Post-Stroke Depression: A Review

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Poststroke depression (PSD) has been recognized by psychiatrists for more than 100 years, but controlled systematic studies did not begin until the 1970s. Meta-analyses addressing almost all major clinical issues in the field have emerged because of the relatively small number of patients included in some stroke studies. In order to build large databases, these meta-analyses have merged patients with rigorously assessed mood disorders with major depressive features with patients scoring above arbitrary cutoff points on depression rating scales, thus missing important findings such as cognitive impairment associated with major but not minor depression. Nevertheless, PSD occurs in a significant number of patients and constitutes an important complication of stroke, leading to greater disability as well as increased mortality. The most clinically important advances, however, have been in the treatment and prevention of PSD. Recent meta-analyses of randomized controlled trials for the treatment of PSD have demonstrated the efficacy of antidepressants. Similarly, randomized controlled trials for prevention of PSD have shown that antidepressants significantly decrease the incidence of PSD compared with placebo. Early antidepressant treatment of PSD appears to enhance both physical and cognitive recovery from stroke and might increase survival up to 10 years following stroke. There has also been progress in understanding the pathophysiology of PSD. Inflammatory processes might be associated with the onset of at least some depressive symptoms. In addition, genetic and epigenetic variations, white matter disease, cerebrovascular deregulation, altered neuroplasticity, and changes in glutamate neurotransmission might be relevant etiological factors. Further elucidation of the mechanism of PSD may ultimately lead to specific targeted treatments.

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Stroke is defined as a sudden loss of blood supply to the brain leading to permanent tissue damage caused by thrombotic, embolic, or hemorrhagic events. Almost 85% of strokes are ischemic, while 12% are hemorrhagic. The incidence of stroke varies dramatically over the life course, with incidence rates between 10 and 20 per 10,000 individuals in the age range of 55–64, while incidence rates increase to 200 per 10,000 individuals for those aged over 85. There are 700,000 strokes annually in the United States and 163,000 stroke-related deaths according to the latest statistics of the American Heart Association (1).

The association of neuropsychiatric disorders with cerebrovascular disease includes depression, anxiety disorder, apathy, cognitive disorder, mania, psychosis, pathological affective display, catastrophic reactions, fatigue, and anosognosia. The first empirical studies of post-stroke depression (PSD) included studies conducted by researchers such as Martin Roth (2), who demonstrated the association between atherosclerotic disease and depression, and Folstein et al. (3), who demonstrated that depression was significantly more common in patients with stroke compared with patients with comparable physical impairments due to orthopedic injuries. The first systematic longitudinal study of PSD found that severity of impairment in activities of daily living, social functioning, and cognitive function were all associated with the existence of PSD (4).

A 1984 study published in *Brain* (5) first identified a significant increase in both major and minor depression among patients with left anterior strokes compared with strokes in other locations. In addition, in 1984, the first randomized, double-blind placebo-controlled treatment trial demonstrated that nortriptyline was effective in treating PSD (6).

The present review will address identification of PSD, as well as its prevalence, risk factors, relationship to physical impairment, cognitive impairment, and mortality. We will also review treatment of PSD, prevention of PSD, etiology, and suggestions for future research.

METHOD

We conducted a literature search using the following databases: MEDLINE/PubMed, EMBASE, CINAHL, PsycINFO, PsycBITE, Cochrane Central Register of Controlled Trials, Internet Stroke Center (www.strokecenter.org/trials), Ovid Central Register of Controlled Trials database, and ClinicalTrials.gov.

Our keywords included "poststroke depression," "depression AND cerebrovascular disorders," "vascular depression," "stroke AND antidepressant," "stroke AND antidepressant AND depression," "poststroke depression AND randomized clinical trial," as well as "poststroke depression AND trial."

Reference lists of each article utilized were searched by hand to identify additional citations not identified by the

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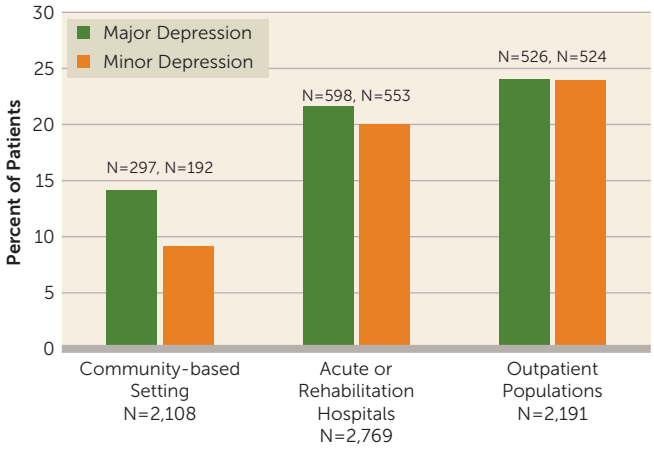
FIGURE 1. The Prevalence of Depression in Various Clinical Settings Following Stroke[a]



[a] Patients were examined using a standardized mental status examination and DSM-IV diagnostic criteria for depression following stroke with major depressive-like features or minor depression defined as more than two but less than five symptoms of major depression. Meta-analyses stating that the prevalence of poststroke depression is 31% miss these important clinical variables.

databases. This is primarily a narrative review that did not utilize the Preferred Reporting Items for Systematic Reviews and Meta-Analysis [PRISMA] because of the limitations of existing meta-analyses in this field discussed under the section on incidence and prevalence of PSD.

Diagnosis of PSD

The DSM-5 defines poststroke 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 cerebrovascular disease is major or minor vascular neurocognitive disorder.

A patient with a diagnosis of mood disorder due to stroke with a major depression-like episode must have depressed mood or loss of interest or pleasure along with four other symptoms of depression lasting 2 or more weeks. Patients with a diagnosis of mood disorder due to stroke with depressive features must have depressed mood or loss of interest or pleasure along with at least two but less than five symptoms of major depression lasting 2 weeks or longer.

Clinically defined vascular depression was proposed in 1997 by Alexopoulos et al. (7), while Krishnan et al. (8) validated such diagnosis on the basis of the presence of subcortical pathology and white matter hyperintensities in MRI scans.

Patients with vascular depression have later age at onset, greater cognitive impairment, less family and personal history of depression, and greater physical impairment than geriatric patients with nonvascular depression. In addition, patients with vascular depression with executive dysfunction and/or patients who show progression of white matter hyperintensities over time have a poor response to treatment with antidepressants and a more chronic and relapsing clinical course (9).

Although vascular depression is related to small-vessel ischemia and PSD usually is related to large-vessel infarction (except lacunar infarcts), most studies have found similarities between these conditions, such as lower frequency of family and personal history of depression, prominent executive dysfunction, and greater disability compared with nonmicrovascular geriatric depression (7, 10–12). One study reported that the significant association between the presence of cardiovascular risk factors and the severity of depression observed in vascular depression is not present in PSD (13). The existing evidence, however, suggests that PSD is one form of vascular depression. Thus, a single cerebral infarct may trigger the same pathophysiological changes of depression as slowly evolving vascular ischemia.

Incidence and Prevalence of PSD

The frequency of PSD has been studied in many countries of the world. The most-quoted studies of prevalence and incidence of PSD have utilized meta-analysis to create large databases (14, 15). The most recent meta-analysis of 61 cohorts including 25,488 patients (15) reported that 31% of patients developed depression at any time point up to 5 years following stroke. A prior meta-analysis of 43 studies published in 2013 included 20,293 patients and reported that the pooled prevalence of PSD was 29% at any time point within 5 years following stroke (14). In addition, the investigators found that the cumulative percent of patients who developed one or more depressions within the first 5 years following stroke ranged from 39% to 52% (14).

The contributions by Ayerbe et al. (14) and Hackett and Pickles (15) are significant because they 1) establish that poststroke depression is a frequent and important complication of stroke and 2) refute prior assertions that the frequency of PSD has been exaggerated (16). However, these meta-analyses have included many studies that have defined PSD based on arbitrary cut-off scores on a depression rating scale. These scales provide information about the frequency and severity of depressive symptoms, but their use as a diagnostic instrument has rarely been validated. On the other hand, it has been clearly established that the existence of depression should be ascertained based on a structured mental state examination and should meet established diagnostic criteria for a specific depressive disorder (17). Thus, these meta-analyses did not distinguish major depression from other forms of depressive disorders occurring after stroke, and many did not examine the time since stroke, the clinical setting (e.g., community or hospitalized patients), or the severity of stroke, all of which may affect the prevalence of depression. We conducted a pooled analysis of studies published prior to 2003 (18) using only studies that used structured interviews and diagnostic criteria to identify major and minor depression in community-based settings, acute or rehabilitation hospitals, or outpatient clinics. The results are shown in Figure 1 and demonstrate that the frequency of PSD depends on the clinical settings where the patients are seen, which is also related to the

severity of stroke. Thus, our knowledge of important clinical differences in the prevalence and incidence of PSD has been lost in the existing meta-analyses of aggregated data.

Risk Factors of PSD

Few prospective studies have examined risk factors to develop PSD. Furthermore, only a few of these prospective studies proposed a specific predictive model, and none of these models were replicated in an independent population of stroke patients (14). The risk factors that have been examined in the literature include genetic factors, age, gender, medical and psychiatric history, type and severity of stroke, lesion location, degree of disability, and social support.

Genetic factors. Common genetic variations might confer vulnerability or resilience to develop psychiatric illness when an individual faces an unusual stressful challenge. A few candidate genes have been examined as risk factors for PSD. The *5-HTTLPR* and the *STin2 VNTR* polymorphisms of the serotonin transporter gene (*SERT*) have been associated with PSD in stroke survivors (19). Epigenetic modifications of *5-HTTLPR* have also been implicated in the onset and severity of PSD. In a recent study of 286 stroke patients, increased methylation status was independently associated with PSD at 2 weeks and at 1 year following stroke, a finding that was only observed in the presence of the 5-HTTLPR *s/s* genotype (20). In addition, among the same group of stroke patients, higher brain-derived neurotrophic factor (BDNF) gene methylation status was associated with incident PSD and more severe symptoms at 12 months follow-up (21).

Demographic factors. A systematic review of 24 studies of stroke patients reported that gender was not a significant risk factor for PSD in 13 out of 21 studies that examined this association. However, one-third of these studies identified female sex as a risk factor for PSD (22). Age was not associated with PSD in 16 of these 21 studies. These findings were replicated in a review of 23 studies including 18,374 stroke patients (23).

Medical and psychiatric history. Major cardiovascular risk factors such as hypertension and hypercholesterolemia appear to have no relation to PSD. However, patients with PSD might be more likely to have a history of diabetes mellitus (22–24). A personal history of depression or anxiety or both was also consistently identified as a risk factor for PSD (22–24). A family history of depression was associated with PSD in the few studies that examined this association (25).

Stroke characteristics and lesion location. The available evidence strongly suggests a significant association between stroke severity and PSD (14, 23). On the other hand, recent systematic reviews argue against an association between PSD and the type (i.e., ischemic or hemorrhagic) or mechanism (i.e., thrombotic, embolic, etc.) of stroke (22–24).

Lesion location has been extensively investigated as a risk factor for PSD. The findings, however, have been inconsistent. Utilizing separate populations of patients in 1984 and 1987, two studies led by Robinson (5, 26) reported that acute stroke patients with left frontal or left basal ganglia lesions had a significantly higher frequency of major or minor depression than patients with other lesion locations. Furthermore, both studies found a significant correlation between the distance of the anterior border of ischemic lesion from the left frontal pole and severity of depression for both cortical and subcortical regions (5, 26). Subsequent analysis by this research group (27) found that the association of PSD with left frontal and left basal ganglia lesions appears to be a transient phenomenon restricted to the first 2 months following stroke, and the correlation of depression severity with distance of the anterior border of the lesion from the frontal pole in the left hemisphere remains significant only during the first 6 months after a stroke. However, subsequent meta-analysis of data from stroke patients who were either acute or chronic and had one or more stroke lesions reported no significant association with lesion location (14, 23). The most recent and largest meta-analysis analyzed 43 studies involving 5,507 stroke patients and reported an odds ratio of 0.99 (95% confidence interval [CI]=0.88–1.11) for the association of stroke location and depression risk (28). This lack of association is hardly surprising given the heterogeneity in the way in which depression was assessed in these studies, the diverse timing of the assessments, the different definitions of lesion location (e.g., left frontal cortical versus left anterior), and the different neuroimaging methods used to determine lesion location. In spite of conflicting results, there are studies that have continued to report the association of PSD with left frontal hemisphere lesions and with proximity to the frontal pole (29).

We still believe there is an association between PSD and left frontal or left basal ganglia lesions within 2 months of a first clinical stroke. This conclusion is also supported by the fact that there is strong scientific evidence of brain lateralization of emotion (30) and that focal brain stimulation using repetitive transcranial magnetic stimulation is only effective when it is administered to the left dorsolateral prefrontal cortex in patients with vascular depression (31). We also believe that identifying the role that lesion location plays in PSD requires the formulation of a new pathophysiological model of the disorder to integrate these disparate findings.

Functional and cognitive impairment. The severity of post-stroke impairment in activities of daily living is the factor most consistently associated with PSD. The severity of disability was found to be significantly related to PSD in 16 out of 18 studies reviewed by Hackett and Pickles (15) and in 24 out of 30 studies reviewed by Johnson et al. (24). However, the strength of the correlation between PSD and impairment in activities of daily living is relatively weak, explaining only about 10% of the variance of severity of PSD (32).

The relationship between PSD and cognitive impairment (especially executive dysfunction) has been well established (18). Initial studies have demonstrated that stroke patients with major depression had significantly lower Mini-Mental State Examination scores than nondepressed patients with similar background characteristics who were matched for both lesion location and lesion volume (33). This finding was replicated in an independent study of stroke patients with left hemisphere lesions who were assessed during the first year after stroke (34). However, it is important to keep in mind the strong association existing between major depression and the presence of cognitive deficits (34), while the recent meta-analyses did not distinguish between subjects with major depression, subjects with minor depression, or subjects with depressive symptoms.

Social support. The available evidence concerning PSD and social support is conflicting, probably because of significant heterogeneity in the definition and evaluation of social support. For instance, although the number of social ties was shown to be inversely correlated with the severity of PSD (18), living situation and marital status have not been consistently associated with PSD (24). However, a prospective study found that lack of social support at admission was associated with the onset of PSD at 3-months follow-up (35).

The Impact of PSD on Stroke Recovery and Mortality and the Effects of Antidepressants

Numerous studies have examined the relationship between depression at the initial examination (which may range from a few weeks following stroke to 6 or more months following stroke) and functional and motor recovery (36–38). Five of six studies that examined whether severity of depression after acute stroke predicted severity of impairment in activities of daily living at 1 year or more of follow-up found that depression severity was an independent predictor of severity of impairment in activities of daily living (18).

Consistent with the previous findings, patients with PSD who responded to treatment with nortriptyline or fluoxetine showed significantly better improvement in activities of daily living than patients with PSD who did not respond to active treatment or placebo (39). Similarly, a longitudinal study has shown that response to treatment of PSD with nortriptyline or fluoxetine over 12 weeks leads to improved cognitive function to the level seen in nondepressed stroke patients that lasts for more than 2 years (40).

Increased mortality associated with PSD is perhaps the most dramatic clinical phenomenon following PSD. The first study to report this phenomenon using standardized interviews to diagnose PSD was published in 1993 (41). In this study, 103 patients were followed up 10 years after their index stroke to determine mortality rates. Patients who developed PSD during the acute poststroke period had significantly higher mortality rates than similarly impaired stroke patients with no in-hospital depression (odds ratio=3.4, 95% CI=1.4–8.4, p=0.007) (41). A similar finding was reported by House et al. (42), who showed that even mild severity of PSD was associated with increased mortality as early as 1 year after stroke. Furthermore, in a cohort of 51,119 veterans hospitalized because of an ischemic stroke, those who developed PSD had a higher 3-year mortality risk than veterans without a mental health diagnosis (43).

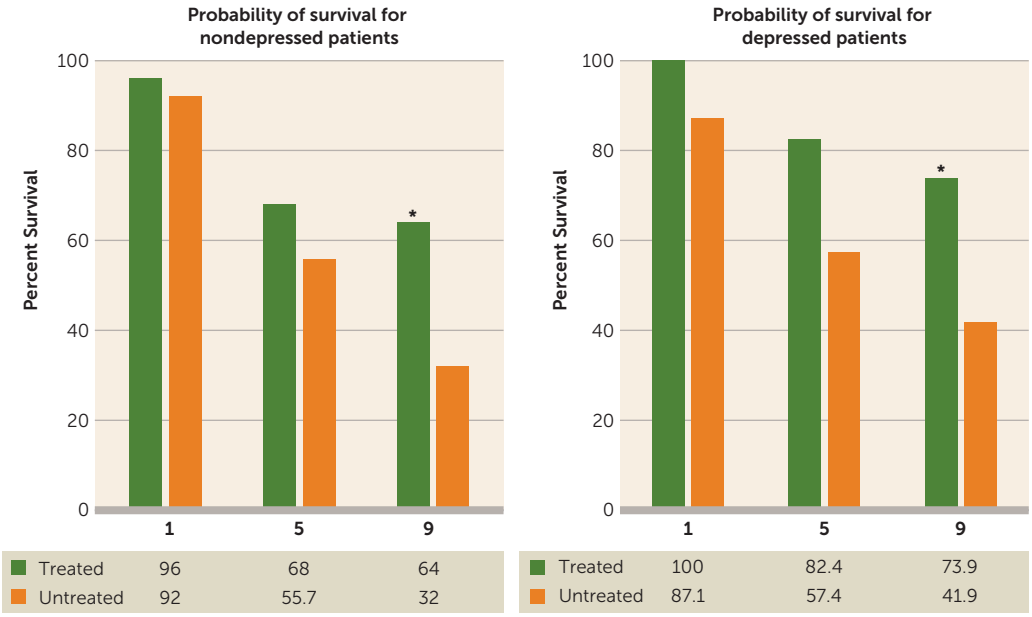
A recent study of 1,354 patients that used the Hospital Anxiety and Depression Scale to assess PSD found that at the 5-year follow-up, patients with a Hospital Anxiety and Depression Scale score ≥7 at 3 months after stroke had a hazard ratio of 1.41 (95% CI=1.13–1.77, p=0.02) of increased mortality compared with patients with scores <7 at 3 months (44, 45). The investigators also reported increased mortality among patients started on selective serotonin reuptake inhibitor (SSRI) antidepressants in the 3 months after stroke. However, this was not a randomized trial, and the data analysis on which this assertion is based does not include all the relevant confounders such as disability, depression severity, and the effect of comorbid medical conditions (44).

The association of PSD with mortality appears to be the result of an increase in cardiovascular mortality (44). We reported that decreased heart rate variability, which has been demonstrated to play an etiological role in mortality associated with depression and myocardial infarction (46), was also associated with PSD (47). Thus, disruption of autonomic system function in patients with PSD might contribute to cardiovascular mortality.

Perhaps the most provocative finding, however, was the relationship of mortality following PSD to treatment with antidepressants (Figure 2) (48). A 9-year follow-up study of patients with or without PSD who had been treated with nortriptyline (100 mg/day) or fluoxetine (40 mg/day) for 12 weeks (N=53) showed that patients receiving active treatment had an increased probability of survival at the 9-year follow-up compared with similar patients given placebo (N=28) (i.e., 59.2% survival for patients treated with nortriptyline or fluoxetine compared with 34.6% for patients given a placebo [adjusted odds ratio=3.7, 95% CI=1.1–12.2, p=0.03]) (48). This finding held when nortriptyline- and fluoxetine-related survival was examined separately and was independent of whether the depression responded to treatment or whether the patient was depressed or not prior to treatment. A beneficial effect of antidepressants on long-term survival after stroke was also observed in a group of 790 veterans with stroke followed over a 7-year period (49).

Three studies analyzed the effect of antidepressants on motor, cognitive, and disability outcomes among nondepressed patients during 12 months following stroke. Chollet et al. (50) found that 12 weeks of fluoxetine (20 mg/day) was more efficacious than placebo to improve motor recovery at 12 weeks assessed using the Fugl-Meyer Motor Disability Scale. Jorge et al. (51) reported that among a group of nondepressed patients with acute stroke, 12 months of escitalopram (5 mg–10 mg/day) enhanced cognitive performance at 12 months assessed by the Repeatable Battery for the Assessment of Neuropsychological Status.

FIGURE 2. Survival Rate for Patients Who Were Depressed and Nondepressed at 3 Months Followed Over 9 Years[a]



[a] Patients were randomly assigned to nortriptyline (100 mg/day), fluoxetine (40 mg/day), or placebo for 3 months. The survival rate of patients given antidepressants was almost twice that of those given a placebo.
* p=0.004.

With regard to disability, a secondary analysis of the results of our previous randomized controlled trial on the efficacy of fluoxetine (20 mg–40 mg/day) and nortriptyline (100 mg/day) to treat PSD showed that when compared with those receiving placebo, nondepressed stroke patients receiving antidepressants had decreased disability measured by the modified Rankin Scale at the 12-month follow-up (52).

In summary, although two of the factors most consistently associated with PSD are functional disability and cognitive impairment, there is clearly a reciprocal relationship with impairment influencing depression and depression influencing impairment. In addition, there is rapidly growing literature indicating that SSRIs following stroke may enhance recovery independent of PSD or their effects on mood (50–52). The findings of a recent meta-analysis of studies assessing the effect of SSRIs on stroke outcomes support this conclusion (53).

Finally, a multicenter randomized controlled trial of the efficacy of citalopram to reduce disability and cardiovascular mortality following stroke (The Efficacy of Citalopram Treatment in Acute Stroke [TALOS] study) is currently underway (54).

Etiological Mechanisms

Like many disorders in psychiatry, there is evidence supporting the role of psychological, social, and biological factors in the mechanism of PSD (55). The most consistent finding in the stroke literature is that PSD is associated with stroke severity and the degree of functional physical and cognitive impairment (23). However, it is uncertain whether the level of impairment is etiologically associated with the development of PSD through a "reactive" psychological mechanism or whether there are biological factors related to brain damage that contribute to the bidirectional relationship between disability and depression.

The association between PSD and biological factors has included empirical evidence suggesting alterations in ascending monoamine systems (56), hypothalamic-pituitary-adrenal (HPA) axis abnormalities (57), disruption of prefrontal-subcortical circuits (58), alterations in neuroplasticity and in glutamate neurotransmission (59), and an excess of proinflammatory cytokines (60). However, a pathophysiological hypothesis of PSD that can integrate these changes into a coherent explanatory model has yet to be formulated.

From a translational approach, there have been several attempts to model PSD in experiments with rodents. We conducted the earliest studies using a rat model of middle cerebral artery ligation. Right hemisphere middle cerebral artery ligation produced significant bilateral depletions of norepinephrine and dopamine in both the cortex and brainstem, as well as hyperactivity and other behavioral changes not seen in rats given sham ligations (61). Further experiments using this animal model demonstrated that the biogenic amine and behavioral effects were lateralized, not occurring after left middle cerebral artery ligation, and lasted up to 4 weeks (62).

In recent years, there has been a renewed interest in modeling the neuropsychiatric consequences of stroke. Kronenberg et al. (63) used a model of mild stroke in mice (i.e., 30-minute middle cerebral artery occlusion that limits the ischemic damage to the basal ganglia). A subgroup of these mice was given citalopram, starting 1 week after middle cerebral artery occlusion. Left, but not right, middle cerebral artery occlusion produced delayed degeneration

of dopaminergic neurons in the left ventral tegmental area, which resulted in reduced dopamine concentrations in the striatum. The behavioral correlates of these neurodegenerative and neurochemical changes were anhedonia and behavioral despair assessed by the sucrose consumption test and forced swimming test, respectively. Chronic citalopram treatment initiated 7 days after stroke, however, prevented the degeneration of dopaminergic neurons and reversed the behavioral phenotype (63).

There have also been animal studies that combined experimental ischemic lesions with social isolation or chronic mild stress protocols implemented during the recovery process after stroke (64). Permanent left middle cerebral artery occlusion with a 14-day chronic mild stress protocol produced a depressive phenotype characterized by decreased exploratory behavior and sucrose consumption, a behavioral effect that was reversed by the administration of citalopram and a 5-HT_{1A} antagonist along with evidence of increased neurogenesis in the hippocampus (64).

Unfortunately, there have been relatively few studies of the mechanisms of PSD in clinical populations. Decreased CSF levels of serotonin or norepinephrine metabolites, however, were significantly associated with severity of PSD (65). It has also been hypothesized that ischemic lesions of ascending monoamine pathways may result in depressive disorders due to abnormal modulation of frontal and cingulate regions involved in mood regulation (18).

There is a growing consensus that ischemic lesions (single and/or multiple) of the neural circuits that connect the prefrontal cortex, basal ganglia, thalamus, and amygdala (independently of their lateralization) may disrupt mood regulation and executive function leading to a similar clinical presentation. Furthermore, there appears to be a threshold by which the confluence of multiple etiological factors or further damage to specific white matter tracts, such as the cingulate bundle, the uncinate fasciculus, and superior longitudinal fasciculus, triggers the onset of clinical depression. Thus, acute ischemia can unveil the presence of vascular depression (58), or a strategically located stroke might produce depression independently of the presence of widespread cerebrovascular pathology.

From a network standpoint, resting connectivity patterns revealed by functional MRI appear to be similar in vascular depression and PSD, with increased activation of the default mode network and limbic structures and decreased activation of task-related networks and the dorsolateral aspects of the prefrontal cortex (66).

Earlier studies also examined the occurrence of HPA axis deregulation in PSD, particularly the association of PSD with elevated cortisol levels and abnormal negative feedback control of cortisol secretion (57). More recently, a number of studies have provided support for the role of proinflammatory cytokines in the development of PSD (56, 60). This hypothesis has been supported by recently published studies in which increased serum concentrations of interleukin-6 (Il-6) were associated with increased severity of somatic symptoms of PSD (67). There is a bidirectional relationship between HPA axis deregulation and the levels of inflammatory cytokines by which high cortisol levels induce an inflammatory response that, in turn, will result in further HPA axis deregulation. Furthermore, increased levels of inflammatory cytokines reduce the synthesis and availability of serotonin through their enhancing effect on the activity of the enzyme indolamine 2, 3-dioxygenase (56).

The recent emphasis on neuroplasticity as a critical neurobiological substrate for depressive disorders suggests that synaptic alterations in the prefrontal cortex and hippocampus may be etiologically implicated in PSD. In support, BDNF levels, one of the regulators of these processes, have been shown to be reduced in PSD (68). A recent study of 216 patients with acute ischemic stroke reported the results of a multivariate analysis showing that lower serum levels of BDNF at admission were an independent predictor of PSD at the 3-month follow-up (69). Furthermore, a meta-analysis performed by Noonan et al. (59) based on 33 studies reported that lower serum BDNF was found in patients with PSD compared with nondepressed control subjects. Additionally, HPA axis deregulation and increased levels of proinflammatory cytokines may inhibit neurogenesis in the hippocampus and decrease the neuroplasticity of the prefrontal cortex contributing to the onset and perpetuation of PSD (70).

Finally, a preliminary study using magnetic resonance spectroscopy found altered glutamate levels in the anterior cingulate cortex of depressed stroke patients (71).

Thus, although there are numerous possible physiological mechanisms related to PSD, many investigators have concluded that this complex disorder, like most of the major psychiatric disorders not associated with stroke, may best be described as a bio-psycho-social disorder. However, this general theoretical framework does little to help us elucidate pathophysiological mechanisms leading to specific symptoms. These different etiological factors described above may have more salient roles in some forms or symptoms of PSD, and also their effects may vary at different times after the stroke. We believe future studies should attempt to identify the mechanism of specific symptoms or clinical characteristics of PSD rather than the whole syndrome.

TREATMENT OF PSD

The randomized double-blind controlled treatment trials of PSD are shown in Table 1. The first randomized double-blind treatment trial was reported in 1984 by Lipsey et al. (6). Patients randomly assigned to nortriptyline (50 mg–100 mg/day) had a significantly greater reduction in Hamilton Depression Rating Scale (HAM-D) scores over 6 weeks of treatment compared with patients given a placebo. The first double-blind controlled trial to examine the efficacy of SSRIs was reported by Andersen et al. in 1994 (72). Among 33 poststroke patients given

TABLE 1. Double-Blind Placebo-Controlled Treatment Studies of Poststroke Depression[a]

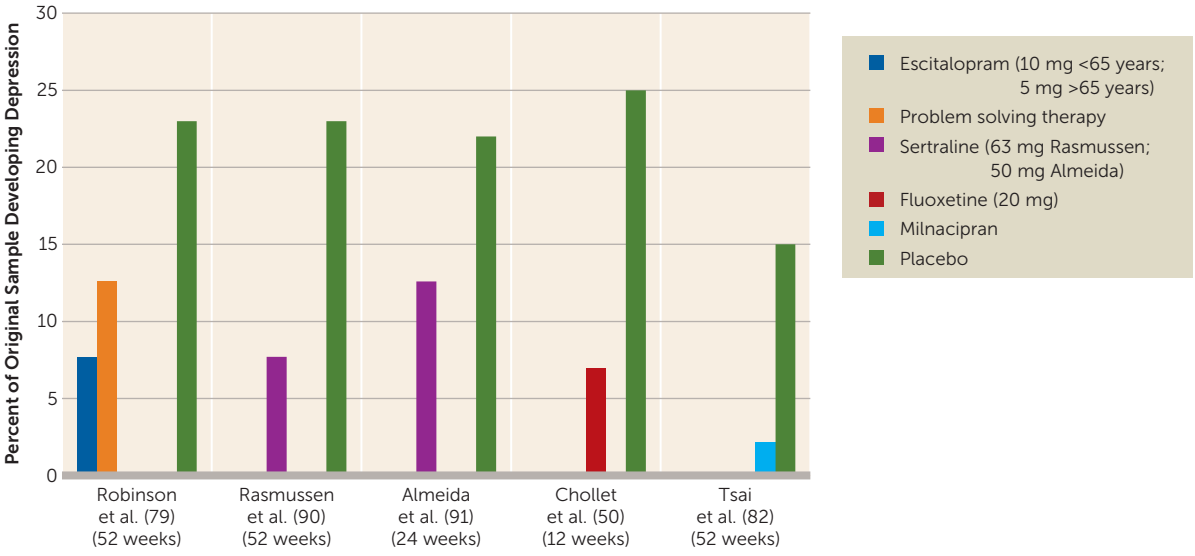
Study	N	Medication (N and Maximum Daily Dose)	Duration	Evaluation Measure	Results	Response Rate	Completion Rate
Lipsey et al. (6)	34	Nortriptyline (N=14; 100 mg/day) Placebo (N=20)	6 weeks	HAM-D; Zung Depression Scale	Intent to treat and efficacy: Nortriptyline> placebo	Completers: nortriptyline, 100%; placebo, 33%;	11 of 14 nortriptyline; 15 of 20 placebo
Reding et al. (83)	27	Trazodone (N=7; 200 mg/day); placebo (N=9)	Mean 32 days (SD=6)	Zung Depression Scale	Efficacy: trazodone> placebo on Barthel Activities of Daily Living Index for patients with abnormal dexamethasone suppression test	NR	
Andersen et al. (72)	66	Citalopram (N=33; 20 mg/day, 10 mg for patients >65 years); placebo (N=33)	6 weeks	HAM-D; Melancholia Scale	Intent to treat: citalopram>placebo	Completers: citalopram, 61%; placebo, 29%	26 of 33 citalopram
Grade et al. (84)	21	Methylphenidate (N=10; 30 mg/day); placebo (N=11)	3 weeks	HAM-D	Intent to treat: methylphenidate> placebo	NR	9 of 10 methylphenidate; 10 of 11 placebo
Robinson et al. (85)	56	Fluoxetine (N=23; 40 mg/day); nortriptyline (N=16; 100 mg/day); placebo (N=17)	12 weeks	HAM-D	Intent to treat: nortriptyline> fluoxetine=placebo	Fluoxetine, 14%; nortriptyline, 77%; placebo, 31%	14 of 23 fluoxetine; 13 of 16 nortriptyline; 13 of 17 placebo
Wiart et al. (86)	31	Fluoxetine (N=16; 20 mg/day); placebo (N=15)	6 weeks	Montgomery Åsberg Depression Rating Scale	Intent to treat: fluoxetine>placebo	Fluoxetine, 62%; placebo, 33%	14 of 16 fluoxetine; 15 of 15 placebo
Fruehwald et al. (87)	54	Fluoxetine (N=28; 20 mg/day); placebo (N=26)	12 weeks	Beck Depression Inventory, HAM-D	HAM-D score >15; fluoxetine=placebo; HAM-D scores < 13; fluoxetine=placebo	HAM-D score ≤13: fluoxetine, 69%; placebo, 75%	26 of 28 fluoxetine; 24 of 26 placebo
Rampello et al. (88)	31	Reboxetine (N=16; 4 mg/day); placebo (N=15)	16 weeks	Beck Depression Inventory, HAM-D	Reboxetine>placebo for intellectually challenged depressed patients	NR	NR
Choi-Kwon et al. (89)	152	Fluoxetine (N=76; 20 mg/day); placebo (N=76)	3 months	Beck Depression Inventory	Fluoxetine=placebo	NR	15 of 76 fluoxetine; 12 of 76 placebo

[a] HAM-D=Hamilton Depression Rating Scale; NR=not reported.

citalopram (10 mg–20 mg/day), there was a significantly greater reduction in HAM-D scores over 6 weeks compared with 33 similarly depressed patients given placebo.

A meta-analysis of 16 randomized controlled trials (12 using antidepressants and four evaluating the efficacy of psychotherapy) that included 1,655 patients found a significant beneficial effect of antidepressant medication, whereas psychotherapy was not more effective than a control intervention (73). Brief psychosocial therapies, however, that place emphasis on care management, psycho-education, and family support can be beneficial to treat or prevent PSD in combination with antidepressant treatment (74, 75).

FIGURE 3. Randomized Controlled Trials for Evaluation of Preventative Treatments for Poststroke Depression[a]



	Robinson et al. (79) (52 weeks)	Rasmussen et al. (90) (52 weeks)	Almeida et al. (91) (24 weeks)	Chollet et al. (50) (12 weeks)	Tsai et al. (82) (52 weeks)
Completers	134	67	56	88	56
Randomized	176	137	92	113	111

[a] Although the trials show very similar results in the percent of patients developing depression with placebo or pharmacological treatment, the Robinson et al. (79), Tsai et al. (82), and Chollet et al. (50) trials had sufficient power to demonstrate statistical significance.

It should be acknowledged that treatment with antidepressants is not without risk. For example, SSRI use has been associated with an increased risk of hemorrhagic complications and increased risk of falls in the elderly (76). Furthermore, other epidemiological studies have reported that SSRIs are associated with increased risk for stroke, myocardial infarction, and all-cause mortality (77, 78). The effect of these antidepressants may be due to interactions with other variables such as depression, disability, and comorbid medical conditions that require further elucidation.

Finally, the American Heart Association recommends the use of antidepressants for PSD, which should be continued after recovery for at least 6 months (32).

Prevention of PSD

Perhaps the major advance in the treatment of PSD has been the demonstration of preventive treatment (Figure 3). The first statistically significant randomized controlled trial of prevention of PSD was conducted by Robinson et al. (79), published in 2008, in which 58 nondepressed acute stroke patients treated with escitalopram (5 mg/day for patients over age 65; 10 mg/day for patients ages 65 and under) over 1 year had an incidence of PSD of 8.5% compared with 11.9% for 59 patients receiving problem solving therapy and 22.4% for 59 patients receiving placebo. Controlling for age, gender, severity of stroke, and severity of impairment, the risk of onset of depression for placebo patients was more than four times greater than the risk for patients treated with escitalopram (adjusted hazard ratio=4.5; 95% CI=2.4–8.2, $p<0.001$).

The most recent meta-analysis of prevention trials summarized the findings of eight randomized controlled trials assessing the efficacy of preventive interventions among 776 initially nondepressed stroke patients (80). Pooled analyses revealed that the likelihood of developing PSD was reduced among subjects receiving active pharmacologic treatment, especially following a 1-year treatment, and with the use of an SSRI. There were no significant active and placebo group differences in the frequency of side effects of nausea, diarrhea, fatigue, and dizziness.

FUTURE DIRECTIONS

As recently as the 1970s, PSD was regarded as a psychological and perhaps inevitable reaction to stroke-related disability. Since that time, progress in ascertaining the diagnosis and prevalence of PSD, the risk factors for PSD, the effect of PSD on physical recovery, cognitive recovery, and mortality, as well as the treatment and prevention of PSD, has been substantial. Thus, it seems to us that identifying additional aspects of the mechanism of PSD is the most urgent need for future research because it may lead to a more specific therapeutic intervention. For example, studies of the role of the association of Il-6 with somatic symptoms of depression (67) and the association of low levels of serum BDNF within hours after stroke with the development of depression after 3 months following stroke (69) are intriguing findings that may lead to identification of how specific symptoms of PSD may be mediated, as well as suggesting that neurotrophic and anti-inflammatory agents may be effective in treating or preventing not only PSD but other neuropsychiatric disorders resulting from stroke (81).

Other urgent areas for future research include determining the mechanisms of increased mortality extending over at least 7 years following PSD and elucidating the mechanism by which antidepressants enhance physical and cognitive recovery after stroke even in the absence of PSD. The neurogenesis induced by SSRIs is a likely potential mechanism.

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