Depression and Stroke: Cause or Consequence?

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ABSTRACT

Depression after stroke is common. Although different opinions exist about the definition, diagnosis, and measurement of outcomes related to depression after stroke, there is little debate about the prevalence of depression symptoms and their impact on stroke survivors and their families. Depression after stroke has long been recognized as a common condition with many negative effects in the poststroke period, but more recently depression has also been identified as an independent stroke risk factor. Given that there are at least 500,000 new ischemic strokes yearly in the United States, a conservative estimate is that 150,000 U.S. stroke survivors develop poststroke depression each year. Because effective treatments exist but are likely underutilized for depression, this is an important example of an evidence-practice gap to which increased efforts to improve care should be made. Such efforts would likely improve not only patient symptoms but may also decrease stroke risk, influence stroke functional recovery, decrease mortality, and reduce poststroke health care utilization. This article provides an overview of depression diagnosis in stroke, reviews the epidemiology of poststroke depression and its associated morbidity and mortality, and reviews existing evidence on the treatment and prevention of poststroke depression.

KEYWORDS: Stroke, depression, recovery, risk factors

Depression after stroke is common. The vast majority of the literature has studied depression after ischemic stroke only, not hemorrhagic stroke; therefore, the term "poststroke depression" (PSD) will be used here to indicate depression related to ischemic stroke unless otherwise specified. Although different opinions exist about the definition, diagnosis, and measurement of outcomes related to depression after stroke, there is little debate about the prevalence of depression symptoms and their impact on stroke survivors and their families. Given

that there are at least 625,000 new ischemic strokes yearly in the United States, a conservative estimate is that at least 185,000 U.S. stroke survivors develop PSD each year. Because effective treatments exist but are likely underutilized for depression, this is an important example of an evidence-practice gap to which increased efforts to improve care should be made. Such efforts not only would likely improve patient symptoms but may also influence stroke functional recovery, decrease mortality, and reduce poststroke health care utilization. This article provides an overview of depression diagnosis in stroke, reviews the epidemiology of PSD and its associated morbidity and mortality, and reviews existing evidence on the treatment and prevention of PSD.

DEFINING DEPRESSION

Depression is a syndromic condition that, like many disorders, is diagnosed and monitored by assessing symptoms. The most commonly used diagnostic algorithm is based on the Diagnostic and Statistical Manual, Fourth Version (DSM-IV) and includes criteria for major depression and minor depression as well as criteria for other categories of depressive disorders (Table 1). Diagnosis of major depression requires persistent low mood or loss of interest in most activities for at least 2 weeks, including some of the following symptoms to total at least five symptoms: weight change (increase or decrease), altered sleep pattern (too little or too much), lack of energy, poor concentration, agitation, reduced self-esteem, suicidal ideas or plans. Minor depression requires three or four of these symptoms, with at least one symptom being depressed mood or loss of interest, for at least 2 weeks.

PSD is typically defined simply as depression that develops after ischemic stroke. Most studies of PSD do not distinguish between major and minor depression diagnoses. Studies of PSD are also complicated by the varied time frames used in this definition, the methods of diagnosing depression, and the different population of stroke patients studied.[1–4] Permeating these meth-

Table 1 DSM-IV Symptoms of Major Depression

At least one of these:

  Depressed mood

  Anhedonia

And some of these to total five symptoms present for at least

  2 weeks:

  Change in appetite/weight (increase or decrease)

  Altered sleep pattern (increase or decrease)

  Lack of energy

  Difficulty concentrating

  Agitation

  Reduced self-esteem

  Suicidal thoughts or plans

odological difficulties is the theoretical problem of evaluating mental functioning in brain-injured patients. Potential difficulties include evaluating mood in patients with language, cognitive, and attentional disturbances and attributing somatic symptoms to mood disorders when the symptoms may be more strongly related to the neurological condition.[3]

Because physical symptoms are a common feature of the poststroke period and because physical symptoms like poor sleep and fatigue are part of the diagnostic assessment of depression yet are also common in nondepressed patients, some authors have questioned whether PSD is overdiagnosed in the poststroke period due to non–depression-related physical complaints. Although this hypothesis seems reasonable, it has not been convincingly demonstrated in a stroke cohort. Robinson and colleagues did not find "overdiagnosis" of PSD with only 2 to 3% of patients having solely somatic symptoms of depression,[5] and we likewise found that although PSD patients had more severe physical depression symptoms after stroke, they did not have a greater number of physical depression symptoms compared with depressed older adults without stroke (Fig. 1).[6] We also compared symptom endorsement on the Patient Health Questionnaire (PHQ)-9 items between depressed and nondepressed patients and found that all symptoms, including sleep, fatigue, appetite, and feeling slowed down or agitated, were at least five times more likely to be endorsed by depressed patients than nondepressed patients.[7]
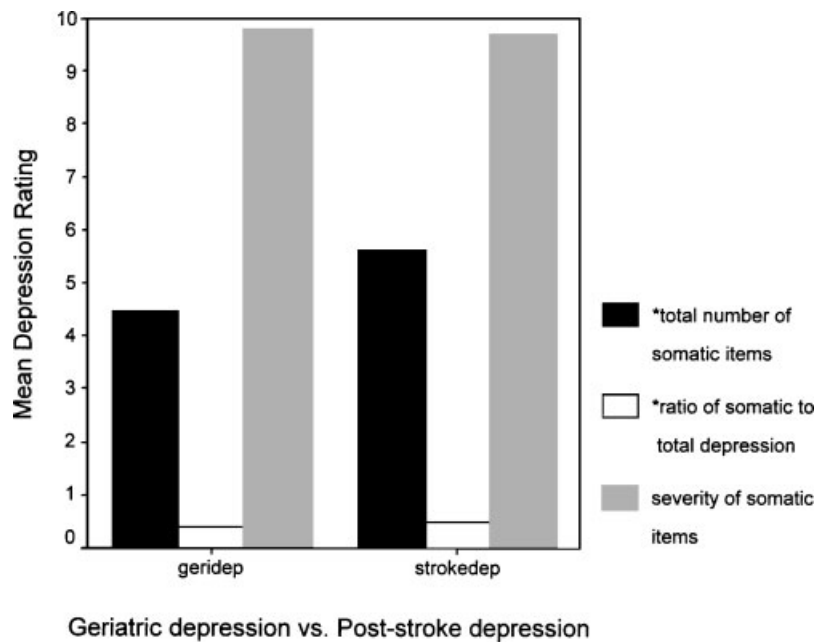
Another key question for PSD diagnosis is how soon after stroke PSD can be reliably diagnosed. Because depression symptoms, and symptoms in general, are heightened at times of illness and elevated situational stressors, persons hospitalized for any condition report more depressive symptoms than those not hospitalized. This makes diagnosis of PSD difficult in the immediate poststroke period. DSM-IV diagnosis requires symptoms to be present for at least 2 weeks, so adherence to a diagnostic rather than a screening algorithm can be helpful in clarifying this issue. Stroke patients may also have symptoms like emotional lability or apathy as a manifestation of frontal stroke and not depression.[8] The relationship between early emotionality and subsequent depression diagnosis in stroke patients has been studied,[9,10] with most authors reporting some association between early emotionality and later depression. Although not all patients with emotionality meet criteria for PSD, these symptoms should prompt follow-up screening after 2 weeks as patients with early emotionality are probably at increased risk for developing PSD.

SCREENING FOR DEPRESSION AFTER STROKE

Several established depression screening tools have been validated in stroke cohorts, and at least one tool has been

Figure 1 Comparison of somatic symptom clusters in PSD versus geriatric depression patients. (PHQ-9 Copyright © 1999 Pfizer, Inc. All rights reserved. Reproduced with permission. PRIME MD TODAY is a trademark of Pfizer, Inc.)

developed specifically for depression screening in stroke survivors.[7,11–15] Before evaluating or choosing a particular tool for use in a stroke population, it is important to understand some critical differences in screening tools. Some tools, like the Center for Epidemiology Studies-Depression (CES-D) and the Beck Depression Inventory, are designed to screen for depression but not to make a particular diagnosis (e.g., differentiate major depression from minor or other depression). Other tools, for example the Zung and the PHQ-9, are designed to be both a screening tool, with an established cut point to indicate patients with a high probability of depression diagnosis, and a diagnostic tool, where not just the overall score but the specific combination of symptoms are taken into consideration and validated against a psychiatric interview to establish diagnostic algorithms for the scales.

This important principle can be illustrated with the PHQ-9, a nine-item scale designed for use in outpatient primary care clinics, which assesses the nine DSM-IV depression symptom criteria for frequency of occurrence during the previous 2 weeks. As a screening tool, the nine items are summed, resulting in a score ranging from 0 (no depressive symptoms) to 27 (all nine symptoms occurring daily).[16,17] In this use, a PHQ-9 score ≥ 10 has been found to have 88% sensitivity and 88% specificity for a diagnosis of major depression. The first two items of the PHQ-9 assess depressed mood and anhedonia, and these two items (the PHQ-2) have also been tested as a depression screening tool in primary care clinics, with score ≥ 3 identified as having 83% sensitivity and 92% specificity for identifying patients with major depression. As a diagnostic instrument, the PHQ-

9 can be used to identify patients with major depression if five or more of the nine symptoms have been present at least more than half the days of the past 2 weeks and if at least one of these five symptoms endorsed is either depressed mood or anhedonia. We have recently shown that the PHQ-9 performs well as a depression screening tool in stroke patients, with 91% sensitivity and 83% specificity for major depression and 78% sensitivity and 96% specificity for any depression diagnosis.[7] Likewise, the PHQ-2 performed nearly as well with sensitivity of 83% and specificity of 84% for major depression and sensitivity 78% and specificity 95% for any depression diagnosis. The PHQ-2, however, can only be used as a screening tool, so patients with a score ≥ 3 on this scale should be administered the remaining seven items for more complete assessment of depression symptoms (including suicidality) and to enable a precise diagnosis of depression.

"POSTSTROKE" DEPRESSION: A MISNOMER?

Another critical issue that has not been well studied is the timing of depression in relation to the stroke. Most commonly, any depression recognized after a stroke has occurred is termed PSD, and whether the depressive symptoms predated the stroke is not ascertained. In our ongoing trial of depression case management versus usual care in stroke survivors, preliminary data in 180 depressed subjects showed that 30% report being on an antidepressant at the time their stroke occurred. This is of interest not only because prior depression has been identified as a risk factor for the development of PSD but

also because depression itself is increasingly recognized as a risk factor for stroke. Despite this conceptual complexity, for ease of use and convention, most authors and researchers continue to use the term "poststroke depression" to refer to any depression present after stroke, regardless of the timing of symptom onset. Further research is needed in this area to better understand depressive symptoms as a risk for stroke, and potential treatment and recovery implications for stroke survivors with longstanding versus more recent depressive symptoms.

DEPRESSION AS A STROKE RISK FACTOR

Depression and depressive symptoms have been recognized as a risk factor for cardiovascular disease and, more recently, as a risk factor for stroke. Although a review of the epidemiology of depression and other psychiatric disorders after myocardial infarction (MI) is beyond the scope of this review, Davies et al have provided a thorough review of the epidemiology and treatment of anxiety and depressive disorders in patients with cardiovascular disease.[18] Several studies have found a link specifically between depressive symptoms and increased risk of stroke (Table 2). In a random sample of 1134 subjects aged 65 and older, prior stroke was associated with a sixfold increase in 2-year risk of depression, even when controlling for functional status, stroke risk factors, and prior depression symptoms.[19] Similarly, in a 6-year prospective cohort study of nearly 2500 older adults, Ostir and colleagues found that stroke risk increased as scores on the CES-D increased (relative risk [RR] of stroke 1.04 for each 1-point CES-D increase) and, conversely, that positive affect scores had a strong inverse relationship with stroke (RR 0.74).[20] In this sample, the authors also demonstrated that baseline depressive symptoms were associated with less recovery in activities of daily living after stroke, MI, or hip fracture, suggesting that the negative impact of depression on recovery after an acute event is likely mediated via multiple physiologic, behavioral, and social mechanisms rather than by an effect on neural plasticity alone.[21] Data from the NHANES study likewise showed that depression symptoms at baseline were

associated with increased stroke risk during an average of 16 years of follow-up even after adjusting for demographic and other vascular risk factors (overall RR of stroke 1.73, 95% confidence interval [CI] = 1.30 to 2.31).[22] The relationship was strongest in blacks (RR of stroke 2.6) and only of borderline significance in white women (RR = 1.52, 95% CI = 0.97 to 2.38). This relationship has also been demonstrated in prospective cohorts from other countries, including the finding in a cohort of 901 Japanese adults aged 40 to 78 years that depressive symptoms increased the 10-year adjusted risk of subsequent ischemic stroke at least twofold.[23] Whether this observed increase in stroke risk is specifically related to depression or is seen with other mental health disorders is not clear, but one Danish population-based study demonstrated that stroke risk was increased 22% in older patients previously hospitalized for depressive disorder but not in those hospitalized for mania/bipolar disorder.[24] This relationship between depression symptoms and stroke does appear to be at least somewhat bidirectional, another factor that complicates its study. Known as the "vascular theory of late life depression," some studies find that the risk of depression in older adults without stroke increases as the number of cerebrovascular risk factors increases, presumably suggesting that depression is related to clinically silent, small-vessel cerebrovascular disease.[25] However, in at least one study the relationship between vascular risk factors and depression was not seen in older adults who had a history of stroke.[26] Further dissecting this complex issue will require longitudinal cohorts in which depression symptoms, vascular risk factors, and vascular outcomes are all well described.[27]

Depression symptoms have been linked not to just increased stroke risk but also increased stroke mortality. Analysis of more than 11,000 subjects in the Multiple Risk Factor Interventions Trial (MRFIT) cohort showed that depression symptoms were independently associated with all-cause mortality and cardiovascular disease mortality during 18 years of follow-up.[28] Importantly, the increased cardiovascular mortality was due to increased stroke mortality (hazard ratio 2.0) but not to increased coronary heart disease mortality. Further support of this relationship was the observation of a linear trend between depression symptoms and

Table 2 Depression as a Stroke Risk Factor

Study	n	Depression Assessment	RR of Stroke (95% CI)
Ostir et al[20]	2478	CES-D	1.04 (1.01–1.09) for each 1-point increase on the CES-D
Jonas et al[22]	6095	Self-report (NHANES interview)	1.73 (1.30–2.31)
Ohira et al[23]	901	Zung SDS	1.9 (1.1–3.5) for total stroke, 2.7 (1.2–6.0) for ischemic stroke
Nilsson et al[24]		Hospitalization for depression	1.22 (1.06–1.41)
Everson et al[29]	6676	Human Population Laboratory Depression scale	1.54 (1.06–2.22) for stroke mortality

CES-D, Centers for Epidemiologic Study–Depression scale; Zung SDS, Zung Self-rating Depression Scale.

mortality, where mortality risk increased as depression symptoms increased. Another prospective cohort study with 29 years of follow-up data also showed that reporting five or more depression symptoms at baseline was associated with a 66% relative increase in stroke mortality, even when other stroke risk factors and change in depression status and other risk factors over time were included in the models.[29]

POSSIBLE MECHANISMS LINKING DEPRESSIVE SYMPTOMS AND VASCULAR RISK

Along with these intriguing epidemiological studies, other interesting pathophysiological data are also emerging related to possible mechanisms of the increased vascular risk in patients with depression. Possible vascular-specific mechanisms linking depressive symptoms and increased vascular risk include serotonin-mediated effects on platelets and increased inflammation (interleukin [IL]-6 and IL-1 β influence depression risk and also stroke risk, possibly via enhanced atherosclerosis). It is not yet clear, however, whether these mechanisms are also related to added vascular risk in patients with PSD. Surface expression of platelet glycoprotein GPIb has been shown to be reduced in stroke patients and in those with depression alone, compared with healthy controls, but no additional reduction was observed in those with both stroke and depression. These data suggest that platelet dysfunction may possibly underlie the observed relationship between depression and increased vascular risk.[30] Another study found that the number of platelet serotonin transporters was low in stroke patients compared with controls, which could theoretically lead to increased platelet aggregation and elevated risk of vascular events.[31] Interestingly, the number of platelet serotonin transporters was not associated with the development of PSD. A possible genetic link between increased risk of depression and increased vascular events has also recently been proposed.[32] This theory suggests that the serotonin gene functional polymorphism may be linked both to increased risk of depression and increased risk of vascular events. Other lines of evidence in this potential relationship come from treatment trials. One study found that in patients with depression after MI, selective serotonin reuptake inhibitor (SSRI) treatment was associated with decreased platelet activation, even in those patients already taking an antiplatelet medication, suggesting a potential mechanism for a reduction in cardiovascular events in depressed patients treated with SSRIs after MI.[33] Another interesting supporting piece of evidence for this mechanism in MI patients is the observation that cognitive behavioral therapy improved depression in post-MI patients but did not reduce subsequent cardiac events, while antidepressant treatment was associated with significantly lower mortality or nonfatal myocardial infarction.[34] Further studies in this area should help clarify whether depression-related disruptions in serotonin and subsequent platelet effects are at least partially related to the relationship between depression and vascular events.

In addition to platelet effects, behavioral factors such as impaired self-management, limited physical activity, impaired social roles and relationships, less collaborative care with providers, and decreased compliance also likely underlie the relationship between depression and vascular disease and may account for the worse outcomes seen in patients with depression in combination with many other medical conditions.[35–39] For example, a longitudinal study of Hispanic subjects found that depressive symptoms were synergistic with diabetes and associated with worse diabetes control and increased micro- and macrovascular complications, even when controlling for multiple sociodemographic characteristics.[35]

Another possible mechanism linking depression and vascular disease is that depressive symptoms may influence the development of other vascular risk factors. Data from the NHANES I Epidemiology Follow-up Study demonstrated in up to 22 years of follow-up that negative affect at baseline was associated with the development of hypertension over time, even when adjusting for baseline blood pressure and other demographic and vascular risk factors.[40] This relationship has been observed in other prospective cohort studies of young adults as well.[41]

PSD EPIDEMIOLOGY

Although methodological differences in study cohorts and methods of depression detection make pooling study results difficult, cumulative evidence indicates that 25 to 40% of stroke patients suffer from PSD, equally divided between major depression and other depressive disorders.[42–54] Importantly, these data come from both practice-based cohorts and population-based studies (Table 3). Foundational work in PSD was done in the 1980s by Robinson and colleagues.[50,51,53] Among their many important contributions were the findings that: (1) the prevalence of DSM-based diagnosis of PSD is at least 30%, (2) PSD usually develops soon after stroke, (3) PSD usually persists throughout the first 6 to 12 months poststroke and often up to 2 years, and (4) PSD is associated with less neurological recovery after stroke. A limitation of this work is the select nature of the population (predominantly hospitalized African-American males). Further, this study was conducted in the early 1980s, before the widespread availability of SSRI and other less toxic antidepressants, and few of the patients with PSD received treatment. Several community-based serial studies have also demonstrated that PSD is frequent, persistent, and undertreated.[42–45,47,49,52,54]

Table 3 Summary of PSD Prevalence Estimates

Study	n	Depression Assessment	Time Poststroke	Prevalence
Andersen et al[42]	285	HDRS	1 year	41%
Astrom et al[43]	80	DSM-III	3 years	16% (12 months); 31% (3 months)
Burvill et al[44]	294	DSM-III	4 months	23%
Fuh et al[45]	45	GDS	Variable	62% (compared with 33% of 1,471 nonstroke subjects)
Herman et al[47]	150	MADRS and Zung SDS	1 year	22–27% (3 months); 21–22% (1 year)
Kotila et al[49]	423	BDI	1 year	47% (3 months); 47% (1 year)
Robinson et al[50]	103	DSM-III	6 months	47%
Pohjasvaara et al[52]	277	DSM-III-R	4 months	40%
Toso et al[54]	1064	BDI, MADRS, DSM-IV	6 months	34%

HDRS, Hamilton Depression Rating Scale; DSM, Diagnostic and Statistical Manual; GDS, Geriatric Depression Scale; MADRS, Montgomery-Asberg Depression Rating Scale; Zung SDS, Zung Self-rating Depression Scale; BDI, Beck Depression Inventory.

A multicenter study in Italy demonstrated DSM-based depression diagnoses in 34% of stroke survivors.[54] The Helsinki Stroke Memory Aging Study[52] reported a prevalence of 40% for any depressive disorder and 26% for major depression at 3 to 4 months post–ischemic stroke; 39% were receiving antidepressant therapy. The FINNSTROKE Study[49] evaluated 321 patients at 3 months poststroke and 311 patients at 12 months and found a depression prevalence of 47% at both time points. Only 17% were undergoing antidepressant drug therapy at 12 months. The Sunnybrook Stroke Study[47] evaluated 150 patients at 3 months and 136 at 12 months and found a prevalence of "marked depressive symptoms" of 27% and 22% at these two time points. Fewer than 25% of depressed patients received antidepressants, and 70% of those depressed at 3 months remained so at 1 year. The Perth Community Stroke Study[44] evaluated 294 patients at 4 months poststroke and found a PSD prevalence of 23%. There were no differences between first-ever and recurrent strokes. At 12 months poststroke, 59% of the men and 30% of the women were still depressed. For those studies that identified major and minor depression it was not apparent that the prognosis differed by type of depressive disorder. The hospital-based studies typically report a higher prevalence of PSD (40% or greater), whereas the community-based studies report prevalences of 20 to 40%. By not assessing patients until 3 to 4 months poststroke, however, most of these community-based studies were not able to assess the prevalence and persistence of early-onset depression and, in particular, its impact on functional recovery and stroke-specific health-related quality of life (HRQOL) during the critical months immediately poststroke.

PSD IMPACTS MANY HEALTH OUTCOMES

PSD is not only common but is also linked to worse outcome in both patients and caregivers after ischemic stroke. Just as depression in general has been associated with poorer functional outcome in a variety of conditions,[58–63] PSD has similarly been linked to worse functional outcome and increased mortality after stroke, even when controlling for other variables. Specifically, depressed patients have been found to have greater impairments at various time points poststroke in activities of daily living.[58–63] This negative effect of PSD was present even after depression remitted[59] and was associated with deterioration in function over time.[58,60] Morris and colleagues also demonstrated that patients with either major or minor depression poststroke were 3.4 times more likely to die during 10-year follow-up, and this risk was even higher in those socially isolated.[64] More recently, data from a nationwide sample of veterans with ischemic stroke who survived at least 30 days poststroke showed that 3-year mortality was increased 25% in those with a new poststroke depression diagnosis compared with those without depression.[65] Finally, there is growing evidence that PSD increases subsequent health care utilization. This relationship has been shown in other conditions,[66–68] but a recent analysis of a national cohort of veterans with ischemic stroke showed that those with depression (and to a lesser extent those with other mental health conditions) poststroke had greater utilization of outpatient health care services and more inpatient admissions, even controlling for other chronic conditions and when mental health outpatient visits were omitted from the analyses.[69]

IMPACT ON STROKE CAREGIVERS

Family caregivers of stroke patients are impacted not only by the stroke itself but also patient PSD. Stroke caregivers in general have higher rates of depression,[70–74] more physical symptoms,[70,74] and higher levels of emotional distress[70,72–74] than caregivers of nonstroke patients. Caregivers of patients with PSD may also be more likely to be depressed themselves.[73] Other factors

that may influence caregiver strain include amount of time spent helping the patient and caregiver health status.[75,76] Caregivers of aphasic patients may be especially likely to experience greater distress and report higher burden.[77] The importance of understanding the complex relationships between caregiver and patient outcomes is increasingly realized,[78,79] as family caregivers play a large role in patient self-management of chronic conditions and in symptom recognition and compliance with treatment.

RISK FACTORS FOR DEVELOPING PSD

Many reports have addressed the question of what specific factors are related to the development of PSD. As with other studies of PSD, the generalizability of these studies are often hampered by selection bias, method of detecting depression, and time frame of assessment. Nonetheless, some reasonably consistent factors emerge as likely risk factors for the development of PSD.

Lesion Location

One of the most studied and debated issues in the field of stroke and depression research is whether specific stroke locations are associated with increased risk of developing depression. This possible explanation for the development of PSD has been attractive to neuroanatomists and neurophysiologists, because theoretically PSD might be more likely to develop after lesions that disrupt central nervous system (CNS) serotonin or norepinephrine pathways. In various analyses, Robinson and colleagues found that left hemisphere lesions, lesions in the right basal ganglia, and lesions closer to the frontal pole were associated with increased risk of developing PSD.[80,81] Another study reported that lesions affecting the pallidum were associated with an increased risk of depression diagnosis 3 months after stroke and that lesion size was also associated with depression risk.[82] Although a well-conducted systematic review of the existing literature did not support the association between any specific lesion location and the development of PSD[83] and population-based studies have generally not found an association between lesion location and PSD, another meta-analysis by Narushima and colleagues did support the relationship of proximity to the frontal pole and PSD risk.[84] One of the difficulties in studying this area, and specifically in conducting meta-analyses, is that a large proportion of the articles on this topic come from overlapping cohorts studied by Robinson and colleagues and thus do not represent independent findings in distinct stroke patients. As new neuroimaging techniques emerge, this issue and the issue of whether lesion location is related to treatment response will likely continue to be studied and debated but, at present, lesion

location should not be used as a variable to determine which stroke patients should be screened for PSD.

Stroke Severity

Many studies have examined the issue of whether persons with more severe stroke are more likely to develop PSD. This can be a complicated issue to examine because these patients are also more likely to have communication and/or cognitive effects of stroke that make depression assessment difficult and because the relationship between stroke severity and depression may be somewhat bidirectional. Stroke survivors with more severe stroke impairments may be more likely to develop depression, but there is also strong evidence that depression after stroke negatively impacts recovery, so cross-sectional studies that do not take into account stroke deficits at the time of stroke onset may reveal only a part of this relationship.

Although the precise relationship may not always be determined and some studies do not report this association,[85,86] multiple studies have found that increased stroke impairment and/or functional dependence are related to PSD at various time points.[87–89] Both Robinson and colleagues[90] and Astrom and associates[43] reported that the relationship between depression and poststroke impairment is dynamic: the strength of their association increased during the first 6 months poststroke and then decreased. Robinson has speculated that reasons for this time-dependent relationship may include: (1) the most impaired patients either are more likely to remain depressed or have worsened depression symptoms over time, (2) depressed patients may have less recovery in function, or (3) other factors influence both depression and impairments/functional recovery poststroke.[91]

Other PSD Risk Factors

Many other factors have also been reported to be associated with increased risk of developing PSD, although again the temporal relationship of these variables is not always clearly evaluated. In addition to lesion location, factors purported to increase risk of developing PSD include: female gender, increasing age, lack of social support, cognitive dysfunction, and prestroke history of depression. One literature synthesis has suggested that the factors most consistently associated with PSD are past history of depression, past personal psychiatric history, dysphasia, functional impairments, living alone, and poststroke social isolation.[92] Differences in study cohorts and measurement of key variables make it difficult to draw widely generalizable conclusions from these data, and so screening of all patients regardless of PSD risk factors seems most appropriate from a clinical standpoint.

SUICIDALITY IN PATIENTS WITH PSD

Because the incidence of successful suicide increases with age, it is important to address the issue of suicidality in stroke survivors. Several reports suggest that suicide rates are increased in stroke survivors, with at least two of these being well-designed population-based cohorts in Denmark in which the risk of suicide was almost twice as high in stroke patients compared with other age-matched persons without stroke.[93,94] Factors in addition to depression symptoms that may be related to this risk include prior history of stroke and increased disability.[95] Many more patients likely have suicidal ideation but do not act on these thoughts: one study reported that 7% of adults with acute medical illnesses (including stroke) had clinically significant suicidal ideation during up to 24 months after the acute event.[96] In our National Institutes of Health (NIH)-funded case management trial in PSD patients, we found that ~10% of stroke survivors endorse "thoughts of death or harming yourself" (item nine from the PHQ-9), but with standardized probe questions, almost all of these represent passive thoughts of death rather than active suicidal ideation (unpublished data). Nonetheless, given the persistent reports of elevated suicide risk in population-based cohorts, these data are another piece of evidence supporting the routine screening for depression in all stroke survivors.

TREATMENT OF DEPRESSION IN STROKE SURVIVORS

Despite the long and extensive history of investigation into the epidemiology and consequences of PSD, surprisingly few well-conducted studies have been done of sufficient size to address critical PSD treatment questions. In general, studies of PSD treatment can be divided into two themes: antidepressants to prevent PSD and antidepressants as treatment of PSD. Recently, Cochrane reviews of antidepressant treatment have been completed for both of these key questions.[97,98] Although both of these reviews conclude that evidence is insufficient to recommend treatment specifically for preventing or treating depression in stroke patients, it would seem overly simplistic and nihilistic to therefore conclude that depression in patients who have had a stroke should therefore remain untreated. This is especially the case as the majority of PSD treatment studies that have been conducted have been small, many have not used rigorous clinical trial methodology, and most trials have demonstrated reduction of depression symptoms in patients on treatment, if not complete remission of depression. Rather, the overwhelming evidence for treating depression, regardless of what other medical conditions coexist, should at present be sufficient for providers to confidently treat depression symptoms in stroke patients. Future trials, like our ongoing National Institute for Neurologic Disorders and Stroke (NINDS)-funded

study of depression case management versus usual care in patients with PSD, will help inform this issue.

To provide help with interpreting the PSD treatment literature, Table 4 details published randomized, blinded, trials of PSD treatment.[99–106] The majority of these studies have tested SSRIs, but a few have used other classes of antidepressant medications. Some trials included only ischemic stroke patients but others included those with hemorrhagic stroke types as well. In general, most studies have demonstrated significant improvements in depression symptoms but not always in complete remission of depression. Whether this reduction in symptoms is clinically meaningful to patients' quality of life and whether treatment of depression affects rate or trajectory of recovery remain important unanswered questions.

Some studies have attempted to compare different antidepressants, but the small sample size raises the question of what difference the study would actually be powered to see. One of these found that citalopram and reboxetine had similar efficacy and low side effect profiles, but that citalopram was more effective in depression with anxiety and reboxetine was more effective in depression with psychomotor retardation.[107] Another study reported that nortriptyline was superior to fluoxetine in efficacy and side effect profile, but this was a very small study with a complicated crossover design and high dropout rate, so conclusions were based on less than 20 participants in each study arm and are thus difficult to interpret.[103]

PREVENTING PSD

Relatively little evidence exists to suggest that treatment of stroke patients to prevent the development of PSD is beneficial, although strategies to address this hypothesis in patients at especially high risk of developing PSD have not been tested. One of the largest prevention trials to date randomized 137 patients to treatment with sertraline versus placebo for 12 weeks.[108] Among treated subjects, 13/70 developed depression by the end of the treatment period, compared with 20/67 in the control group ($P = < 0.05$). Another study randomized 100 stroke patients to the SSRI mianserin versus placebo for 1 year after stroke regardless of depressive symptoms.[109] Early treatment with antidepressants did not prevent PSD, likely due to the high dropout rate (only 64 patients had 12-month outcome assessment) and small sample size. Another small study did show significant benefit for preventing depression, with 2 of 35 mirtazipine-treated patients developing depression compared with 14 of 35 control patients ($P = < 0.05$).[110] Finally, a small randomized, placebo-controlled trial of fluoxetine 20 mg within 2 weeks of stroke onset did not reduce depression symptoms compared with placebo at 4 weeks but was associated with reduced depression

Table 4 Randomized, Placebo-Controlled Clinical Trials of Antidepressants for Treatment of PSD

Study	Drug, Duration	Drug vs Placebo	Results
Lipsey et al[99]	Nortriptyline, 6 weeks	17 vs 22	HAM-D improved 11.5 points (14 to 2.5) in drug group vs 7 (16.5 to 9.5) in placebo group ($P = 0.0006$)
			Zung depression score improved 18 vs 12 points ($P = 0.03$)
Reding et al[100]	Trazodone, ~4 weeks	27 total	Randomized 27 admitted inpatients in stroke rehabilitation to trazodone vs placebo, whether or not they were depressed
			Improved Zung scores in the subgroup of 16 patients who had a positive DST
Andersen et al[102]	Citalopram, 6 weeks	33 vs 33	HAM-D improved 8 (19.4 to 11.4) in drug group vs 4.8 (18.9 to 14.1) in placebo group ($P < 0.05$)
			In the 59 completers, HAM-D more likely to fall $\geq 50\%$ in drug than in placebo group (59% vs 28%, $P < 0.05$)
Fruehwald et al[106]	Fluoxetine, 12 weeks	26 vs 24	HAM-D improved in 8 of treatment group compared with 6 of placebo group ($P > 0.05$)
Murray et al[105]	Sertraline, 26 weeks	62 vs 61	31 in treatment group compared with 34 in placebo group ($P > 0.05$)
Wiart et al[104]	Fluoxetine, 6 weeks	16 vs 15	MADRS decreased in 16.7 in treatment group compared with 8.5 in placebo group ($P < 0.05$)
Ohtomo et al[101]	Aniracetam, 12 weeks	108 vs 65	Clinician impression of no depression at end of treatment in 52 of treatment group compared with 32 in placebo group ($P > 0.05$)
Robinson et al[103]	Fluoxetine, nortriptyline, 12 weeks	23 vs 16 vs 17	Successful treatment in 10/16 nortriptyline, 2/23 fluoxetine, and 4/17 placebo patients
			Significantly lower HAM-D scores in nortriptyline group (9.0) and placebo group (12.2) than fluoxetine group (18.5)

HAM-D, Hamilton Depression Inventory; MADRS, Montgomery-Asberg Depression Rating Scale.

symptoms at 12 weeks and 18 months. This suggested a relatively high rate of spontaneous remission of early depression symptoms, but also demonstrates potential intermediate and long-term benefit of antidepressant treatment in patients with depression after stroke.[111]

Regardless of whether they are used for prevention or treatment of PSD, even less is known about other classes of medications and nonpharmacological depression treatments, including psychostimulants,[112,113] tricyclic antidepressants,[114,115] and buspirone.[116] Other studies have included short-term non–placebo-controlled trials[117] or open trials of antidepressants and placebo.[118,119] There are even fewer studies of nonpharmacological treatments, like psychotherapy[120] or electroconvulsive therapy, for PSD.[121] However, two recent studies suggest a possible role for nonpharmacological treatments in reducing anxiety poststroke. In one of these, a supportive program (three telephone calls and one home visit) after stroke did not reduce depression symptoms at 6 months poststroke compared with usual care, but did reduce anxiety and improve subjects' SF-36 Role-Emotional scores.[122] Another study reported that an educational program reduced patient anxiety (not depression) at 6 months compared with usual care.[123] Further studies of this type, employing proven depression treatments like cognitive behavioral therapy and using proven delivery models like telephone-based counseling and collaborative care, should be undertaken in stroke survivors.[124]

Not surprisingly, in light of the relatively meager amount of high-quality treatment evidence, many important questions remain unanswered. Although the notion that PSD is undertreated is generally supported by the community-based studies and by surveys in the United States, undertreatment of PSD was not found in a recent Swedish national survey.[125] In this self-report survey, 14% of stroke survivors had depressive symptoms and 25% of those with stroke were taking an antidepressant. However, 8% of those reporting depressive symptoms were not treated. Stroke survivors were significantly more likely to be taking an antidepressant than those without stroke. As antidepressant use has become more convenient and better accepted culturally, and medications with less side effects have become available, it may be that more patients will be treated. Conversely, recent negative press about antidepressants, particularly SSRIs, and suicide risk in children may reduce providers' willingness to treat and patients' acceptance of treatment.

Another critical question that is still largely unanswered is whether treatment of PSD reduces mortality risk. One study that has shed some light on this is

the trial of fluoxetine, nortriptyline, and placebo for 12 weeks in the first 6 months poststroke.[126] During 9 years of follow-up, those patients who completed the full dose of antidepressant therapy ($n = 53$) had significantly lower mortality than those receiving placebo for 12 weeks ($n = 28$). However, the relatively high number of "noncompleters" ($n = 23$) and their relationship to the analysis in this report make it somewhat difficult to draw firm conclusions regarding the data. For example, perhaps other unmeasured characteristics that differed between completers and noncompleters in the study are associated with subsequent mortality risk. Other questions that need further study include: (1) Does the improvement in depression symptoms translate to remission of depression diagnosis and to improved quality of life in stroke survivors? (2) Do early symptoms of PSD (i.e., in the first 1 to 2 months) need to be treated, or does PSD during this time period often spontaneously improve? (3) Does treatment of PSD influence stroke recovery? (4) If patients are not depressed soon after stroke, how likely are they to become depressed later? (5) Do symptoms of emotionality immediately after stroke predict the likelihood of subsequent depression? One recent small study suggested that the early initiation of antidepressants in patients with PSD may be important. In this study ($n = 62$), those who received antidepressant treatment within 1 month poststroke had less functional impairment at 3 months and at 2 years poststroke compared with those who received antidepressants after 1 month poststroke.[127]

WHO SHOULD DIAGNOSE AND TREAT PSD?

Although neurologists may or may not elect to manage depression in their patients, in some patients with chronic progressive neurological disease the neurologist may in effect be a primary care provider. Thus, knowing the current best practices in depression assessment, treatment, and care delivery in primary care may be beneficial. Stroke patients have complicated post–acute outpatient needs, including review of diagnostic tests, adjustment of medications to treat stroke risk factors, assessment of rehabilitation needs, and symptom management. These competing patient and provider demands can make depression detection difficult. In some managed care settings, including the Veterans Health Administration (VHA), annual depression screening for all patients in primary care is a performance measure. Because almost one third of patients screen positive for depression at their first neurology clinic visit, neurologists may also want to adopt a brief, self-completed depression screening tool like the PHQ-9 in their outpatient clinic materials.[128] In addition to initiating an antidepressant, key components of quality depression care include a follow-up visit within 6 weeks of initial

diagnosis and maintenance of antidepressant therapy for at least 6 months. One care model that can help ensure adequate follow-up and promote adherence to medication management is telephone-based psychotherapy and care management.[124,129] At the very least, neurologists should consider screening all stroke patients for depression in the first few months poststroke, and then either initiating treatment or ensuring prompt communication with primary care providers to initiate and monitor treatment.

FUTURE DIRECTIONS/CONCLUSION

Much work remains to be done to better understand the reasons why stroke survivors develop depression, to predict what treatments are most likely to be efficacious in ameliorating or preventing depression, and to understand how depression influences stroke recovery across the spectrum of behavioral, anatomical, chemical, and genetic mediators. Likewise, much work also remains to be done to ensure that patients and providers recognize the symptoms of depression after stroke and that patients receive and accept best practices in treating depression.

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