Post-stroke Depression: Epidemiology, Diagnosis, Risk Factors, and Management

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Abstract
Post-stroke depression (PSD) is a widely encountered complexity of stroke, which is of notable importance. PSD is multifactorial in origin; however, depression after stroke is unrecognized, infrequently diagnosed, and undertreated. This review presents epidemiology, diagnosis and diagnostic tools, risk factors, and management of PSD. About one-third of patients experience depression after stroke. It is important to reliably screen and diagnose post-stroke depression as well as measure its severity. PSD is associated with various risk factors and stroke characteristics. If left untreated, PSD can worsen several other common post-stroke conditions. There is strong evidence that early initiation of antidepressant therapy in non-depressed stroke patients is associated with reduced risk for the development and effective prevention of post-stroke depression. PSD needs special attention, and consensus should be reached regarding the diagnosis and management of PSD.

Keywords: Stroke; Depression; Diagnosis; Risk factors; Management

Introduction
A stroke is defined as an abrupt onset of a neurologic deficit that is attributable to a focal vascular cause [1]. Post-stroke depression (PSD) is a widely encountered complexity of stroke, which is of notable importance. To date, there is no discrete definition of PSD, but according to the Diagnostic and Statistical Manual, Fourth Edition (DSM-4), post-stroke depression is “mood disorder due to general medical condition stroke” [2]. The most recent Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) defines post-stroke mood disorders as mood disorders due to stroke with depressive features, major depressive-like episode, or mixed-mood features. The only disorder in DSM-5 that is specific for the cerebrovascular disease is major or minor vascular neurocognitive disorder [3]. PSD is multifactorial in origin [4]. Despite a plethora of research on the risk factors of PSD in past decades, evidence is still lacking at the clinical level [5]. The management of PSD is essential, and the use of anti-depressant therapy has shown to be effective but needs to be better established [6]. However, depression after stroke is unrecognized, infrequently diagnosed, and undertreated [7,8]. In this review article, epidemiology, diagnosis and diagnostic tools, risk factors, and management of PSD is discussed.

Literature Review
Epidemiology
Most studies show that about one-third of patients experience depression after stroke [9]. The prevalence and severity of depression in stroke patients is elevated between six months and two years after a stroke. Some studies report that the prevalence rate has ranged from 9% to 34% in the first three to six months, increasing to 30% to 50% within the first year [4]. According to epidemiological studies, nearly 30% of stroke patients develop depression, either in the early or in the late stages after stroke [9]. A recent meta-analysis of 28 studies estimates that 31% of stroke survivors have depression at some time up to five years after a stroke [10]. In another meta-analysis, depression has a prevalence of 29% and remains stable in the first 10 years after stroke; furthermore, the cumulative incidence is 39-52% within the first five years following a stroke [11]. In general, accurate statistics of the incidence and prevalence of PSD is difficult to estimate because of methodological differences and weak concordance across studies [9,12]. Both major and minor depression have been reported in stroke patients [13], with a higher prevalence of major depression occurring soon after a stroke [14]. The prevalence of major depression changes over time, with the highest rates from three to six months after stroke and later declines to 50% of initial frequency at one year [15]. Studies that investigate the prevalence of minor depression report it to be 22% at two months post-stroke [16] and 8% at four months post-stroke [17]. One study report that the mean frequency of major depression is 19.3% and minor depression is 18.5% among patients in acute and rehabilitation hospitals, whereas the mean frequency of major depression is 14.1% and minor depression is 9.1% in community settings [18]. Research suggests that clinicians should be cautious about depression in stroke survivors, even years after a stroke, for they remain at persistent high risk of depression [19]. Altieri et al. indicate that the prevalence of PSD is frequent even after minor stroke, and it is not related to impairment intrinsically [20].

There are racial and ethnic differences in PSD. Non-Hispanic whites are more likely to be diagnosed with PSD than other racial or ethnic groups, even after adjusting for potential risk factors [21]. Hispanic stroke patients are less than half the odds of full PSD in the early period (at one month following a stroke) compared to non-Hispanic whites, but there is no significant difference in PSD between Hispanics and non-Hispanic whites in the later period (at 12 months following a stroke) [22]. Compared with whites, minority populations in the United States bear higher risks of unfavorable stroke outcomes, which might translate into a higher prevalence of PSD, but population-based studies are lacking [23]. A few years ago, The American Heart Association estimated that there are 5 million stroke survivors in the U.S., of which 2.4 million may have PSD, approximately half suffering...
from major depression. It is also likely that more than 3 million of these patients experienced depression at some time since their initial stroke [13].

**Diagnosis and diagnostic tools**

The American Psychiatric Association DSM-4 produces diagnostic criteria for mood disorder due to a general medical condition (stroke). It also specifies symptom criteria for major depression [13,24]. DSM-4-test revision characterizes depression as the regular presence of more than five out of nine depressive symptoms over a two-week period [25]. The latest DSM-5 provides certain diagnostic criteria for depressive disorder due to another medical condition (Table 1) [26]. Various researchers use DSM-4 as the reference measure for diagnosis of post-stroke depression and found it to be reliable with good diagnostic concordance [27,28], strong sensitivity, and specificity [7]. To date, there have been no studies testing the specificity and sensitivity of DSM-5 for diagnosing depression. It is important to determine whether the mood disturbance is due to a general medical condition when using the DSM diagnostic measures [26]. Some studies have used the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis for depression [29], which was developed in part by the American Psychiatric Association and classifies depression by code. The selection of code is based on severity (mild, moderate, or severe) and status. Depending on the number and severity of the symptoms, a depressive episode may be specified [30]. Diagnosis of depression is conducted in the studies using structured interviews such as Composite International Diagnostic Interview (CIDI) or Structured Clinical Interview for DSM-IV-Patient Edition (SCID-P, DSM-IV) or Mini-Mental State Examination (MMSE) [13,25,27,31]. The broadly used technique is to perform a structured interview and apply findings to established diagnostic criteria like DSM-IV-TR [13].

There are three key factors that need to be considered before determining the necessity for screening of PSD:

1. The validity and reliability of screening tools to detect PSD;
2. Whether treatment of PSD improves depressive symptoms; and
3. Whether PSD screening improves outcomes.

There are several tools that are used to assess depression, and they can be classified into two types: Self-report and Observer-rating [24]. A list of instruments utilized in the assessment of post-stroke depression is shown in Table 2. Beck Depression Inventory (BDI), Hamilton Rating Scale for Depression (HRSD), Clinical Global Impression (CGI) and DSM, 3rd edition revised diagnosis, are useful in assessing Rating Scale for Depression (HRSD), Clinical Global Impression is shown in Table 2. Beck Depression Inventory (BDI), Hamilton Depression Scale (GDS) due to its easy administration, strong positive predictive value, and reliable specificity as well as sensitivity [33]. Although performance of Patient Health Questionnaire 9 (PHQ-9) and PHQ-2 in the stroke population is adequate, they are preferable over other instruments for early detection of PSD because they are brief and easy to use [27]. Consistent with these studies, the findings of a meta-analysis to investigate the most accurate tool for detecting PSD report that the Center for Epidemiological Studies Depression Scale (CES-D), HRSD, PHQ-2, and PHQ-9 are promising choices and should not be used separately but followed by comprehensive clinical evaluation [28]. In addition, a clinical prediction model should be developed to identify stroke patients at risk of PSD. de Man-van Ginkel et al. developed the Post-stroke Depression Prediction Scale (DePreS) to enable clinicians to estimate the risk of PSD in the first week after stroke. This prediction scale may improve clinical assessment provided it is followed up with adequate treatment [25].

Each measurement tool has its own advantages and limitations and should be used after careful consideration according to the user's settings within the contexts of suitability and feasibility. It is important to reliably screen and diagnose post-stroke depression as well as measure its severity. Detection and diagnosis of post-stroke depression is often inconsistent, and compliance with guidelines for screening is inadequate. Identified barriers to routine screening include time pressures and concerns about screening tools [34].

**Risk factors**

PSD is associated with various risk factors and stroke characteristics. Risk factors that are related to PSD are a history of prior stroke, history of prior depression, female gender, living isolated, and social distress prior to stroke [35]. However, another study shows that there is no relation of PSD with age, sex, social class, cognitive impairment, or pre-stroke physical illness, whereas significant associations with major functional impairment, living in a nursing home, being divorced, and heavy intake of alcohol pre-stroke are found in males [36]. Younger stroke survivors in the 25-54 age group experience significantly higher levels of depressive symptoms as compared to the 55-64 age group [37].

**Psychosocial factors:** These pose a risk in the development of depression after stroke, and life events pose a significant risk for developing depression at six months after stroke [38]. This suggests that financial, familial, and health-related stress at baseline would be indicative of depressive symptoms after stroke [37]. In women, stress is associated with depression, and females show greater reactivity than males to stressful life events, so there is a link between stress reactivity and depressive symptoms [39].

**Genetic predispositions:** Serotonin (5HT) and BDNF (brain-derived neurotrophic factor) polymorphisms are shown to be associated with PSD. A significant interaction between 5-HT2R2 1438A/G and BDNF val66met polymorphisms for major PSD and,

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**Table 1: DSM-5 criteria for depressive disorder due to another medical condition.**

**With depressive features:** Full criteria are not met for a major depressive episode.

**With major depressive-like episode:** Full criteria are met (except criterion C) for a major depressive episode.

**With mixed features:** Symptoms of mania or hypomania are also present but do not predominate in the clinical picture.
between 5-HTTLPR and BDNF val66met polymorphisms for all PSD are also reported [40].

**Vascular factors**: Individuals with hypertension, hyperhomocysteinemia, and other factors associated with cerebral small vessel disease (SVD) are more prone to post-stroke depression [41]. Cerebral small vessel disease increases the risk of depression after stroke [42]. Some risk factors for small vessel cerebrovascular diseases may also be risk factors for depression in chronic phase after stroke. Hypertension may have a greater impact than other vascular risk factors on PSD [43].

**Socio-economic factors**: Lower income, poor social support, and poor activities of daily life are risk factors for stroke patients to get depression [44]. Another study linked patient's socioeconomic status like worsening effects of financial strain, poverty or lack of personal resources with depression [45]. A meta-analysis that assessed predictors of PSD reported that patients with lower participation in stroke-specific and gender-specific health behaviors as well as quality of life indices [55]. Presence of aphasia [48] and prosodic markers may also be predictive of PSD [49].

**Radiological risk factors**: The existence of multiple infarcts, infarct affecting each side of the posterior limbs and genu of internal capsule, and cortical, sub-cortical areas in the temporal lobe are related to PSD [50]. A well-known risk factor for post-stroke depression is left hemisphere stroke with PSD although all studies do not agree with this proposition. One study mentioned that the location of stroke lesions in frontal lobes or basal ganglia has been associated with greater risk of depression within one year of a stroke. No significant relation between left-hemisphere stroke and PSD. Nonetheless, the association between right-hemisphere stroke and frequency of depression has been demonstrated [52]. Conversely, a retrospective study in Korea observed that lesions on the left hemisphere are associated with depression, but lesions on the right hemisphere are associated with lower rates of depression in stroke patients [53]. The degree of impairment of activities of daily living (ADL) following stroke relates to whether or not PSD occurs in a person [54]. Early and late-onset of depression have been associated with increased risk of disability and reduced quality of life (QoL) one year after a minor stroke [46]. Among adults who experienced a stroke, major depression is associated with lower participation in stroke-specific and gender-specific health behaviors as well as quality of life indices [55].

A meta-analysis that assessed predictors of PSD reported that disability following stroke and history of depression prior to stroke was associated with depression.
are more consistently associated. The other predictors included cognitive impairment, stroke severity, lack of social or family support, and anxiety [11]. A recent DEPRESS (Depression Predictors after Ischemic Stroke) study in France evaluated predictors of depression within six months of ischemic stroke and described that female gender, past history of depression, major physical disability, previous history of stroke, recent stressful life event exposure prior to stroke, and pathologic crying are important predictors of post-stroke depression occurring within six months after ischemic stroke [56]. The risk factors that have been consistently accompanying PSD are female sex, former history of depression or psychological illness, functional limitations, and cognitive impairment [34]. Biochemical factors: According to biogenic amine hypothesis, it is hypothesized that due to ischemia, cerebral lesions interrupt projections ascending from brainstem to cortex containing biogenic amines such as serotonin (5-HT), dopamine (DA) leading to reduced bioavailability of biogenic amines in limbic structures of frontal lobe, temporal lobe and basal ganglia, further resulting in neuropsychiatric symptoms like depression [57]. Decreased levels of biogenic amines are observed in stroke patients with depression compared to non-depressive stroke patients [58].

Discussion

Management (Pharmacologic and Non-pharmacologic interventions)

PSD, if left untreated, can worsen several other common post-stroke conditions such as malnutrition, incontinence, pain, fatigue, and sleep issues [59]. There are a variety of treatment options for post-stroke depression. There is strong evidence that early initiation of antidepressant therapy in non-depressed stroke patients is associated with reduced risk for the development and effective in preventing post-stroke depression [60]. Current practice often involves providing an antidepressant (often an SSRi) to stroke survivors with depression, for it is possible to assess them for depressive symptoms [61]. Heterocyclic antidepressants such as Nortriptyline, Imipramine, and Mianserin, and Selective Serotonin Reuptake Inhibitors (SSRIs) such as Citalopram, Fluoxetine, Sertraline are shown to be effective in the treatment of post-stroke depression [62-64]. Randomized controlled trials were not conducted to determine the effectiveness of Serotonin and norepinephrine reuptake inhibitors SNRIs like Venlafaxine and Duloxetine in PSD although single-group design studies showed effectiveness in reducing depression among patients with stroke [62]. Pharmacologic treatment of post-stroke depression is associated with improved functional recovery, and moderate evidence that treatment with antidepressants is associated with improved long-term survival [65]. Even if current antidepressant treatment can improve depressive symptoms, neither the optimal drug nor the optimal lengths of treatment, have been identified [66]. Non-pharmacological therapies, such as ongoing individualized contact and support provided via various care provision models, are associated with less deterioration of mood and/or mental health state following a stroke [62]. The cognitive behavioral therapy (CBT) intervention has positive effects on depressive symptoms in PSD [66] and is both less costly and effective from a societal perspective and less costly and slightly more effective in terms of QoL [60]. Dense cranial electroacupuncture stimulation (DCEAS) could be effective in reducing stroke patient’s depressive symptoms [67]. Superficial electrical stimulation in non-invasive cranial electroacupuncture (n-CEA) group may be beneficial in improving movement disability of stroke patients. A combination of DCEAS and body acupuncture can be considered a treatment option for neuropsychiatric sequelae of stroke. Use of repetitive transcranial magnetic stimulation is shown to be associated with reduced symptoms of depression [68]. Psychosocial interventions in addition to antidepressant therapy may be effective in treating post-stroke depression [62]. Facilitation of participation in valued activities may be effective in reducing the incidence or severity of post-stroke depression as well as enhancing an individual’s perception of their health-related quality of life.

Conclusion

There is an unmet need to develop therapies for PSD. Further studies are required to determine the effectiveness of screening tools in clinical settings. Future research should focus on elucidating the mechanisms of PSD to facilitate specific interventions. Randomized clinical trials should investigate optimal antidepressant therapy and evaluate efficacy and tolerability of treatments. Thus, PSD needs special attention, and a consensus should be reached regarding management of PSD.

References


