor deficits, without PSD, were randomly assigned to a 3-month treatment with Fluoxetine or placebo. The authors reported that, after 90 days, the early prescription of Fluoxetine with physiotherapy enhanced motor recovery. Besides, they noted that the early use of Fluoxetine prevented PSD. In a recent meta-analysis, 52 trials randomizing 4,059 patients to SSRI or control were assessed (28 used fluoxetine, 7 sertraline, 10 paroxetine, 5 citalopram, 1 escitalopram, and 1 either sertraline or fluoxetine). The authors concluded that the favorable effects of SSRIs on disability, depressive symptoms, and neurological deficit scores were greater in participants who were depressed at randomization, but this may be due to quality bias. Besides, the authors report evidence of benefits of SSRIs in patients without depression, especially fluoxetine, the most studied drug. SSRIs appeared to improve dependence, disability, neurological impairment, anxiety and depression after stroke, despite the heterogeneity of the trials and several methodological limitations. Large, well-designed trials are needed to determine whether SSRIs should be routinely given to patients with stroke.

![Figure 1](image-url) An integrative model of factors involved in post stroke depression pathogenesis. ADLs: activities of daily living.
Although it has not been used in a randomized controlled trial, electroconvulsive therapy has also been reported to be effective in treating PSD\(^6\). Another emerging technique for the treatment of PSD is non-invasive brain stimulation, which encompasses two main techniques: repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). TMS depolarizes neurons using potent, focal electromagnetic fields that are generated beneath the coil positioned over the patient's head. The electric depolarization, thereafter, induces action potentials. When applied repetitively and for several days, rTMS is able to induce clinical effects in several psychiatric disorders and is already used as a clinical (non-experimental) treatment in several countries, including Brazil. tDCS, in turn, is based on the application of a weak (0.5-2mA), direct electric current in the brain using electrodes placed over the head. Clinical effects are observed in several psychiatric disorders when applied for daily several days. These techniques might be particularly suitable for PSD as their side effects are limited to discomfort over the local of the application of the electrode/coil – i.e., they can induce depression improvement without systemic side effects.

Despite the emerging evidence of these techniques, they are relatively poorly investigated in the context of major depression secondary to clinical disorders, including PSD. For instance, there are only two randomized, double-blinded clinical trials evaluating the efficacy of rTMS in PSD, studying 18 and 20 patients\(^58,59\). Both studies applied high-frequency (stimulatory) rTMS over the left dorsolateral prefrontal cortex, observing improvement of depressive symptoms. For tDCS, there is only one case report describing a patient with PSD, who showed marked improvement of symptoms after a 10-day course of tDCS\(^60\). In this context, there is one ongoing large double-blinded, randomized clinical trial enrolling 48 patients with PSD in the University of São Paulo, Brazil, which will provide more evidence regarding the use of tDCS for PSD treatment. This trial is registered at clinicaltrials.gov (NCT01525524).

Finally, psychological treatment in isolation has been found to be no more effective than placebo. Psychotherapeutic approach associated with antidepressant use appears to be of some benefit. In the meta-analysis of Hackett et al., a small but significant effect was found for psychotherapy in preventing PSD\(^53\).

### Conclusion

A narrative review of the literature was conducted to present a comprehensive panorama on PSD. It should be noted that, due the extent of the addressed theme, we opted to perform a non-systematic search. This method, however, imposes limitations associated with its non-quantitative nature. On the other hand, it was possible to describe in a detailed manner several aspects associated with this complication of stroke.

As discussed above, depression is the most frequent psychiatric complication of cerebrovascular disorder. It is clear that it influences prognosis and functional recovery and its approach must be guaranteed for every stroke patient. Despite its great clinical relevance, there is little insight into its underlying etiological mechanisms and treatment. For this reason, research addressed to elucidate the pathophysiological mechanisms of PSD are important. In Brazil, despite the great impact of cerebrovascular diseases, data are scarce even for the implications of PSD, indicating the need for epidemiological surveys to characterize the population affected by poststroke neuropsychiatric syndromes in the country.

A multidimensional approach taking into account biological, psychological and social perspectives is currently the most reasonable to the understanding of depressive symptoms following stroke, and to foster the development of evidence-based therapeutic strategies.

### Acknowledgments

This work was funded by CNPq and Fapemig.

### Disclosure

The authors report no conflicts of interest.

### References