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Post Stroke Depression

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Abstract

Depression is the most common neuropsychiatric disorder affecting over one third of all stroke patients. The presence of depression after a stroke greatly affects the ability of patients to participate in rehabilitation and can even affect their long-term mortality. Poststroke depression is a well-documented and studied aspect of stroke management because of the implications it has on morbidity, mortality and recovery. Despite post stroke depression being a well-studied phenomenon, it remains underdiagnosed. The development of poststroke depression is multifactorial and has been evaluated from the cellular, genetic, and environmental perspective. Using numerous studies this chapter will review facets of post stroke depression such as epidemiology, etiology and treatment, while evaluating how this phenomena effects patient recovery and rehabilitation.

Keywords: stroke, depression, post stroke depression, elderly, serotonin, anxiety, recovery, rehabilitation, function, rehab, acute stroke, ischemic, hemorrhagic, mood

1. Introduction

Stroke is one of the leading causes of long-term disability in the United States and is the third leading cause of mortality [1]. Brain parenchyma is densely packed with millions of neurons, where any assault such as an ischemic or hemorrhagic stroke can leave a patient with debilitating deficits [2]. A few of these deficits include the inability to speak or understand language; loss of vision, complete paralysis of one side of the body, quadriplegia, persistent balance issues, and loss of the ability swallow independently. Neuropsychological changes are also very common and well documented in poststroke patients; however, the number of patients that suffer from these changes are grossly underestimated [3].

More than one-third of all stroke survivors experience some form of depression [4]. Depression after a stroke can manifest in many different ways including feelings of anger, frustration, hopelessness, guilt, mental slowing, fatigue, irritability, changes in appetite, social withdrawal, loss of interest in activities they once found enjoyable (also known as anhedonia), or even suicidal thoughts [2]. Patients that suffer from poststroke depression, often have these symptoms missed or undertreated. Recovery and rehabilitation can be adversely affected if post stroke depression is not adequately treated. This can result in increased length of stay at postacute care facilities, increased morbidity, decreased quality of life and even increased mortality [5]. Numerous depression scales have been used to define poststroke depression including the Beck Depression Inventory (BDI), Montgomery-Åsberg Depression Rating Scale (MADRS), Centre for Epidemiologic Studies Depression

scale (CES-D), Zung self-rating depression scale and the Hamilton Depression Rating Scale (HDRS) [5]. Post stroke depression has a great impact on the health-care system as well as on the individual patient. In this chapter, we will examine all aspect of depression as it relates to stroke by using these scales and large meta-analyses to define post-stroke depression, and assess how it relates to stroke and recovery.

2. Epidemiology

Advancements in acute medical therapies have led to the reduction of mortality due to acute ischemic or hemorrhagic stroke [5]. Studies have shown that 10% of patients recover without any residual deficits, a quarter have mild residual deficits, while 50% are severely disabled or require skilled nursing care within a medical facility able to manage their needs [6]. Along with severe physical disability, patients that suffer from a stroke also experience neuropsychiatric changes. The most common neuropsychiatric sequelae, post-stroke, are depression and anxiety [7]. Patients that survive stroke often experience anxiety and depression related to making adjustments to their new reality [7]. With more patients surviving stroke, quality of life becomes an area of focus. Poststroke depression has been regarded as one of the most important measures for quality of life after an acute stroke. The presence of depression after stroke results in impaired recovery, decreased participation in rehab efforts, impaired cognition, and even increased mortality. The majority of the expressed concern from patients is related to their ability to work and provide financial stability for themselves/their families, the ability to manage their activities of daily living, and the loss of their functional independence [7].

The term poststroke depression puts a focus on ischemic rather than hemorrhagic strokes, which is mostly due to the fact that ischemic strokes have been studied more in the literature, and thus will be the focus of this chapter [8]. Poststroke depression can occur anywhere from days to years after an acute ischemic event with the peak incidence of poststroke depression occurring between 3 months and 2 years, even if the patient's symptoms are improving [9]. Patients that experience the onset of poststroke depression at or after 7 weeks from the acute event are less likely to have a spontaneous remission of this depression [9]. In the acute phase, patients that had a longer inpatient hospital stay were seen to score higher on the Beck Depression Inventory than those that were in the community or in a rehabilitation facility. However, many of these studies have excluded patients that are aphasic, have cognitive impairment, or experienced pre-stroke depression. This may be one of the main reasons that poststroke depression may be underdiagnosed and undertreated [10].

2.1 Demographics associated with poststroke depression

Patients younger than 60 are seen to have higher depression scores poststroke. In the general population, major depression is more prevalent in patients younger than 65 years old [11]. In multiple studies that adjusted for pre-stroke depression it was found that more than 30% of the patients younger than 65 could be diagnosed as having clinical depression using the Center for Epidemiologic Studies Depression Scale (CES-D). It was found that within this younger age group there was a higher rate of depression associated with lower socioeconomic status, familial stress, and the ability to provide financial stability [7, 11]. However, having good social support has been found to be protective against poststroke depression [7, 11]. Adults over the age of 65 represent the majority of stroke patients, which can skew the data.

However, multiple meta-analyses have shown that when controlling for other variables such as sex, patients younger than 65 experienced more poststroke depression, and more obvious depressive phenotype [6, 11].

Biologic sex and poststroke depression is a controversial issue. Numerous meta-analyses have looked at the relationship between 'gender' and how it affects or predicts poststroke depression. The results were mixed when looking at data from across the globe. In some studies, women have been found to experience double the risk of poststroke depression compared to men [12, 38]. The gender disparity may be related to how each sex reacts to stressful life events. Women have been demonstrated to have more stress in reaction to negative life events, such as a stroke, which results in feelings of depression [12]. On self-reported survey, women were seen to indicate they have more depressive symptoms, compared to men, when age was controlled for [12]. The risk factors for women developing depression after an acute stroke were: pre-stroke psychiatric comorbidity, age younger than 65, and impairment in cognition [13]. Similarly, men with higher level of physical disability after a stroke had more depressive symptoms than women, or men with less physical disability. In multicenter analysis from China, and India, these studies found that male sex had a higher correlation with poststroke depression [10, 15]. However, there may be confounding factors when evaluating sex differences and poststroke depression. For example, in China there may be a higher number of men in the general population [14]. In the Indian study there were more men in the study [10]. In the USA, it is possible that there is a higher rate of self-reporting by women, as well as under reporting of depressive symptoms in men, based on their level of physical disability [14]. Therefore, more studies need to be done in this area to determine if gender is a definitive predictor of poststroke depression.

Socioeconomic status and education related to poststroke depression is also difficult to measure, due to multiple confounders and conflicting data. However, reviewing the meta-analysis of patient demographics and poststroke depression has shown that patients with lower overall education levels have an increased risk for poststroke depression with mild depressive symptoms [13]. A large meta-analysis of the literature found that there is an association between more years of education and lower risk for depression after a stroke. This study demonstrated that on average the participants in the study without poststroke depression had 0.32 years of education more than those that did have depressive symptoms after their stroke [16]. The symptoms that were seen in this data set were defined as mild depressive symptoms, but could not be classified as clinically depressed. However, this may also have confounding factors in this category. Patients that have lower socioeconomic status have been shown to have lower levels of education [16]. They may also be exposed to environmental factors that put them at increased risk for stroke, such as unhealthy diet, unhealthy lifestyle, more perceived stress, exposure to second hand smoke, and pollution in urban areas [10, 13, 16]. These factors may increase their risk of stroke, and thus their risk for poststroke depression.

3. Comorbidities associated with poststroke depression

Comorbid conditions prior to a stroke can affect the development of depression after an acute ischemic event. Conditions such as diabetes, and preexisting psychiatric disorders like depression, anxiety, and bipolar disorder can all have an effect on poststroke depression [17, 18]. One meta-analysis has demonstrated that patients that have vascular risk factors such as diabetes are at a higher risk for developing poststroke depression [17]. This is not thought to be related to the vascular depression theory, which will be discussed later in this chapter. In a Chinese study, it was

shown that at 3 months after an acute stroke, patients with diabetes were more likely to develop poststroke depression. This was an independent risk factor for the development of poststroke depression at or after 3 months [17]. The hypothesis behind this is based on the pathophysiology behind both diabetes and poststroke depression, which involves the inflammatory pathway, and the hypothalamic pituitary access. This will be discussed later in the chapter.

Preexisting psychiatric disorders such as depression, anxiety, and bipolar disorder can also predispose patients to worse poststroke depression in the subacute phase, which is within 3 months [17]. One meta-analysis that looked at predictors of poststroke depression found that of the patients that had a preexisting mood disorders such as dysthymia, major depression, minor depression, anxiety, agoraphobia and adjustment disorder were all associated with increased risk of worsening depression after a stroke. Of 1058 patients with reported depression prior to their stroke, 27% had worse depressive symptoms after the acute ischemic event [18]. Premorbid anxiety was also predictive of worsening anxiety after the stroke. Anxiety poststroke results in impaired response to adverse events increased perceived stress and more depressive symptoms [18].

4. Poststroke depression etiology

Poststroke depression has been defined as a mood disorder resulting from a general medical condition, by the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV, meaning it does not carry with it the same definition of major depression [16]. There has been some debate about the etiology of poststroke depression, where multiple hypotheses exist, including but not limited to disruption to monoamine pathways, inflammatory cytokines, and hypothalamic–pituitary axis within the brain that modulates mood. The other belief is based on a psychosocial model, where depression develops after a stroke due to inability to adjust to new life circumstances, inability to care for oneself, fear of recurrence, financial insecurity and carrying a new diagnosis [7].

4.1 Localization of poststroke depression

One question that has been analyzed extensively with no definite answers is the location of a stroke as a predictor of poststroke depression. These studies used techniques such as voxel-based symptom lesion mapping, diffusion tensor imaging (DTI), functional magnetic resonance imaging (MRI), and positron emission tomography (PET) scans [19]. Functional neuroimaging has sought to determine neuronal circuitry to discover how damage to these circuits results in mood or personality changes. These imaging modalities demonstrate that there is less activity in the frontal cortex, anterior cingulate, dorsolateral and caudate nucleus, in patients that are experiencing depression. In pilot studies using DTI, there has been some data demonstrating that damage to the fronto-striato thalamic pathway and pathways involving emotional control, reward systems and decision making can lead to increased risk of poststroke depression [19]. DTI changes were seen in stroke patients that had damage to the genu and splenium of the corpus callosum, frontal lobe white matter and anterior left corona radiata, resulting in increased levels of apathy [20]. A few theories about lesion location and depressive symptoms include-anhedonia as associated with the stroke volume affecting the hypothalamic-pituitary-adrenal axis, and increased risk for depression in patients with basal ganglia, and frontal lobe strokes [20]. A study by Paradiso and colleagues demonstrated that patients who had left hemispheric strokes were likely to have

more depressive symptoms [19]. They proposed that right hemispheric strokes experience fewer depressive symptoms due to anosognosia. If the patient is unaware of his or her deficits, they will less likely feel depression related to their loss of function. Left hemispheric strokes have also been seen to have an earlier onset of poststroke depression, usually in the first 6 months poststroke [13].

One of the models that have been proposed is that subcortical strokes like those in the basal ganglia, and strokes in the frontal lobes can result in disrupted serotoninergic and norepinephrinergic pathways that can be associated with poststroke depression [21]. The belief is that strokes that affected the amine-containing axons between the brainstem and specifically the left cerebral cortex would result in decreased production of serotonin (5-HT) and norepinephrine [22]. A reduction of these neurotransmitters in the frontal and temporal lobe limbic structures, and in the basal ganglia could result in difficulty with mood regulation [19]. This theory was supported by the finding that there were low levels of the 5-HT metabolite, 5-hydroxyindoleacetic acid in the cerebrospinal fluid (CSF).

4.2 Biomarkers associated with poststroke depression

Inflammatory cytokines were also thought to be related to the development of poststroke depression [23, 24]. Jioa and colleagues found that interleukin (IL)-6 was elevated in patients with post-stroke depression, even after controlling for confounders, with a confidence interval of 95% [23]. The elevation of IL-6 in patients that have strokes could possibly predict the development of poststroke depression [23, 24]. In another meta-analysis, brain-derived neurotrophic factor (BDNF) was found to be involved in the development of depression and poststroke depression [25, 26]. In these studies, a low serum level of BDNF in the acute phase after a stroke was associated with the development of poststroke depression. BDNF is inherently involved in hippocampal plasticity and memory [27]. One study found a significant negative relationship between BDNF and NIHSS [25–27]. In rodent models, low levels of BDNF in the hippocampus that had an acute stroke exhibited depressed behavior, however if BDNF was overexpressed there was a marked decrease in depressed behavior [21]. Increased BDNF in the rodent model also resulted in reduced infarct size and improved functionality of the rodent [25].

Increased serum level of C-reactive protein (CRP), neopterin, ferritin, and glutamate could also be related to poststroke depression [24]. Proinflammatory markers such as tumor necrosis factor (TNF)-α, interleukins (IL)-1β, IL-6, IL-1, and interferon gamma (IFN-γ) were associated with the development of poststroke depression [23, 24]. Additionally, inflammatory cytokines can activate the hypothalamic pituitary adrenal axis [24]. Activation of the HPA access can also lead to the downstream release of glucocorticoids, which can also result in increased blood glucose levels, and potentially diabetes if this is a chronic process. After an acute stroke, patients often exhibit increased levels of serum adrenocorticotropic hormone, and cortisol. These hormones result in higher mortality and worse neurologic outcome [23]. Increased cytokine activity could also result in greater expression of genes involved in the metabolism of tryptophan such as indoleamine 2,3 dioxygenase (IDO) [27]. If IDO expression increases, tryptophan will be converted to kynurenine and not 5-HT. The downstream effect could result in decreased levels of 5-HT in the limbic system, temporal lobes, frontal lobes, and basal ganglia, which could potentially result in depression [27].

4.3 Genetic association with poststroke depression

There have also been studies that have shown a genetic contribution to poststroke depression. Multiple studies have evaluated the 5-HT gene located on

chromosome 17q11.1-17q12, which encodes the serotonin transporter [25–27]. In a meta-analysis of 7 studies, there was a significant relationship between 5-HTTLPR polymorphism and the development of poststroke depression symptoms. 5-HTTLPR is an exon of the 5-HT transporter gene polymorphism [25, 26]. The hypothesis is that this gene polymorphism responds to the increased activity of the amygdala when responding to negative stimuli. An increase in 5-HTTLPR serum level has been positively associated with threefold increased risk of developing poststroke depression [25–28]. Another 5-HT polymorphism that has been analyzed is the STin2 VNTR, which is located within intron 2. It has variable number tandem repeats 9, 10, or 12. Repeats of the 9-allele have been well documented to be associated with multiple psychiatric disorders such as bipolar disorder, and major depression [25–28]. Repeats of the twelfth allele have been linked to the development of schizophrenia and bipolar affective disorder. It has been demonstrated that patients with variable tandem repeats of 9/12 and 12/12 were likely to have more depression after a stroke [25–28].

4.4 Psychosocial association with poststroke depression

Lastly, psychosocial factors must be considered when assessing who is at risk for poststroke depression. After suffering a life-altering event such as a stroke, even if there are no severe deficits, patients can undergo an adjustment period. They may feel depressed about the new diagnosis of a stroke. There is also the concern of getting back to their normal life routine such as working, caring for dependents, and caring for their own activities of daily living (ADLS) [11, 12]. Patients that do not have good social support tend to experience more depression after a stroke due to feeling helpless, and alone. Patients may also experience anxiety, related to the fear that another stroke may occur. Financial costs of health care also play a role in postacute stroke depression. If a patient is unable to work there may be a concern about medication compliance, affording medication, affording postacute special services like physical therapy or occupational therapy [11, 12].

5. Poststroke depression in elderly

Although there is a growing prevalence of stroke in patients aged 65 and younger, the majority of strokes affect patients that are elderly. With the prolonged life expectancy, there is an increased risk for stroke in the aging population, with 70% risk being after the age of 65 [29]. In patients older than 80 years old that suffer from strokes, there is a greater risk of fatality, prolonged hospitalization, complications, and increased postacute care needs [30]. In elderly patients that suffer from stroke, depression may be difficult to diagnose. This is largely due to the symptoms being a vegetative phenotype. It is also confounded because depression is the most common psychiatric disorder among the elderly—with 1% of the elderly population having a formal diagnosis of major depression, and 15% with depressive symptoms according to the National Institutes of Health Consensus development conference [31]. This poses a challenge that practitioners face in distinguishing between premorbid depression, inherent stroke symptoms and poststroke depression, given that many of the features overlap. Some such features include cognitive impairment, psychomotor retardation, and social withdrawal [29]. One measure used to assess poststroke depression in the elderly is the geriatric depression scale (GDS) [32]. This is a self-reported scale where patients answer yes and no questions to determine if a patient is experiencing some form of depression. A score greater than 6 indicates that the patient is likely experiencing some form of depression.

This scale is highly sensitive and predictive of poststroke depression in the geriatric population [32]. However, the GDS cannot be used by aphasic stroke patients or those with cognitive impairments caused by a stroke.

5.1 Vascular dementia and poststroke depression

Alexopoulos and colleagues found that elderly stroke patients that suffered ischemic strokes demonstrated increased encephalomalacia and MRI hyperintensities that would predispose these patients to develop depression [33]. Their study suggested that these changes were not seen in elderly patients that had depression without vascular risk factors. Elderly patients that have been observed to have signs of depression, but do not have any vascular risk factors were found to have less white matter hyperintensities on MRI, which were similar to the nondepressed controls [31]. It has also been demonstrated that patients that suffered from depression without vascular insult had phenotypically different depression with features of more agitation, aggression, feelings of guilt and dysphoria. This is the theory of vascular depression in the elderly [33]. The hypothesis behind vascular depression states that chronic small vessel changes or non-symptomatic cerebrovascular events accumulate over time, resulting in the disruption of cortico-striato-pallido-thalamo-cortical (CSPTC) pathways [31]. Vascular dementia is described as a subcortical phenomenon. This type of depression differs from poststroke depression, in that they are silent, and the patient is not aware that they have suffered a stroke [31]. In a Japanese sample, greater than 80% of the patients that had major depression had MRI evidence of multiple silent infarcts [32]. Up to 75% of these depressed patients had lesions in the basal ganglia and thalamus [31, 33].

Three pathways associated with CSPTC were proposed in the way that vascular depression can present phenotypically. Within the CSPTC are the orbitofrontal pathway, the cingulate pathway, and the dorsolateral pathway. Injury over time to the orbitofrontal pathway can result in irritability and disinhibition [31]. The cingulate pathway can cause apathy, and lack of initiative if injured, and lastly, injury to the dorsolateral pathway can result in poor speech productions, and inability to learn. These symptoms can all be seen in elderly depression. Prefrontal dysfunction has shown to have a poor or delayed response to antidepressants in elderly patients [31, 33]. However, early administration of antidepressants, particularly selective serotonin reuptake inhibitors have been shown to improve neuropsychological rehabilitation in elderly stroke patients.

Lacunar infarcts have been seen to result in more depression among Alzheimer patients especially basal ganglia strokes and cortical strokes were found to have more cognitive impairment [31]. Severe cognitive impairment was also seen to be one of the leading causes of depression in the elderly. There are some questions of whether cognitive impairment or dementia can increase the risk of stroke, and thus poststroke depression among the elderly, or do strokes result in cognitive decline and vascular depression [31]. Dementia and depression can be difficult to differentiate. In the elderly, pseudodementia can be secondary to depression however, the opposite is also true. This is a "what came first" type of scenario with dementia, stroke and vascular depression [31].

Although vascular depression and poststroke depression are different in the way they affect a patient, they likely lay on a continuum. Both are secondary to a vascular event, and both result in depression. Vascular depression has a higher incidence in elderly patients as they have an accumulation of more subcortical white matter changes that are seen as hyperintensities on MRI FLAIR. Poststroke depression is less subtle since the patient is usually aware that they have had a stroke [31, 33]. There may be a growing incidence of vascular depression among young patients,

due to poorly controlled hypertension, tobacco, diabetes, drug use, and poor diet and lifestyle choices causing small vessel disease. These risk factors put all patients at risk for an acute stroke, and chronic small vessel disease.

6. Large strokes and the effect on poststroke depression

In patients that suffer from large ischemic or hemorrhagic strokes, they are often left with a serious physical disability [2]. A proximal middle cerebral artery occlusion can result in severe expressive, or receptive aphasias, hemiparesis, facial weakness, sensory loss inability to swallow, neglect, apraxia, and a propensity toward developing seizures [34]. If the patient is relatively young, the probability of cerebral edema is high, which could result in complications such as brain herniation if a hemicraniectomy is not performed. Intracerebral hemorrhage in these vascular territories can result in similar findings that may necessitate an extra ventricular drain to remove blood from the ventricles, or a decompressive hemicraniectomy to evacuate the hemorrhage [34]. A patient with a large stroke in the posterior circulation can result in the patient being obtunded, having chronic balance issues, hemiparesis, vision loss, and ataxia [3].

Patients that survive these large strokes often experience the most debility, with the majority becoming bedbound, requiring a percutaneous endoscopic gastrostomy tube for nutrition and tracheostomy tube for assistance with breathing. Due to the severity of their disability, these patients require 24-hour care, by their families or nursing professionals. The majority of these patients experience severe depression and guilt, due to feeling like a financial or physical burden on their loved ones [35]. They also experience loss of autonomy due to their deficits. They are no longer able to manage their own activities of daily living, which results in feelings of inadequacy, and resentment for those that are doing the caregiving. Depression has also seen to be positively correlated with the national institute of health stroke scale (NIHSS) which measures stroke severity, wherein the higher the stroke scale, the more severe the depressive symptoms [36].

Patients with large strokes and increased debility often require management in a skilled nursing facility (SNF). At SNF, the patients do not participate in as much rehabilitation activities, as compared to other stroke patients in an inpatient rehabilitation setting [32]. These patients are therefore at disadvantage because their exposure to rehabilitation is limited. The combination of decreased functionality, less access to rehabilitation, and depression impairs the recovery for these patients. They too lose the desire to participate in meaningful interaction due to their disability [32].

7. Challenges in diagnosing depression after stroke

Diagnosing depression after a stroke may be difficult for practitioners given that stroke patients can have complex symptoms. The physicians that treat stroke patients should be aware that over a third of patients experience depression after a stroke, and to note that even subtle changes in behavior could represent an aspect of poststroke depression [17]. Small changes like irritability, frustration, extreme fatiguability, and refusing to partake in physical therapy and occupational therapy. Another challenge is that many symptoms of stroke and depression overlap, such as fatigue, pain, decreased motor activity, and decreased verbal output [7]. Only a few of the depression scales used to assess poststroke depression include somatic symptoms in their evaluation. The Beck Depression Inventory is one such scale. However, again some somatic symptoms from the stroke itself can be mistaken as a

positive finding on a depression scale. It is important to be able to tease apart what symptoms are due to a stroke and what symptoms are related to depression. If a diagnosis of poststroke depression is missed, it can negatively affect how the patient recovers, and even affect their mortality.

The symptoms that make the diagnosis of poststroke depression the most difficult are aphasia, anosognosia, neglect, abulia and cognitive disabilities that result from their stroke [37]. Unfortunately, the majority of studies that evaluate poststroke depression exclude patients with these symptoms. This is largely due to their inability to answer questions, fill out questionnaires, or because it is difficult for medical staff to assign a score to the patient based on their daily interactions. Aphasia is independently associated with an increased risk of developing poststroke depression [37]. However, three scales have been developed to assess depression in aphasic patients. These scales include the Stroke Aphasic Depression Questionnaire-10 (SADQ-10), the Aphasia Depression Rating Scale (ADRS), and the Perceived Stress Scale (PSS). The (SADQ/SADQ-10/SADQH-10) and the Aphasia Depression Rating Scale are based on the observation of other people to determine if the patient being assessed is in fact depressed or not. The SADQ-10 used caregivers as the observers, with non-aphasic patients as the controls [37]. A value of 14/30 or higher was correlated with the development of depression and depressive symptoms with a sensitivity of 70% and specificity of 77%. The ADRS scoring system used external signs that could be observed such as fatigue, insomnia, changes in weight, and signs of anxiety. A score of 9/30 or higher was associated with the development of depression with a sensitivity of 83% and specificity of 71% [37]. After a comparative analysis, it was determined that either one of these tools could be used for assessing depression in aphasic patients. A review of the current studies could be more generalizable if aphasic patients were included and analyzed with these scales.

8. Poststroke depression effect on morbidity and mortality

Poststroke depression was found to be an independent predictor of symptom severity after a stroke, and difficulty with managing activities of daily living [35]. In a meta-analysis of seven studies, poststroke depression was found to have an association with increased mortality [39]. Specifically, patients that experienced early poststroke depression as defined to be within 3 months of stroke onset, were found to have 1.5 increased risk of death. A literature review by Robinson and colleagues, found that using the Hospital Anxiety and Depression scale (HADS), patients that had a score greater than 7 at 3 months had increased mortality than those with a score less than 7 [38]. These scores were evaluated up to 5 years poststroke, and the hazard ratio was found to be 1.41. It was seen that mortality was increased in patients with poststroke depression that were younger than 65 years old [38]. Their study also demonstrated that in greater than 50,000 veterans that suffered an ischemic stroke, those that developed poststroke depression had higher rates of mortality within 3 years of that acute event. The hypothesis behind this being that early poststroke depression can occur in a patient with a severe disability such as neurocognitive decline, paralysis, aphasia, or dysphagia [38]. Due to the severity of their post-stroke symptoms these patients may be at increased risk of death due to complications like pneumonia secondary to dysphasia or infection from decubitus ulcers. Another hypothesis is that patients that are suffering from poststroke depression may be less likely to be compliant with medical recommendations, such as healthy diet, avoiding tobacco, alcohol, drug use, scheduled follow up appointments and medication compliance [37, 38]. These factors can increase the risk of mortality. Another theory states that mortality associated with poststroke depression may be related to

cardiovascular mortality [38, 39]. There is an association between depression and myocardial infarction, where it was found that depressed patients had less heart rate variability. This finding was also seen in patients with poststroke depression. This could put these patients at risk for myocardial infarction and subsequently, death. This meta-analysis also highlighted the idea that pharmacologic antidepressants have a mixed response in poststroke depression [38].

9. Treatment of poststroke depression

In order to treat poststroke depression, it needs to be accurately diagnosed. Currently the DSM IV is used to diagnose this disorder, along with multiple depression rating scales such as the Hamilton Rating Scale for Depression, Beck Depression Inventory, Montgomery-Åsberg Depression Rating Scale, Center for Epidemiological Studies Depression Scale, Zung self-rating depression scale and the Post-Stroke Depression Rating Scale [5]. There are many challenges in diagnosing depression in a patient after an acute stroke. Many of these patients have a somatic component to their symptoms, like pain, fatigue, or limited speech after a cerebrovascular event. These symptoms can confound a depression scale that account for somatic symptoms— like the Beck Depression Index [5]. Depending on which scale is used to measure depression in these patients, there may be an overestimation or underestimation of depression. Since the hypothesis that stroke results in disruption of the monoamine pathways, there has been a focus on antidepressants like selective serotonin reuptake inhibitors, or tricyclic antidepressants to target poststroke depression. However, the role of antidepressants has been debated. There are some studies that show efficacy and reduction in mortality, and some that show a minimal effect or even adverse side effects [38–40]. Selective serotonin reuptake inhibitors (SSRIs) are well tolerated and can lead to fewer symptoms of depression at 3 weeks of use [40]. It is one therapy that is thought to work well in all age groups, regardless of comorbid conditions. SSRIs are better tolerated in all populations, compared to tricyclic antidepressants (TCA) [39, 40]. One endpoint found that patients that were started on SSRI early had decreased risk of myocardial infarction and recurrent stroke [40]. In a meta-analysis by Robinson and colleagues, the use of nortriptyline or fluoxetine demonstrated improvement in activities of daily living in poststroke depression compared to patients on placebo [38]. This study also demonstrated that the continued use over 12 weeks resulted in improved cognition in patients with poststroke depression, where the effect could last up to 2 years. Not only do SSRI inhibit reuptake of serotonin, but it was demonstrated in rodent models that SSRIs can decrease infarct volumes, reduced inflammation and increase neuroplasticity by modulating BDNF expression [38]. SSRI was also found to increase neurogenesis in the hippocampus, and improve cerebral blood flow autoregulation which is thought to be related to the upregulation of BDNF [27, 38].

In the fluoxetine in motor recovery of patients with acute ischemic stroke (FLAME) trial, fluoxetine use for 3 months was tested to see if it would improve motor recovery in patients with hemiparesis [41]. This trial was used to assess if the use of fluoxetine would change the Fugl-Meyer motor scale (FMMS) score which is an index used to test motor recovery, with a score of 100 representing complete motor function without any deficit. Two groups were analyzed a fluoxetine dose of 20 mg was the placebo and a 40 mg dose was used as the test treatment. At 3 months there was a significant improvement in motor function among the patients in the treatment arm [41]. At 90 days modified rankin scale (MRS) scores were better in the treatment arm as well. The frequency of depression was lower in the treatment arm when assessed with the MADRS score at 90 days. Even in patients that did not receive intravenous thrombolysis, their FMMS scores at 90 days were higher in the

treatment arm. Patients that were assessed to be depressed at the onset of the trial, based on MADRS score, were excluded from this trial [41]. Pretreatment with SSRI prior to stroke was also an exclusion criterion. Although the FLAME trial seemed to be promising for improving motor function in poststroke patients and reducing depression within that 3-month period, newer studies have shown the use of SSRI prior to stroke, was negatively associated with ambulation poststroke [8].

In a study by Etherton et al., it was found that the use of SSRI prior to an acute stroke was associated with a decrease in discharges back to the patient's home, and increasing need for ambulatory aids [8]. When examining the patients in the two groups: pre-SSRI/spread vs. non antidepressant, there were no significant difference in admission NIHSS or length of hospital stay. The authors thought this may be due to the possibility that patients that were on SSRI or antidepressants prior to admission for their stroke event may have suffered a stroke before or TIA, resulting in a larger stroke burden. Another ischemic event could cause recrudescence of old stroke symptoms due to an increased burden on that area that was receiving adequate blood flow, which could lead to the patient having more needs such as rehabilitation at discharge. Pre-SSRI use was also associated with increased mortality at 30 days, and worse stroke severity in patients with hemorrhagic stroke [8].

Another criticism for the use of SSRIs was due to the increase in the risk of major bleeding or death. In a meta-analysis of 31 case-controlled studies, it was found that SSRI use was associated with risk of major bleeding events, with the increased risk being 41% [40, 42]. This meta-analysis also examined cohort studies that evaluated the use of SSRI vs. non-SSRI in association with major bleeding risk of 36%. The pooled data from the meta-analysis found that SSRI was associated with major bleeding risk with an odds ratio of 1.41. Gastrointestinal bleeding accounted for the majority of these major bleeding events, with a few intracerebral hemorrhage cases [42]. The hypothesis behind the increased bleeding risk is that platelet activity is inhibited by serotonin. This hypothesis is strengthened by the idea that patients taking SSRI have less myocardial infarctions and fewer strokes. The major bleeding risk associated with SSRI are amplified with adjunct use of non-steroidal anti-inflammatory drugs (NSAIDS) [42].

Overall, antidepressants such as SSRI and TCA have been thought to be the best initial treatment for post-stroke depression. SSRI are overall better tolerated in all populations [40]. These antidepressants can help patients combat poststroke depression enough to allow them to participate in rehabilitation efforts. Psychotherapies such as cognitive behavioral therapy (CBT) have been studied to assess if it would be beneficial in the treatment of poststroke depression. Due to the small sample size of the studies, and other limitations there was no real effect seen with CBT [5]. It may be an area of adjunct therapy for patients with severe poststroke depression that need more than pharmaceutical treatment. However, the use of CBT should not delay the initiation of treatment with antidepressants.

10. Depression and stroke rehabilitation

Depression after stroke strongly affects the way patients participate in and respond to rehabilitation. Depression has been linked with decreased participation in rehabilitation efforts which in turn results in more increased morbidity and mortality and decreased quality of life. In a Japanese study that evaluated poststroke depression in patients admitted to a rehabilitation center, their results demonstrated that the patients that were identified as having poststroke depression had less response to rehab and minimal improvement in activities of daily living and functional independence measures [32]. This study found that the level of independence in the activities of daily living at the time of discharge from rehab was related to the severity of poststroke

depression at the time of admission. Poststroke depression had a negative 5-year correlation with the ADL. Psychological factors accounted for a large part of how patients responded to rehabilitation [32]. This study found that patients with post-stroke depression experience feelings of hopelessness and were thus not motivated to participate in rehabilitation. Depression in these patients also leads to listlessness and inattention, which predisposed the patients with poststroke depression to falls. Thus, another reason why mortality is higher in patients with poststroke depression. Falling was also correlated with a decreased ability to manage their ADL [32].

Another study on depression and rehabilitation found that patients with hemiparesis and poststroke depression had 51% less participation in rehabilitation activities [43]. This study showed that any amount of depression after a stroke can affect a patient's quality of life despite the severity of the stroke. This is because each patient has a unique response to acute stress. The perceived stress score is valuable in rehabilitation because it helps practitioners identify which patients are more at risk of developing depression. If they are identified early, treatment of depression can be initiated, and rehabilitation does not need to be adversely affected. Some of the indexes used to measure the quality of life in patients with poststroke depression include the Stroke Specific Quality of Life Scale SS-QOL, stroke impact scale, Barthel index of ADL as well as the multiple depression rating scales [43]. The Scandinavian Stroke Scale (SSS) and Bergman Balance Scale (BBS) are measures used to assess the progress of rehabilitation, which is more encompassing than the Modified Rankin Score [10]. If patients are able to meaningfully participate in rehabilitation, studies have proven that symptoms of depression can improve, and their quality of life scores increase as well [43]. This coupled with the use of antidepressants can help patients with depression poststroke manage their symptoms of depression and improve their functional outcome. It could also help prevent a subsequent ischemic event [43].

Depression has also been found to be a risk factor for stroke [44]. This has been demonstrated even when controlling for confounders like tobacco use or substance use. Patients with psychosocial stressors put patients at an increased risk of stroke [11, 12, 44, 45]. Not only do these patients have an increased risk of hypertension, and diabetes, but also have an increased prevalence of tobacco use and substance use that also put them at greater risk for an ischemic stroke [44]. A meta-analysis by Dong and colleagues, looked at 17 prospective studies that included greater than 200,000 patients [45]. Of this subset of patients, greater than 6000 had a positive association between depression and a second stroke. A depressed patient had 34% higher risk of developing stroke, even when age and sex were controlled for [45]. Thus, stroke and depression may be a part of a vicious cycle where a stroke results in depression and then depression results in another stroke. This process repeats and, in turn, hinders recovery and rehabilitation. Thus, proving again why it is important to diagnose depression after a stroke, and treat it adequately.

11. Poststroke depression and effect on the health care system

Poststroke depression can increase the burden on the healthcare system. In two literature reviews the effect of depression after a stroke was assessed by looking at large veteran populations [46, 47]. These studies demonstrated that patients that suffered from poststroke depression had on average a longer hospital stay, as well as increased outpatient and inpatient physician visits over 1 year. These patients also had a higher likelihood of having significant deficits such as dysphagia after their stroke, and complex comorbidities that required frequent hospital visits, or prolonged stays in nursing facilities/rehabilitation centers [47]. They were also noted to have higher risk of a subsequent stroke within 1 year of their first stroke, and readmissions for complications related to their strokes such as aspiration

pneumonia, or falls [47]. In Husaini and colleague's analysis of 17,010 patients from Tennessee, their study demonstrated that patients with stroke and depression had higher average health care costs than patients with only stroke, or stroke with another comorbid psychiatric disorder, even while controlling for age, sex and race [48]. On average stroke patients with depression had a healthcare cost of $77,864, compared to $47,790 in patients with stroke only these costs are due to increase use of diagnostic tests, increased pharmacologic interventions, and addition therapist and physician consultations [47, 48]. If poststroke depression could be identified early, and treated it could reduce the total cost to the patient, and could decrease the overall healthcare burden (**Figure 1**).
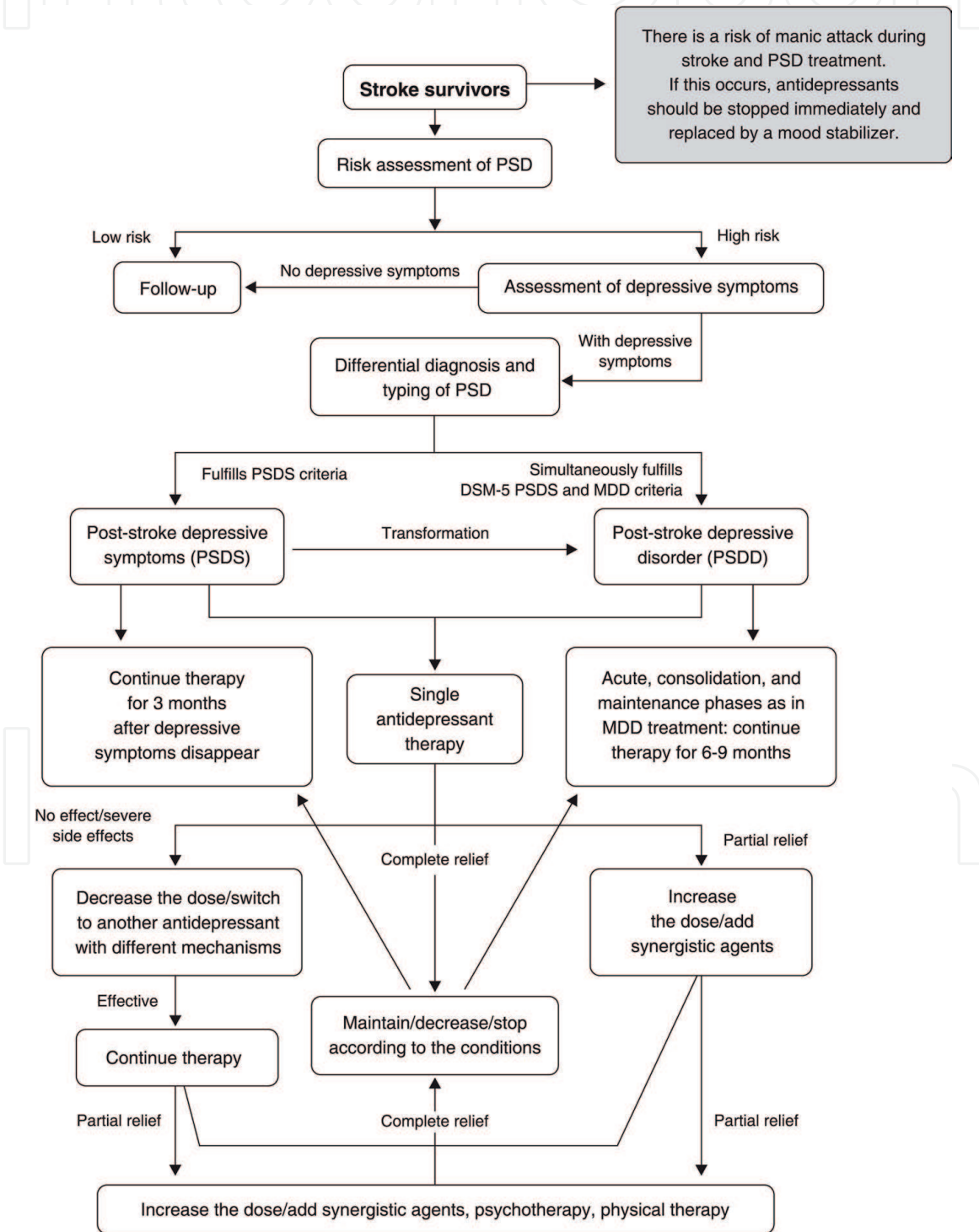

Figure 1.
The diagnostic and treatment procedures of PSD. MDD = major depressive disorder; PSD = poststroke depression [49].

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12. Conclusion

Depression and stroke have a bidirectional relationship where one acts as a risk for the other. Poststroke depression is an area of study that has evolved over the years. New studies on its etiology have been discovered, and continued research efforts are providing more insight on the questions we still have, such as the associations of lesion location, the role of inflammation, neuroplasticity, and even genetics. Some patients are more at risk than others for developing poststroke depression, but the main goal is detection, management, and rehabilitation. Detecting poststroke depression is important, so treatment can be initiated as soon as possible, thus reducing morbidity, mortality, and assisting these patients with participating in rehabilitation efforts. Rehabilitation not only improves function in these patients, but also has beneficial effects on depression as well. If patients can effectively partake in rehabilitation efforts, their quality of life scores have been shown to improve (with quality of life being a measure for depression in these patients). Improvements in perceived quality of life can have downstream effects resulting in a reduction of readmissions to the hospital, and outpatient visits, and thus a reduction in the healthcare burden caused by this disease process. If depression can be effectively managed, patients will be more likely to have meaningful participation in poststroke rehabilitation, and reduce the risk of morbidity and mortality associated with their stroke.

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References

[1] CDC. Stroke facts [Internet]. 2019. Available from: https://www.cdc.gov/stroke/facts.htm [Accessed: 02 April 2019]

[2] Johns Hopkins Medicine. Effects of stroke [Internet]. 2019. Available from: https://www.hopkinsmedicine.org/health/conditions-and-diseases/stroke/effects-of-stroke [Accessed: 20 March 2019]

[3] Bartoli F, Lillia N, Lax A, Crocamo C, Mantero V, Carra G, et al. Depression after stroke and risk of mortality: A systematic review and meta-analysis. Stroke Research and Treatment. Article ID 862978. 2013;**2013**:11. DOI: 10.1155/2013/862978. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3606772/ [Accessed: 12 March 2019]

[4] National Stroke Association. Depression [Internet]. 2019. Available from: https://www.stroke.org/we-can-help/survivors/stroke-recovery/post-stroke-conditions/emotional/depression/ [Accessed: 03 April 2019]

[5] Paolucci S. Epidemiology and treatment of post-stroke depression. Neuropsychiatric Disease and Treatment. 2008;**4**(1):145-154. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2515899/ [Accessed: 20 March 2019]

[6] Alajbegovic A, Djelilovic-Vranic J, Alajbegovic S, Nakicevic A, Todorovic L, Tiric-Campara M. Post stroke depression. Medical Archives – Journal of the Academy of Medical Sciences in Bosnia and Herzegovina. 2014;**68**(1):47-50. DOI: 10.5455/medarh.2014.68.47-50. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4272477/ [Accessed: 15 March 2019

[7] Oni O, Olagunju A, Olisah V, Aina O, Ojini F. Post-stroke depression: Prevalence, associated factors and impact on quality of life among outpatients in a Nigerian hospital. South African Journal or Psychiatry. 2018;**24**. DOI: 10.4102/sajpsychiatry.v24i0.1058. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6138133/ [Accessed: 22 March 2019]

[8] Etherton M, Siddiqui K, Schwamm L. Prestroke selective serotonin reuptake inhibitor use and functional outcomes after ischemic stroke. Stroke and Vascular Neurology. 2017;**3**(1). DOI: 10.1136/svn-2017-000119. Available from: https://svn.bmj.com/content/3/1/9 [Accessed: 30 March 2019]

[9] Robinson RG, Bolduc PL, Price TR. Two-year longitudinal study of poststroke mood disorders: Diagnosis and outcome at one and two years. Stroke. 1987;**18**(5):837-843. Available from: https://www.ncbi.nlm.nih.gov/pubmed/3629640 [Accessed: 11 March 2019]

[10] Srivastava A, Taly AB, Guptra A, Murali T. Post-stroke depression: Prevalence ad relationship with disability in chronic stroke survivors. Annals of Indian Academy of Neurology. 2010;**13**(2)123-127. DOI: 10.4103/0972-2327.64643. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2924510/. [Accessed: 01 April 2019]

[11] McCarthy M, Sucharew H, Alwell K, Moomaw C, Woo D, et al. Age, subjective stress, and depression after ischemic stroke. Journal of Behavioral Medicine. 2015;**39**(1):55-64. DOI: 10.1007/s10865-015-9663-0. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4724284/ [Accessed: 30 March 2019]

[12] Mazure CM, Weinberger AH, Pittman B, Sibon I, Swendsen J. Gender and stress in predicting

depressive symptoms following stroke. Cerebrovascular Disease. 2014;**38**: 240-246. DOI: 10.1159/000365838. Available from: https://www.karger. com/Article/FullText/365838 [Accessed: 01 April 2019]

[13] Paradiso S, Robinson RG. Gender differences in poststroke depression. The Journal of Neuropsychiatry and Clinical Neurosciences. 1998;**10**:41-47. DOI: 10.1176/jnp.10.1.41. Available from: https://neuro.psychiatryonline.org/doi/ pdf/10.1176/jnp.10.1.41 [Accessed: 29 March 2019]

[14] Poynter B, Shuman M, Diaz-Granados N, Kapral M, Grace S, Stewart D. Sex differences in the prevalence of post-stroke depression: A systematic review. Psychosomatics. 2009;**50**(6):563-569. DOI: 10.1016/ S0033-3182(09)70857-6. Available from: https://www.ncbi.nlm.nih.gov/ pubmed/19996226 [Accessed: 28 March 2019]

[15] Wang Z, Zhu M, Su Z, Guan B, Wang A, Wang Y, et al. Post-stroke depression: Different characteristics based on follow-up stage and gender-a cohort perspective study from Mainland China. Neurological Research. 2017;**39**(11):996-1005. DOI: 10.1080/01616412.2017.1364514. Available from: https://www.ncbi.nlm. nih.gov/pubmed/28828931 [Accessed: 26 March 2019]

[16] Backhouse E, Mchutchison C, Cvoro V, Shenkin S, Wardlaw J, Priller J. Cognitive ability, education and socioeconomic status in childhood and risk of post-stroke depression in later life: A systematic review and meta-analysis. PLOS One. 2018;**13**(7). DOI: 10.1371/journal.pone.0200525. Available from: https://www.ncbi.nlm.nih.gov/ pmc/articles/PMC6047794/ [Accessed: 19 March 2019]

[17] Zhang Y, He JR, Liang HB, et al. Diabetes mellitus is associated with late-onset post-stroke depression. Journal of Affective Disrorders. 2017;**221**:222-226. DOI: 10.1016/j.jad.2017.06.045. Available from: https://www.ncbi.nlm. nih.gov/pubmed/28654846 [Accessed: 23 March 2019]

[18] Mitchell AJ, Sheth B, Gill J, Yadegarfar M, Stubbs B, Yadegarfar M, Meader N. Prevalence and predictors of post stroke mood disorders: A meta-analysis and meta-regression of depression, anxiety and adjustment disorder. General Hospital Psychiatry. 2017;**47**:48-60. DOI: 10.1016/j. genhosppsych.2017.04.001. Available from: https://www-sciencedirect-com. ezproxy.uthsc.edu/science/article/pii/ S0163834317301433?via%3Dihub . [Accessed: 28 March 2019]

[19] Gozzi SA, Wood AG, Chen J, Vaddadi K, Phan TG. Imaging predictors of poststroke depression: methodological factors in voxel-based analysis. British Medical Journal. 2014;**4**(7). DOI: 10.1136/ bmjopen-2014-004948. Available from: https://www.ncbi.nlm.nih.gov/pmc/ articles/PMC4091263/ [Accessed 28 March 2019]

[20] Pasi M, VanUden I, Tuladhar AM, de Leeuw FE, Pantoni L. White matter microstructural damage on diffusion tensor imaging in cerebral small vessel disease clinical consequences. Stroke. 2016;**47**(6). DOI: 10.1161/ STROKEAHA.115.012065. Available from: https://www.ahajournals.org/ doi/10.1161/STROKEAHA.115.012065. [Accessed: 28 March 2019]

[21] Villa RF, Ferrari F, Moretti A. Post-stroke depression: Mechanisms and pharmacological treatment. Pharmacology & Therapeutics. 2018;**184**:131-144. DOI: 10.1016/j. pharmthera.2017.11.005. Available from: https://www-sciencedirect-com. ezproxy.uthsc.edu/science/article/ pii/S0163725817302899?via%3Dihub [Accessed: 28 March 2019]

[22] Nickel A, Thomalla G. Post-stroke depression: Impact of lesion location and methodological limitations—A topical review. Frontiers in Neurology. 2017;**8**:498. DOI: 10.3389/fneur.2017.00498. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5613107/ [Accessed: 16 March 2019]

[23] Jiao J, Cheng C, Ma Y, Huang J, Dai M, Jiang C, et al. Association between inflammatory cytokines and the risk of post-stroke depression, and the effect of depression on outcomes of patients with ischemic stroke in a 2-year prospective study. Experimental and Therapeutic Medicine. 2016(3):1591-1598. DOI: 10.3892/etm.2016.3494. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4998048/ [Accessed: 24 March 2019]

[24] Levada O, Troyan A. Poststroke depression biomarkers: A narrative review. Frontiers in Neurology. 2018;**9**:577. DOI: 10.3389/fneur.2018.00577. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6055004/ [Accessed: 03 April 2019]

[25] Guo WY, Zhang ZH, Mu JL, Liu D, Zhao L, Yao ZY, et al. Relationship between 5-HTTLPR polymorphism and post-stroke depression. Genetics and Molecular Research. 2016;**15**(1):1-6. DOI: 10.4238/gmr.15017460. Available from: http://www.funpecrp.com.br/gmr/year2016/vol15-1/pdf/gmr7460.pdf [Accessed: 17 March 2019]

[26] Zhao Q, Guo WY, Yang D, Yang T, Meng X. Serotonin transporter gene 5-HTTLPR polymorphism as a protective factor against the progression of post stroke depression. Molecular Neurobiology. 2016;**53**:1699-1705. DOI: 10.1007/s12035-015-9120-7. Available from: https://link-springer-com.ezproxy.uthsc.edu/content/pdf/10.1007%2Fs12035-015-9120-7.pdf. [Accessed: 01 April 2019]

[27] Lobinoux I, Kronenberg G, Endres M, Schumann-Bard P, Freret T, Filikowski R, et al. Post-stroke depression: Mechanisms, translation and therapy. Journal of Cellular and Molecular Medicine. 2012;**16**(9):1961-1969. DOI: 10.1111/j.1582-4934.2012.01555.x. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3822966/. [Accessed 01 April 2019]

[28] Kohen R, Cain KC, Mitchell PH, Becker K, Buzaitis A, Millard SP, et al. Association of serotonin transporter gene polymorphisms with poststroke depression. Archives of General Psychiatry. 2008;**65**(11):1296-1302. DOI: 10.1001/archpsyc.65.11.1296. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2679964/. [Accessed: 01 April 2019]

[29] Kelly-Hayes M. Influence of age and health behaviors on stroke risk: Lessons from longitudinal studies. Journal of American Geriatric Society. 2010;**58**:325-328. DOI: 10.1111/j.1532-5415.2010.02915.x. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3006180/ [Accessed: 07 April 2019]

[30] Saposnik G, Cote R, Phillips S, Gubitz G, Bayer N, Minuk J, et al. SORCan Working Group. Stroke outcome in those over 80. Stroke. 2008;**39**(8). DOI: 10.1161/STROKEAHA.107.511402. Available from: https://www.ahajournals.org/doi/10.1161/strokeaha.107.511402 [Accessed: 04 April 2019]

[31] Alexopoulos G, Bruce M, Silbersweig D, Kalayam B, Stern E. Vascular depression: A new view of late-onset depression. Dialogues in Clinical Neuroscience. Sep 1999;**1**(2):68-80. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3181568/ [Accessed: 22 March 2019]

[32] Tsuchiya K, Fujita T, Tozato F, Sato D, Midorikawa M, Mariyama Y

et al. Post-stroke depression inhibits improvement in activities of daily living in patients in a convalescent rehabilitation ward. Journal of Physical Therapy Science. 2016;**28**(8):2253-2259. DOI: 10.1589/jpts.28.2253. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5011572/ [Accessed: 01 April 2019]

[33] Alexopoulos GS, Meyers BS, Young RC, Kakuma T, Silbersweig D, Charlson M. Clinically defined vascular depression. American Journal of Psychiatry. 1997;(4):562-565. DOI: 10.1176/ajp.154.4.562. Available from: https://www.ncbi.nlm.nih.gov/pubmed/9090349 [Accessed: 21 March 2019]

[34] Gupta R. Hemicraniectomy in malignant middle cerebral artery infarction. Stroke. 2011;**42**(2). DOI: 10.1161/STROKEAHA.110.605642. Available at: https://www.ahajournals.org/doi/10.1161/STROKEAHA.110.605642. [Accessed: 01 April 2019]

[35] Ostwald, S, Turner, I, Bernal, M, Cron, S, Godwin, K. Stress experienced by stroke survivors and spousal caregivers during the first year after discharge from inpatient rehabilitation. Top Stroke Rehabilitation. 2009;**16**(2):93-104. DOI: 10.1310/tsr1602-93. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2748854/ [Accessed: 02 April 2019]

[36] Ilut S, Stan A, Blesneag A, Vacaras V, Fonforeanu VS. Factors that influence the severity of post stroke depression. Journal of Medicine and Life;**10**(3):167-171. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5652262/. [Accessed: 01 April 2019]

[37] Laures-Gore J, Farina M, Moore E, Russell S. Stress and depression scales in aphasia: relation between the aphasia depression rating scale, stroke aphasia depression questionnaire-10, and the perceived stress scale. Top Stroke Rehabilitation. 2016;**24**(2):114-118. DOI: 10.1080/10749357.2016.1198528. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27348232

[38] Robinson R, Jorge R. Post-stroke depression: A review. American Journal of Psychiatry. 2015;**173**(3):221-231. DOI: 10.1176/appi.ajp.2015.15030363. Available from: https://ajp.psychiatryonline.org/doi/10.1176/appi.ajp.2015.15030363 [Accessed: 14 March 2019]

[39] Bartoli F, Brita C, Crocamo C, Clerici M, Carra G. Early post-stroke depression and mortality: Meta-analysis and meta-regression. Frontiers in Psychiatry. 2018;**9**:530. DOI: 10.3389/fpsyt.2018.00530. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6221899 [Accessed 25 March 2019]

[40] Mortense J, Larsson H, Johnsen S, Andersen G. 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**(2):420-426. DOI: 10.1161/STROKEAHA.112.674242. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23306326 [Accessed: 17 March 2019]

[41] Chollet F, Tardy J, Albucher J, Thalamas C, Berard E, et al. Fluoxetine for motor recovery after acute ischemic stroke (FLAME): A randomized placebo-controlled trial. Lancet Neurology. 2011;**10**(2):123-130. DOI: 10.1016/S1474-4422(10)70314-8. Available from: https://www.ncbi.nlm.nih.gov/pubmed/21216670 [Accessed: 29 March 2019]

[42] Laporte S, Chapelle C, Caillet P, Beyens M, Bellet F, Delavenne X, et al. Bleeding risk under selective serotonin reuptake inhibitor (SSRI)

antidepressants: A meta-analysis of observational studies. Pharmacological Research. 2017;**118**:19-32. DOI: 10.1016/j.phrs.2016.08.017. Available from: https://www.sciencedirect.com/science/article/abs/pii/S1043661816307769 [Accessed: 24 March 2019]

[43] Micaela Silva S, Carlos Ferrari Corrêa J, da Silva Mello T, Rodrigues Ferreira R, Fernanda da Costa Silva P, Ishida Corrêa F. Impact of depression following a stroke on the participation component of the international classification of functioning, disability and health. Disability and Rehabilitation [s. l.]. 2016;**38**(18):1830-1835. Available from: http://search.ebscohost.com.ezproxy.uthsc.edu/login.aspx?direct=true&db=cmedm&AN=26728302&site=eds-live [cited 1 April 2019]

[44] Pan A, Sun Q, Okereke O, Rexrode, KM, Hu FB. Depression and the risk of stroke morbidity and mortality: A meta-analysis and systematic review. The Journal of the American Medical Association. 2011;**306**(11):1241-1249. DOI: 10.1001/jama.2011.1282. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3242806/ [Accessed: 05 April 2019]

[45] Dong J, Zhang YH, Tong J, Qin LQ. Depression and risk of stroke. Stroke. 2011;**43**(1). DOI: 10.1161/STROKEAHA.111.630871. Available at: https://www.ahajournals.org/doi/10.1161/STROKEAHA.111.630871. [Accessed: 02 April 2019]

[46] Towfighi, A, Ovbiagele, B, Husseini, N, et al. Poststroke depression: A scientific statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2016;**48**(2). DOI: 10.1161/STR.0000000000000113. Available from: https://www.ahajournals.org/doi/10.1161/STR.0000000000000113 [Accessed: 18 March 2019]

[47] Jia H, Damush TM, Qin H, et al. The impact of poststroke depression on healthcare use by veterans with acute stroke. Stroke. 2006;**37**(11). DOI: 10.1161/01.STR.0000244783.53274.a4. [Accessed: 23 April 2019]

[48] Husaini B, Levine R, Sharp L, et al. Depression increases stroke hospitalization cost: An analysis of 17010 stroke patients in 2008 by race and gender. Stroke Research and Treatment. 2013;**2013**:7. DOI: 10.1155/2013/846732. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3608101/ [Accessed: 23 April 2019]

[49] Zhao FY, Yue YY, Li L, Lang SY, Wang MW, et al. Clinical practice guidelines for post stroke depression in China. Brazilian Journal of Psychiatry. 2018;**40**(3). DOI: 10.1590/1516-4446-2017-2343. Available from: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1516-44462018000300325 [Accessed: 04 April 2019]