Recent Advances in Poststroke Depression

Haresh M. Tharwani, MD, Pavan Yerramsetty, MD, Paolo Mannelli, MD, Ashwin Patkar, MD, and Prakash Masand, MD

Corresponding author
Haresh M. Tharwani, MD
Duke Psychiatry Specialty Clinic, 2000 Regency Parkway, Suite 280, Cary, NC 27518, USA.
E-mail: tharw001@mc.duke.edu

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Depression is the most common psychiatric complication after stroke. Its prevalence varies from 20% to 80%, and it is underdiagnosed and undertreated. It has significant impact on rehabilitation, motor recovery, activities of daily living, social and interpersonal life, and mortality. Several studies have shown that biological and psychosocial factors play significant roles in the development of this disabling disease. Recent research shows that neurochemical processes also may play some role in the pathophysiology of this condition. Several trials have shown evidence that the older, as well as newer antidepressants and psychostimulants may reduce/prevent depressive symptoms after stroke. At this point there are no clear guidelines available to choose safe and effective treatments. Drugs are selected based on their efficacy and side effect profile in these patients. More research is needed to understand the pathophysiology of depression after stroke. There also is a need for more randomized clinical trials to better treat patients with this condition.

Introduction

Depression (major and minor) is the most common psychiatric complication after an individual sustains a clinically apparent stroke (as evidenced by neuroimaging) [1]. Even with its high prevalence, it is underdiagnosed and undertreated. Poststroke depression (PSD) has been associated with increased distress, disability, poor rehabilitation, morbidity, mortality, and suicidal thoughts [1]. Do the negative outcomes associated with stroke lead to the development of PSD in these patients, or does the depression in the poststroke period cause these negative outcomes? The authors note that studying this disease may in fact give us significant insight into the pathophysiology of all forms of depression in general.

Much of the literature on PSD notes a significantly increased mortality associated with PSD (in comparison to those poststroke patients without depression) [2,3,4•,5,6]. PSD seems to be associated with an increase in inpatient and outpatient medical utilization over the long term [2]. PSD has been studied for more than 100 years, but we still face several challenges to understand its precise pathophysiology and effective pharmacotherapy.

Epidemiology

Over the past several years, various researchers have attempted, with very little agreement, to quantify the prevalence of PSD. The prevalence across these varied studies ranges from 20% to 80% [7,8], depending greatly upon the tools of assessment, the size and diversity of the population studied, prior personal history of depression, and the evaluation time after stroke, as well as varying diagnostic criteria of depression itself. Conservative estimates tended to be very specific in using *DSM IV* criteria for major and minor depressive disorders, often excluding severely disabled (yet potentially depressed) patients with aphasia, anosognosia, cognitive impairment, or delirium [9–11]. These studies also often focused on depression diagnoses at only one specific time period poststroke. On the other hand, studies with higher levels of prevalence tried to assess depression in a wide range of patients, in effect including some patients unable to verbally describe their depression [2,8,9]. Instead, these studies often focused on such global depressive behaviors as crying, included a disproportionate number of hospitalized patients (who have greater disability), and did not correct for past depressive history of the stroke patients [3,7,12]. Given that there are approximately 600,000 strokes per year in the United States, this means a sizeable number of Americans (not even considering even larger population counts around the world) are suffering with PSD each year [1]. In any epidemiologic study of a disease, it also is important to examine the risk factors that predispose a stroke patient to PSD. Ouimet et al. [12], in a meta-analysis of 25 articles describing the psychosocial risk factors for PSD, noted that a history of depression, personal psychiatric history, dysphasia, functional impairment, living alone, and poststroke social isolation all correlated with a higher probability of a PSD diagnosis.

Pathophysiology of PSD

Biological hypothesis

Stroke is one of the few diseases considered by *DSM IV* to directly cause depression [13]. Searching for such a biological cause has been a primary driving force in PSD research. One group of researchers, led by Robinson et al. [4•,14], has proposed a primary biological mechanism causing PSD whereby ischemic insults directly affect neural circuits involved in mood regulation. More specifically, one researcher noted that the disruption of frontal-subcortical circuits after stroke led to a depletion in cortical biogenic amines [8]. This biological mechanism has been supported by a number of findings. First, as early as 1977, scientists had noticed that stroke survivors had a higher prevalence of major depression compared with physically ill patients with a similar disability level [1]. This seemed to suggest that some biological effect of the stroke itself was causing the depression, rather than the level of distress/disability being caused by the particular illness.

Over the past 20 years, a plethora of studies have also supported or challenged the specific lesion hypothesis first posited by Robinson et al. [14] in 1981, which has sought to find specific stroke-related lesions that cause PSD [14–17]. Initial support for this argument came from several small studies noting a correlation between PSD and left anterior cortical and left basal ganglia lesions. More specifically, notes this group, PSD severity was correlated with the "proximity of the anterior border of the lesion on computed tomography scan (CT) to the frontal pole in the left hemisphere but not in the right hemisphere" [18]. However, these bold claims have not come without significant criticism, particularly from Carson et al. [17] (described subsequently). Another piece of supportive evidence for the biological understanding of PSD centers around the presence of depression in the context of anosognosia or silent infarcts. If PSD is a result of a psychological response to the stroke itself, the main argument of the advocates of psychological hypothesis, then how can we explain the presence of clinical depression in patients who, due to their stroke, are not cognitively aware of their disability? In the case of patients developing depression after a silent infarct (not symptomatic, but verified by MRI), a condition known as vascular depression, there is a similar issue of the patient's lack of awareness of his or her own condition. Although it is outside the scope of this paper, there is an ever-growing literature on vascular depression that notes a similar process as described previously of a disruption of the mood-regulating neural circuits by specific ischemic lesions [8,19,20].

Psychosocial hypothesis

Several studies in the late 1990s seem to refute the earlier proposed increase in depression's prevalence after stroke as compared with conditions with similar disability [1]. In a similar light, Carson et al. [17] performed a meta-analysis of 48 studies discussing the relationship between PSD and lesion location. They noted that "a patient's risk of depression is not related to where the cerebral lesion is located" [17].

A unique argument for the psychological basis of PSD put forth by these researchers relates to the similarity of symptoms and treatment response profiles between functional depression and PSD. Their argument is that if PSD is caused by specific brain lesions and the subsequent disruption of neural circuitry, it should have a significantly different symptom and treatment profile than functional depression. This is further strengthened by their claim that the symptom profile of PSD is also significantly different than that of vascular depression, a condition that the biological camp had linked etiologically with PSD [1].

These researchers have noted that many of the risk factors for PSD are also risk factors for more traditional functional depression. As described earlier in this paper, severity of disability (regardless of whether that disability is a stroke) is one of the most important predictors for the development of depression. Summarizing the middle ground position held by many present-day PSD researchers, Whyte and Mulsant [1] state that, "Any particular stroke survivor may have a poststroke depression that is purely biological in origin, or purely psychosocial, or truly multifactorial. Overall, most poststroke depressions appear to be multifactorial in origin and consistent with the biopsychosocial model of psychiatric illness."

Lastly, there is some discussion of potential psychosocial or even genetic vulnerabilities in certain populations that might predispose them to depression after a stroke.

Current and Future Research Directions

Much of the PSD research in the last year has focused on the composition of the neurochemical environment after stroke. One study by Craft and DeVries [21••] has hypothesized that pathophysiologic processes happening acutely after stroke significantly contribute to the etiology of PSD. Noting that stroke is associated with a dysregulation of the hypothalamic-pituitary-adrenal axis and neuroinflammation, they sought to flesh out the implications of this unique chemical environment on a patient's psychological health through the use of animal models of stroke progression. Although rats do not express "depression" in any observable way, researchers have for a long time recognized that anhedonia is an observable behavior in these animals. Given a choice between sucrose solution and water, rats will preferentially choose sucrose solution. Anhedonic rats—in this case rats with induced strokes—will consume less sucrose solution than their control counterparts. After designing elaborate experiments using glucocorticoid and interleukin (IL) agonists to gauge anhedonia in their rats, Craft and DeVries [21••] concluded that IL-1 (but not glucocorticoids) mediates the poststroke development of anhedonia. Treatment of these rats with IL-1 receptor antagonist restored sucrose con-

sumption among stroke rats but did not alter the drinking behavior of the nonstroke rats.

Building on this and other studies of the role of cytokines in the development of mood disorders, Spalletta et al. [22] have proposed a "cytokine hypothesis" that seeks to explain the pathophysiology of PSD. They begin by citing several studies that have noted significantly lower concentrations of 5-hydroxy indoleacetic acid, a serotonin metabolite in the cerebrospinal fluid, in PSD patients compared with similarly matched nondepressed stroke patients. Next they noted studies showing that various proinflammatory cytokines (IL-1, IL-6, IL-18, and tumor necrosis factor-α [TNF-α]) were consistently found in increasing amounts in poststroke patients. Echoing the work of Craft and DeVries [21••] described previously, Spalletta et al. [22] continued by emphasizing that administration of proinflammatory cytokines such as IL-1β and TNF-α can induce depression-like behavior in rats, and that increased levels of such cytokines can be found in patients with dysthymia or major depressive disorder. These particular cytokines also have been shown to upregulate the enzyme indoleamine 2,3-dioxygenase (IDO), which catalyzes the increased metabolism of tryptophan, thereby limiting the supply of tryptophan needed for serotonin synthesis. Their resulting "cytokine hypothesis" of PSD is developed as follows: the increased production of proinflammatory cytokines (IL-1β, IL-18, and TNF-α) resulting from stroke leads to an exaggerated inflammatory state, which then activates in a widespread fashion the IDO enzyme, leading ultimately to a widespread decrease in the production of serotonin. As evidenced by the trials with selective serotonin reuptake inhibitors (SSRIs) in the treatment of depression, enhancing the chronically low levels of serotonin (as in the poststroke state) can lead to the eradication of depressive symptoms in some patients.

A final intriguing development in the etiology of PSD has emerged from genome studies of stroke patients with major depression. Building on the middle ground approach's hypothesis of certain genetic predispositions to PSD, Ramasubbu et al. [23] examined variations of serotonin transporter-linked promoter region (5-HTTLPR) functional polymorphism in 26 stroke patients with major depression and in 25 nondepressed stroke patients of similar genetic backgrounds. This particular polymorphism was chosen as a possible candidate gene for susceptibility to PSD because the serotonin transporter gene regulates 5-HTT availability, which is vitally important in maintaining the homeostasis of serotonin function. They concluded that "the 5-HTTLPR genotype is associated with the expression of major depression after stroke, and the liability is significantly increased when the S-allele [short allele] is in the homozygous state. Conversely the homozygosity of L-allele [long allele] provides a protective effect" [23].

The short allele may be particularly important for one of two reasons, they continue. First, the presence of this allele may result in decreased expression of 5-HTT, ultimately resulting in the reduction of 5-HT reuptake and 5-HT in general. Second, the short alleles may be more vulnerable than their long counterparts to stress reaction in response to stroke deficits, ultimately resulting in higher rates of PSD.

Evidence-based pharmacotherapy of PSD

Several studies to examine the role of pharmacotherapies and psychosocial interventions have been performed. We review and focus on published clinical trials for the treatment/prevention of PSD to date. For better understanding of the studies and their results, we present data in table form (Tables 1 and 2) and briefly discuss them.

Most of the antidepressants have been studied in treatment and prevention of PSD. Among the tricyclic antidepressant class, nortriptyline is the best-studied drug. Nortriptyline was more efficacious in preventing depression than fluoxetine and placebo in three different studies, but it was less well tolerated than fluoxetine [24–27]. Imipramine and desipramine showed a 46.5% improvement in depressive symptoms in a noncontrolled study [28].

Fluoxetine is the first- and most-studied SSRI for both treating and preventing PSD, although it has somewhat questionable efficacy. Two separate fluoxetine treatment outcome studies showed efficacy in reduction of depressive symptoms at 18 months but not within the first 3 months. A separate study didn't show a difference between fluoxetine and placebo [25,29–31]. One study looked at preventing PSD (fluoxetine vs nortriptyline) and found that both drugs prevented depressive symptoms compared with placebo. One study looked at mortality rate with fluoxetine and nortriptyline, and both showed decreased mortality compared with placebo [27]. Sertraline is the second-most studied SSRI in both treatment and prevention of PSD. Two separate sertraline studies did not differentiate from placebo [32,33]. Of two separate prevention studies, one study did not differentiate from placebo, but the other prevented depressive symptoms compared with placebo [34]. Citalopram (the most selective SSRI) is the third SSRI studied in PSD. Two double-blind (citalopram vs placebo; citalopram vs reboxetine) studies have shown that it is efficacious in improving depressive symptoms on Beck Depression Inventory [35,36]. It has not been studied in the prevention of PSD. To the best of our knowledge, the other three SSRIs (paroxetine, fluvoxamine, and escitalopram) have not been studied for either treatment or prevention of PSD. Trazodone, an old antidepressant with potential for orthostasis, has been studied in one treatment and one prevention study. It was not efficacious in reducing symptoms, but patients had greater improvement in activities of daily living. Trazodone was better than placebo in preventing PSD in one study. Reboxetine, a norepinephrine reuptake inhibitor not available in the United States, was compared with citalopram and showed

Table 1. TCAs and SSRIs clinical trials

Authors	Site	Objective	Study design	Number of subjects		Primary outcome	Additional scales	Medication, *mg/d*	Duration, *weeks*	Primary outcome results
				Active	Placebo					
Lipsey et al. [24]	US	Treatment	Randomized, double-blind, placebo-controlled	17	22	*DSM III*	HDRS, ZDS	Nortriptyline, 20–100	4–6	Nortriptyline > placebo
Lauritzen et al. [28]	Denmark	Treatment	Randomized, double-blind	10	No placebo	HDRS	Melancholia scale	Desipramine, 66 (mean)	6	Imipramine: 46.5% improvement in HDRS scores; desipramine: 35%; difference between 2 treatments insignificant
Lauritzen et al. [28]	Denmark	Treatment		10	No placebo	HDRS	Melancholia scale	Imipramine, 27 (mean)	6	
Robinson et al. [25]	US/Argentina	Prevention	Randomized, double-blind, placebo-controlled	17	8	HDRS		Fluoxetine, 10–40	12	Fluoxetine = placebo
Robinson et al. [25]	US/Argentina	Prevention		15	8	HDRS		Nortriptyline, 25–100	12	Nortriptyline > fluoxetine and placebo
Narushima et al. [26]	US	Prevention	Randomized, double-blind, placebo-controlled	15	16	*DSM IV*	HDRS	Nortriptyline, 25–100	21 months	Nortriptyline and fluoxetine both effective in preventing depression
Narushima et al. [26]	US	Prevention		17	16	*DSM IV*	HDRS	Fluoxetine, 10–40	21 months	
Jorge et al. [27]	US	Prevention	Randomized, double-blind, placebo-controlled	40	33	HDRS	*DSM IV*	Fluoxetine, 10–40	12	Patients receiving antidepressants had lower mortality than those taking placebo
Jorge et al. [27]	US	Prevention		31	33	HDRS	*DSM IV*	Nortriptyline, 25–100	12	

HDRS—Hamilton Depression Rating Scale; SSRI—selective serotonin reuptake inhibitor; TCA—tricyclic antidepressant; ZDS—Zung Depression Scale.

Table 2. Atypical antidepressants clinical trials

Authors	Site	Objective	Study design	Number of subjects		Primary outcome	Additional scales	Medication, *mg/d*	Duration, *weeks*	Primary outcome results
				Active	Placebo					
Reding et al. [41]	US	Treatment/ prevention	Randomized, double-blind, placebo-controlled	14	8	Clinical diagnosis	ZDS	Trazodone HCl, 50–200	4	No difference between trazodone and placebo; greater improvement in ADL scores with trazodone
Roh et al. [42]	Korea	Prevention	Randomized, double-blind, placebo-controlled	32	33	Physician assessment		Indeloxazine, 20	12	Indeloxazine > placebo in improving emotional disturbance
Raffaele et al. [43]	Italy	Prevention	Randomized, placebo-controlled	11	11	ZDS		Trazodone HCl, 300	45 days	Trazodone > placebo in ZDS scores
Dahmen et al. [37]	Germany	Treatment	Open-label, uncontrolled	12	Not available	HDRS	MADRS	Venlafaxine, 150	5	Positive treatment response (decreased HDRS) observed in 10 of 12 patients
Palomaki et al. [44]	Finland	Prevention	Randomized, double-blind, placebo-controlled	51	49	*DSM III-R*	HDRS, BDI, CGI	Mianserin, 10–60	52	No difference between mianserin and placebo
Kimura et al. [38]	Japan	Treatment	Open-label, uncontrolled	12	Not available	HDRS		Milnacipran, 60–150	6	70% of patients were in remission at end of study
Rampello et al. [45]	Italy	Treatment	Randomized, double-blind, placebo-controlled	16	15	HDRS	BDI	Reboxetine, 8	16	Reboxetine > placebo in HDRS and BDI scores
Niedermaier et al. [39]	Germany	Treatment/ prevention	Open-label, randomized	35	35	*DSM IV*		Mirtazapine, 30	52	40% of placebo patients developed PSD vs only 5.7% of mirtazapine patients

ADL—Amsterdam Depression List; BDI—Beck Depression Inventory; CGI—Clinical Global Impression scale; HCl—hydrochloride; HDRS—Hamilton Depression Rating Scale; MADRS—Montgomery-Asberg Depression Rating Scale; PSD—poststroke depression; ZDS—Zung Depression Scale.

efficacy in reducing depressive symptoms in patients who had hypoactive (retarded) PSD [36]. To date, reboxetine has not been studied in the prevention of PSD.

Venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SNRI), was efficacious in reducing depressive symptoms in one study. It has not been studied in the prevention of PSD [37]. An open-label treatment outcome study with milnacipran showed a 70% remission rate at the end of the study [38]. In a treatment/prevention, open-label study of mirtazapine (a serotonin antagonist and norepinephrine agonist), 40% of placebo subjects developed PSD, compared with 5.7% of the mirtazapine group [39]. Maprotiline (a monoamine oxidase inhibitor), in the one and only double-blind study, was not effective in preventing PSD [31]. To our knowledge, duloxetine (an SNRI), bupropion (a dopamine and norepinephrine reuptake inhibitor), and selegline patch have not been studied in the treatment or prevention of PSD. Methylphenidate (a psychostimulant) showed efficacy in preventing PSD in one double-blind study [40].

Discussion

PSD is a well-studied psychosomatic disorder in the literature. Several national and international studies have been published in the past 40 years, since its recognition. There is convincing evidence that the disease process is not purely biological or psychological. It affects almost one third of poststroke patients, but it often is not diagnosed and treated effectively. Current studies have used various tools to diagnose and assess prevention/treatment outcomes, so it is difficult to compare study results. New tools need to be developed to diagnose and treat this prevalent disorder. Pre- and postimaging studies before and after treatments (pharmacotherapies and psychosocial interventions) may help us to better understand pathophysiology and treatment outcomes. Currently, nortriptyline shows better efficacy than any other antidepressant available, but its side effect profile and drug interactions limit its use in clinical practice. Newer, especially dual-acting, compounds need to be studied more in this patient population.

Conclusions

Again, PSD (major and minor) is a common psychiatric problem on neurology and rehabilitation units and in nursing homes. More education and training are required for health professionals who treat this patient population. Early recognition with newer screening tools may improve recovery, rehabilitation, and mortality.

Newer standard screening and diagnostic tools with newer and safer treatments will not only help us to treat this patient population effectively but also to decrease health care burden and cost.

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