Poststroke Depression

A Scientific Statement for Healthcare Professionals From the American Heart Association/American Stroke Association

The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists.

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Abstract—Poststroke depression (PSD) is common, affecting approximately one third of stroke survivors at any one time after stroke. Individuals with PSD are at a higher risk for suboptimal recovery, recurrent vascular events, poor quality of life, and mortality. Although PSD is prevalent, uncertainty remains regarding predisposing risk factors and optimal strategies for prevention and treatment. This is the first scientific statement from the American Heart Association on the topic of PSD. Members of the writing group were appointed by the American Heart Association Stroke Council’s Scientific Statements Oversight Committee and the American Heart Association’s Manuscript Oversight Committee. Members were assigned topics relevant to their areas of expertise and reviewed appropriate literature, references to published clinical and epidemiology studies, clinical and public health guidelines, authoritative statements, and expert opinion. This multispecialty statement provides a comprehensive review of the current evidence and gaps in current knowledge of the epidemiology, pathophysiology, outcomes, management, and prevention of PSD, and provides implications for clinical practice. (Stroke. 2016;47:00-00. DOI: 10.1161/STR.0000000000000113.)

Key Words: AHA Scientific Statements • depression • management • prevention & control • screening • stroke • treatment

Depression occurs in approximately one third of stroke survivors at any one time and is associated with poor functional outcomes and higher mortality. Although poststroke depression (PSD) is one of the most common complications after stroke, few guidelines exist regarding assessment, treatment, and prevention of PSD. This scientific statement summarizes published evidence on the causes, predisposing factors, epidemiology, screening, treatment, and prevention of PSD; illuminates gaps in the literature; and provides management implications for clinical practice.

Methods

Writing group members were nominated by the committee chair on the basis of their previous work in relevant topic areas and were approved by the American Heart Association Stroke Council’s Scientific Statement Oversight Committee and the American Heart Association’s Manuscript Oversight Committee. Poststroke depression: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2016;47:00-00. doi: 10.1161/STR.0000000000000113.

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Committee. Multiple disciplines were represented, including neurology, psychiatry, psychology, neurorehabilitation, primary care, epidemiology, biostatistics, and nursing. The writing group met by telephone to determine subcategories to evaluate. These included 9 sections that covered the following: incidence, prevalence, and natural history; pathophysiology; predictors; functional outcomes; quality of life (QOL); healthcare use; mortality; screening; and management and prevention. Each subcategory was led by a primary author, with 1 to 3 additional coauthors. Full searches of PubMed, Ovid MEDLINE, Ovid Cochrane Database of Systematic Reviews, Ovid Central Register of Controlled Trials databases, Internet Stroke Center/Clinical Trials Registry (http://www.strokecenter.org/trials/), and National Guideline Clearinghouse (http://guideline.gov/) were conducted of all English-language articles on human subjects, published through February of 2015. The evidence was organized within the context of the American Heart Association Framework. Drafts of summaries and suggestions/considerations for clinical practice were circulated to the entire writing group for feedback. Sections were revised and merged by the Chair. The resulting draft was reviewed and edited by the Vice-Chair, and the entire committee was asked to approve the final draft. Changes to the document were made by the Chair and Vice-Chair in response to peer review, and the document was again sent to the entire writing group for suggested changes and approval. A summary of findings is available in the Table.

Incidence, Prevalence, and Natural History of PSD

Depression is common after stroke, affecting approximately one third of stroke survivors at any one time after stroke (compared with 5%–13% of adults without stroke), with a cumulative incidence of 55%.\(^1\) Hackett et al performed a systematic review and meta-analysis of 51 studies conducted before June 2004 and revealed a pooled frequency estimate of PSD of 33% (95% confidence interval [CI], 29%–36%).\(^7\) All studies included ischemic stroke, most included intracerebral hemorrhage, and the majority excluded subarachnoid hemorrhage and transient ischemic attack. Valid methods were used to ascertain depression in these studies. The primary end point was the proportion of patients who met the diagnostic category of depression, which included the following: (1) depressive disorder, depressive symptoms, or psychological distress, as defined by scores above a cut point for abnormality on a standard scale; (2) major depression, or minor depression (or dysthymia) according to the third, fourth, and fifth editions of the Diagnostic and Statistical Manual of Mental Disorders, or other standard diagnostic criteria using structured or semistructured psychiatric interviews. Ayerbe et al’s subsequent systematic review and meta-analysis of 43 cohorts published before August 2011 (n=20,293) revealed a similar pooled frequency of PSD of 29% (95% CI, 25%–32%).\(^8\) The frequency remained fairly constant for the first year after stroke and diminished slightly thereafter (28%; 95% CI, 23%–34% within 1 month of stroke; 31%; 95% CI, 24%–39% at 1–6 months; 33%; 95% CI, 23%–43% at 6 months to 1 year; and 25%; 95% CI, 19%–32%) beyond 1 year). Only 5 studies in Ayerbe et al’s systematic review reported other measures of natural history of PSD: incidence in year 1 ranged from 10% to 15% (2 studies); cumulative incidence ranged from 39% to 52% (3 studies with follow-up periods between 1 and 5 years); and 15% to 50% of patients with PSD within 3 months of stroke recovered 1 year later. All longitudinal studies revealed a dynamic natural history, with new cases and recovery of depression occurring over time.\(^8\) Little is known about whether the natural course of PSD differs in those with a history of depression before stroke.

Hackett et al updated their systematic review and meta-analysis in 2014\(^4\) to include all published observational studies with prospective consecutive recruitment of stroke patients and assessment of depression or depressive symptoms at prespecified time points (until May of 2013; 61 studies; n=25,488; 29 cohorts were also in Ayerbe et al’s review). Their study revealed similar results, with depression present in 33% (95% CI, 26%–39%) at 1 year after stroke, with a decline beyond 1 year: 25% (95% CI, 16%–33%) up to 5 years, and 23% (95% CI, 14%–31%) at 5 years.\(^1\) Prevalence of PSD was lower beyond 1 year: Subgroup analyses revealed a pooled prevalence estimate of 31% (95% CI, 27%–35%) for the 48 studies (n=23,654) including individuals with a history of depression; 34% (95% CI, 29%–39%) for the 25 studies (n=19,218) including individuals with aphasia; and 33% (95% CI, 28%–38%) for the 25 studies (n=56,58) of people with first-ever stroke.\(^1\)

In Hackett’s and Ayerbe’s meta-analyses, the prevalence rates did not differ significantly over time during the first year after stroke (within 1 month from stroke, 1–6 months, or 6–12 months) or by setting (hospital, rehabilitation, or population based). The studies included in Hackett’s and Ayerbe’s reviews were heterogeneous in nature, using a variety of methods to diagnose depression and different thresholds for the same scale. The hospital- and rehabilitation-based studies had numerous exclusion criteria (such as excluding those with a history of depression), thus limiting their generalizability. Statistical quality and presentation of methods and results were poor in many studies, and important covariates (such as history of depression) were not included in multivariable models in most studies. Few of the multivariable models were likely to be stable as the ratio of events per variable in the model met or surpassed the recommended minimum.

In summary, approximately one third develop PSD at some point after stroke. The frequency is highest in the first year, at nearly 1 in 3 stroke survivors, and declines thereafter.

Pathophysiology of PSD

The pathophysiology of PSD is poorly understood. The cause of PSD is likely multifactorial—with biological and psychosocial components—and may vary depending on timing after event. An understanding of the pathophysiology of PSD may aid in its management; for example, PSD resulting from biological causes could potentially respond better to pharmacological therapy, whereas PSD resulting from psychosocial causes could possibly respond more favorably to psychotherapy and social support interventions.

Studies have revealed an association between PSD and poststroke cognitive and functional deficits, indirectly suggesting that PSD may be a psychological reaction to these deficits.\(^9,10\) In addition, numerous psychosocial risk factors for
PSD are also risk factors for depression without stroke, such as past psychiatric history, premorbid neurotic personality traits, and social isolation.\(^{11,12}\)

In contrast, evidence suggests that PSD has underlying biological causes and is not merely a psychological response to new disability or a life-threatening event. First, 1 study showed that depression was more common after stroke than other physical illnesses with similar levels of physical disability\(^{13}\); however, other studies have not corroborated these findings.\(^{14,15}\) Second, PSD has been observed in individuals with anosognosia.\(^{16}\)

Third, late-onset depression has been associated with white matter disease and small silent infarcts.\(^{12,17,18}\) Fourth, poststroke depressive-like symptoms have been noted in several animal models.\(^{19,20}\) Last, depression has been reported after transient ischemic attack and minor stroke (National Institutes of Health Stroke Scale score ≤5 at discharge).\(^{21,22}\)

Proposed biological factors contributing to PSD include lesion location, genetic susceptibility, inflammation,
neurogenesis in response to ischemia, alterations in neurotrophic factors, disruption of cortico-striato-pallido-thalamic-cortical projections, and alterations in serotonergic, noradrenergic, and dopaminergic pathways, leading to changes in amine levels. The hypothesis that lesion location was associated with PSD gained popularity in the 1970s when Robinson et al reported associations between laterality of experimentally induced stroke, brain catecholamine concentrations, and activity in rats and subsequently between left hemispheric (particularly frontal) strokes and PSD in humans. Numerous cohort studies subsequently investigated the association between lesion location and PSD; a meta-analysis of 35 cohorts published before August of 1999 and a subsequent systematic review and meta-analysis of 35 cohorts published before January of 2014 found no association between PSD and lesion location. Subgroup analyses stratified by time since stroke onset to assessment for PSD showed that between 1 and 6 months after stroke, right hemispheric strokes were associated with lower odds of PSD (odds ratio [OR]=0.79; 95% CI, 0.66–0.93). In contrast, a meta-analysis of 52 studies published before July 2003 found a weak relationship between PSD and right hemispheric lesions (overall weighted mean effect size=−0.0801; 95% CI, −0.146–−0.014; P=0.014). The authors of this meta-analysis appropriately indicated that the effect size was small and may not have practical significance. When they only included high-quality studies, there was no relationship between PSD and lesion location. The various systematic reviews used slightly different selection criteria for the included studies and distinct statistical methods for the meta-analysis. All 3 systematic reviews identified limitations to the analyses because of multiple sources of heterogeneity such as varying time intervals between stroke and depression assessment, different depression scales, exclusion of patients with aphasia, and heterogeneous methods of reporting results. Studies assessing genetic associations with PSD have been limited and small. Higher serotonin transporter gene (SLC6A4) promoter methylation status in the presence of the SLC6A4 linked promoter region (5-HTTLPR) s/s genotype was associated with PSD at 2 weeks and 1 year after stroke, as well as worsening of depressive symptoms over the first year after stroke (n=286 stroke subjects). In that same cohort, a higher brain-derived neurotrophic factor methylation status and the brain-derived neurotrophic factor val66met polymorphism were independently associated with prevalent PSD (n=286 stroke subjects). Alleles associated with reduced anti-inflammatory cytokine function such as the interleukin-4 + 33C/C and the interleukin-10 -1082A/A genotypes have also been associated with PSD (n=276 stroke subjects). Proinflammatory cytokines may play a role in PSD by inducing alterations of the hypothalamic-pituitary-adrenal axis and decreasing serotonin synthesis. Studies have alluded to a direct involvement of the serotonergic system, regardless of the degree of disability and lesion location.

A meta-analysis of the most studied biological markers of PSD (cerebral blood flow, cortisol levels, inflammatory marker levels, brain-derived neurotrophic factor levels, and brain volume/atrophy) including studies through June of 2012 (33 studies; n=1893 participants) showed associations between PSD and high postdexamethasone cortisol levels (OR, 3.28; 95% CI, 1.28–8.39), lower serum brain-derived neurotrophic factor levels (standardized mean difference, −0.52; 95% CI, −0.84 to −0.21), smaller amygdala volumes (standardized mean difference, −0.45; 95% CI, −0.89 to −0.02), and overall brain perfusion reduction (standardized mean difference, −0.35; 95% CI, −0.64 to −0.06). There were no significant associations between PSD and inflammatory markers such as C-reactive protein, interleukin-6, interleukin-18, or tumor necrosis factor-alpha. Inflammation assessed within a mean of 35 days after stroke; however, the studies included individuals with transient ischemic attack and silent stroke and apathy (without diagnosis of depression), potentially obscuring the results. Despite the aforementioned weaknesses and additional limitations (relatively small number of studies, different scales to assess depression), this meta-analysis suggested that cerebral perfusion reduction, higher cortisol levels and low levels of neurotrophic factors, and amygdala volume reduction may be promising biological markers for PSD.

In summary, the pathophysiology of PSD is complex and likely involves a combination of biological and psychosocial factors. Further research is needed to develop a better understanding of PSD pathophysiology with an aim to develop targeted interventions for prevention and treatment.

Predictors of PSD

Three independent systematic reviews of observational studies without corresponding meta-analyses (Hackett et al: 20 cohorts, n=17934; Kutlubaev et al: 23 cohorts, n=18374; De Ryck et al: 24 cohorts, n=14642; Ayerbe et al: 10 cohorts, n=16045) have identified consistent predictors of depression after stroke. There were few overlapping cohorts in the reviews reflecting the different inclusion and exclusion criteria set by the review authors. The data indicated that physical disability, stroke severity, depression before stroke, and cognitive impairment consistently had a positive association with the development of PSD. Other factors that have been identified as predictors include a lack of family and social support after stroke and anxiety after stroke. Older age, female sex, diabetes mellitus, stroke subtype, education level, living alone, and previous stroke have not shown a consistent association with the subsequent development of depression. People with transient ischemic attacks and those with obvious speech disturbances or communication difficulties (eg, aphasia, confusion, or dementia), impaired consciousness, severe cognitive decline or subarachnoid hemorrhage were excluded from most studies limiting our ability to generalize these findings. The statistical methods in most of the studies included in these systematic reviews were poor, and most of the samples were too small for multivariate analyses.

In summary, a multitude of studies have evaluated predictors of PSD, but because of differences in inclusion and exclusion criteria, statistical methods, and inadequate sample sizes for multivariate analyses, generalizability is limited. The most consistent predictors of PSD have been physical disability, stroke severity, history of depression, and cognitive
impairment. Further studies are needed to develop a better understanding of predictors of PSD.

**Association Between PSD and Functional Outcomes**

PSD might conceivably influence functional outcome by limiting participation in rehabilitation, directly decreasing physical, social, and cognitive function, or perhaps affecting the biological process of neuroplasticity. A systematic review of 14 studies before May of 2013 with 4498 participants assessing the association between PSD and stroke outcome (4 population-based studies [n=2800], 5 hospital-based [n=800], and 5 rehabilitation-based [n=898]) revealed that PSD had a consistent adverse effect on outcomes. In 6 of 8 studies, depression was associated with poor functional outcomes (3 of 5 with multivariable analyses); the other 2 studies found no association between PSD and functional improvement. A lifetime history of depression and active depression affected functional outcome at 3 and 12 months in 1 cohort study.

A randomized controlled trial (RCT) comparing fluoxetine to placebo within 5 to 10 days after stroke showed lower PSD occurrence rates and significant improvement in motor function in the fluoxetine group. Even after statistically controlling for the reduction in depression, motor improvement was improved in the fluoxetine group. This finding raises the question of whether depression prevents motor recovery (and this negative effect is reversed by treatment), or whether there may be some effect of fluoxetine or selective serotonin reuptake inhibitors (SSRIs) in general on neuroplasticity and motor recovery. Indeed, other studies have shown that SSRI use after stroke generally improves motor recovery. The factors influencing whether PSD worsens outcome, and methods to counteract these effects, require further exploration.

In summary, PSD is associated with poorer functional outcomes after stroke. Treatment with fluoxetine was associated with lower PSD occurrence rates and improvement in motor recovery in 1 RCT. Further research is needed to assess the effect of PSD on outcomes and to develop optimal strategies to counteract these effects.

**Association Between PSD and QOL**

To date, the association between PSD and poststroke QOL has not been explored in a systematic review or meta-analysis. Individual studies have found that poststroke depressive symptoms are associated with reduced poststroke QOL as measured by the Short-Form General Health Survey, EuroQol questionnaire and Assessment of Quality of Life. Poststroke mood change is 1 of the factors with the greatest effect on poststroke QOL. Stroke survivors’ cognitive and language impairments may necessitate proxy responses for self-reported outcomes. Proxies tend to report worse QOL scores than do stroke survivors themselves. These differences make it necessary to carefully examine the composition of outcomes, cohorts, and use of proxies to look for potential biases in studies exploring the association of PSD and QOL.

In summary, a few studies suggest that PSD adversely affects QOL. Further research is needed to elucidate the independent effect of PSD on QOL and to determine how to improve QOL in individuals with or at risk for PSD.

**Effect of PSD on Healthcare Use**

To date, no systematic review has assessed the association between PSD and healthcare use; however, individual studies have shown that PSD is associated with higher rates of healthcare use after stroke, including inpatient healthcare use and total healthcare use. In 2 large Veterans Health Administration cohorts in the United States, those with PSD had longer lengths of stay and higher outpatient and inpatient use in the 12 months after stroke. In addition to PSD, other mental health diagnoses after stroke have also been associated with increased healthcare use.

Although the relationship between PSD and subsequent healthcare use is established, few studies, and none specifically in stroke patients, have assessed whether treatment of depression is associated with a decrease in healthcare use. Addressing this question is complex, given that healthcare use and depression treatment are understandably confounded. One study among patients aged 65 years and older with prior thromboembolic events (including some with stroke) found that antidepressant use was not associated with an increase or decrease in healthcare use; but no large, high-quality studies of the relationship between depression treatment and subsequent healthcare use in patients with PSD have been published.

In summary, a few studies have shown an association between PSD and healthcare use. Further studies are needed to evaluate the effect of treatment of PSD on subsequent healthcare use.

**Association Between PSD and Mortality**

PSD has been associated with higher mortality rates after stroke. A systematic review and meta-analysis of studies published before November of 2012 (13 studies; 59598 individuals with stroke: 6052 with PSD and 53546 from comparison groups) revealed a pooled OR of 1.22 (95% CI, 1.02–2.26) for increased/early mortality at follow-up for individuals with PSD. The association between PSD and mortality was strongest in individuals <65 years of age. Adjustment for comorbidities, smoking, alcohol use, SSRI use, social support, and adherence with medications did not change these associations. A subsequent study of stroke survivors followed in the South London Stroke Register revealed that individuals with PSD had a greater risk of mortality (HR, 1.41; 95% CI, 1.13–1.77). The association between PSD and mortality was strongest in individuals <65 years of age. Adjustment for comorbidities, smoking, alcohol use, SSRI use, social support, and adherence with medications did not change these associations. Individuals who started SSRIs after stroke had higher risk of mortality, independently of PSD at 3 months (HR, 1.72; 95% CI, 1.34–2.20).

This study should be interpreted with caution because numerous models were used to describe the association between depression and mortality, and the only common factors between these models were age, sex, ethnicity, and stroke severity. The relationship between SSRIs...
and mortality requires a rigorous analysis of the interactions with other key variables such as depression, disability, and comorbid medical conditions.

In summary, PSD is associated with higher mortality after stroke.

Screening for PSD

Stroke patients present unique challenges to identifying depression. Stroke-related neurological symptoms such as aprotosodic speech, abulia, or flat affect may hinder healthcare practitioners' identification of PSD, whereas aphasia may lead to undiagnosed and inadequate treatment of depression. A high index of suspicion by all members of the interdisciplinary treatment team is therefore necessary to accurately recognize depression. Cues of PSD can be subtle, such as refusal to participate in therapy. Patients can experience emotional lability or a pseudobulbar affect after a stroke, often prompting the team to erroneously diagnose a patient with PSD. Emotional lability can be frustrating for the patient and family; however, symptoms typically decline over time and do not require treatment for depression.

Screening is useful for prevalent conditions that can be effectively treated but not readily detected without screening. Three key factors are important to consider when determining whether screening is useful for PSD: (1) the validity and reliability of screening tools to detect PSD; (2) whether treatment of PSD improves depressive symptoms, QOL, functional outcomes, and mortality; and (3) whether PSD screening improves outcomes. In this section, we address the first and third points. The second point will be addressed in the following section on management.

Screening Tools for PSD

The optimal screening tool for PSD remains unclear. Meader et al conducted a meta-analysis to determine which screening and reliability of screening tools to detect PSD; (2) whether treatment of PSD improves depressive symptoms, QOL, functional outcomes, and mortality; and (3) whether PSD screening improves outcomes. In this section, we address the first and third points. The second point will be addressed in the following section on management.

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Implication for Clinical Practice

In summary, 24 studies (n=2907 participants) showed that the CES-D, HDRS, and PHQ-9 had high sensitivity for detecting PSD; however, the studies had several limitations, including generalizability.

Effects of Screening for PSD on Outcomes

The controversy surrounding routine screening for PSD lies in the third question: does screening for PSD improve outcomes? In the primary care setting, initial RCTs found little if any benefit from screening for depression; although screening improved recognition and treatment, it did not improve depressive symptoms or outcomes. Subsequent RCTs showed that depression screening in combination with a collaborative care intervention—a multiprofessional approach to patient care involving a structured patient management plan and interventions, scheduled patient follow-ups, and enhanced interprofessional communication—improved outcomes. Collaborative care for depression can include a variety of interventions from the simple (telephone calls to encourage medication compliance) to the complex (intensive follow-up including structured complex psychosocial interventions). Studies that are based in primary care have shown that essential elements of collaborative care programs are the use of evidence-based protocols for treatment, structured collaboration between primary care providers and mental health
specialists, active monitoring of adherence to treatment and of outcomes, and (in some cases) structured programs of psychotherapy delivered in primary care.\textsuperscript{69} In nonstroke populations, collaborative care programs have resulted in improved control of depression\textsuperscript{70} and comorbid illness\textsuperscript{68} in a cost-effective manner.\textsuperscript{71} On the basis of this evidence, the US Preventive Services Task Force recommends routine screening for depression in primary care settings where adequate systems are in place to ensure accurate diagnosis, effective treatment, and appropriate follow-up.\textsuperscript{72}

The studies of PSD screening combined with collaborative care in populations with stroke are scarce and small. The AIM (Activate-Initiate-Monitor) RCT (N=188) used a care management strategy (n=89 at 12 weeks) in which nurse care managers supervised by study physicians used psychoeducational sessions to Activate survivors and families to understand depression and accept treatment, Initiate antidepressant treatment, and Monitor treatment with scripted bimonthly telephone calls. The control condition (n=93 at 12 weeks) was usual care with the same number of telephone sessions that focused only on recognition and monitoring of stroke symptoms and risks. Remission (HDRS<8) was achieved in 39\% vs 23\% (\textit{P}=0.01) favoring the intervention group. Reduction of depression symptoms (HDRS<8 or a 50\% reduction in scores from baseline) was achieved in 51\% versus 30\% (\textit{P}=0.005), favoring the intervention group.\textsuperscript{73} Although another study (n=652) revealed that implementation of clinical improvement teams increased the diagnosis and provision of treatment for PSD, the presence or absence of depression was not measured as an outcome.\textsuperscript{74}

Other facts to consider are costs associated with screening, the yield of systematic screening (ie, will it identify more cases than would be identified without routine screening), and whether treatment of depression in those who may have been missed without screening (ie, milder cases) is effective. Although multiple guidelines recommend routine screening for depression in poststroke patients,\textsuperscript{75-79} it is important to note that the guidelines were not developed on the basis of RCT evidence showing that PSD screening improves outcomes.

**Implication for Clinical Practice**

Systematic screening for PSD may improve outcomes, provided that processes are in place to assure accurate diagnosis, timely and effective treatment, and follow-up. Further research is needed to determine whether screening for PSD—in conjunction with collaborative care to ensure timely intervention, treatment, and follow-up—improves outcomes in diverse populations of stroke survivors.

**Depression in Caregivers**

Caregivers are also at particular risk for depression and declining health. Depression rates of stroke caregivers may even exceed that of stroke patients.\textsuperscript{80} Risk factors include older age of caregiver, stroke severity, and spouse compared with next of kin. Caregivers who experience strain associated with caring for a disabled elderly person are at increased risk of mortality themselves.\textsuperscript{81} The members of the stroke care team should also be cognizant of the caregiver and offer mental health support when there is suspicion for depression or maladaptive behavior.

**Management and Prevention of PSD**

**Management: Pharmacotherapy to Treat PSD**

Few RCTs have examined the efficacy of antidepressants to treat PSD. These RCTs were heterogeneous, typically had small sample sizes, often were of short duration, and varied in critical aspects of their design including characteristics of the study population, method for screening and diagnosing PSD, and operational definitions of primary and secondary outcomes. Rather than relying on a structured psychiatric interview and established diagnostic criteria, many pharmacotherapy trials defined PSD with an arbitrary cutoff score on a scale measuring the severity of depressive symptoms. Furthermore, the RCT that enrolled the greatest number of patients with PSD to date (n=285) did not use a rigorous operational diagnosis of depression to ascertain cases.\textsuperscript{82} Most trials excluded individuals with aphasia, cognitive impairment and psychiatric comorbidity, limiting their generalizability. In addition, patients with PSD were enrolled at different times after an index stroke, although clinical correlates of depression vary with time, affecting the probability of response. Treatment objectives have been vague; few of the RCTs provided a clear definition of what they considered remission or response and consequently failed to report their respective rates.

A meta-analysis by Hackett et al.\textsuperscript{83} tried to overcome these shortfalls while reviewing 12 RCTs of the efficacy of antidepressant medication to treat PSD (n=1121). Given the limitations described above, the authors were mostly restricted to providing a narrative review of the available evidence. Nonetheless, the data suggested a beneficial effect of antidepressants on remission (pooled OR for meeting criteria for depression: 0.47; 95\% CI, 0.22–0.98) and response, measured as a >50\% reduction in mood scores (pooled OR, 0.22; 95\% CI, 0.09–0.52). Adverse events were more frequent among those subjects who received the active medication compared with those who received placebo. These included central nervous system side effects (OR, 1.96; 95\% CI, 1.19–3.24), gastrointestinal side effects (OR, 2.37; 95\% CI, 1.38–4.06) and other side effects (OR, 1.51; 95\% CI, 0.91–2.34). There were insufficient trials of each of the antidepressants to conduct meta-analyses by antidepressant. Since the aforementioned systematic review, there have been no new publications of double-blinded, placebo-controlled trials examining the efficacy of pharmacological agents to treat PSD, with the exception of a trial of nefiracetam that proved to be equivalent to placebo in treating PSD.\textsuperscript{84} The available evidence on the efficacy of psychostimulants is mostly limited to case reports and open label trials. Methylphenidate may be useful in inpatient settings or when promptness of response is required. A small RCT (n=21) of its efficacy was conducted in the late 1990s in stroke rehabilitation settings. When compared to placebo, methylphenidate significantly reduced the severity of depressive symptoms and was associated with improved motor recovery.\textsuperscript{85} Stimulants have been used to augment partial responses to SSRIs, especially in the presence of residual cognitive impairments or...
fatigue; however, given their cardiovascular side effects and potential for inducing reversible vasoconstriction syndrome, larger, adequately powered RCTs, with long-term follow-up are needed to determine whether they are effective in improving outcomes after stroke.

**Implication for Clinical Practice**

In summary, 12 trials (n=1121) suggested that antidepressant medications may be effective in treating PSD; further research is needed to determine optimal timing, threshold, and medications for treatment.

**Management: Neuromodulation**

Preliminary evidence (n=92 patients) from a small RCT suggested that noninvasive brain stimulation techniques such as repetitive transcranial magnetic stimulation might be effective among depressed stroke patients who do not respond to a trial with antidepressants.

There are no RCTs of electroconvulsive therapy in stroke survivors with PSD; however, electroconvulsive therapy has been used as a last resort to treat refractory PSD. Treatment should be started at the lowest effective energy levels, using pulsatile currents, increased spacing of treatments (2–5 days between treatments), and fewer treatments in an entire course (ie, 4–6). Nondominant unilateral electroconvulsive therapy is the preferred technique.

In summary, further studies are needed to determine the efficacy of neuromodulation on treating PSD.

**Management: Psychosocial Interventions to Treat PSD**

A Cochrane review and meta-analysis first published in 2004 and updated in 2008 (3 trials including 445 participants) indicated a paucity of well-designed trials of psychosocial interventions for the treatment of PSD with no evidence of benefit of psychotherapy (cognitive behavioral therapy, motivational interviewing, a supportive psychological intervention) over control conditions for treating PSD. Several ongoing trials were identified in that review, 4 of which have been published since 2007. Three of these individual trials indicated a benefit of brief psychosocial therapies for established PSD and for prevention.

Two RCTs included people with ischemic stroke screened for depressive symptoms within 1 to 4 months after stroke. The diagnosis of major or minor depression was confirmed with a structured clinical interview consistent with the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition criteria or the Stroke Aphasic Depression Questionnaire 10-item version (cutoff ≥26) or the visual analogue sad item (cutoff ≥50) completed by a nurse, relative, or caregiver. The primary outcome of depression was measured using HDRS at 9 weeks, 6 months, and 1 year in 2 trials by outcome assessors masked to the participant’s study group and uninvolved in the treatment, and at 3 and 6 months after randomization using the Stroke Aphasic Depression Questionnaire 21-item hospital version completed by a relative or caregiver.

In the Living Well With Stroke Study (N=101), ischemic stroke survivors were randomized to a brief psychosocial intervention (n=48), which comprised 9 sessions of counseling by psychosocial nurse practitioners about behavioral observation, information about adapting to stroke and mood, and problem solving, versus usual care (n=53) including follow-up with their own provider and informational literature from the American Stroke Association. Antidepressants were recommended by the participants’ providers for both groups. Remission or greater reduction in depression symptoms was achieved more often in the intervention group than usual care at all time points (9 weeks, 6 months, and 1 year). Remission (HDRS ≤9) was 47% versus 19% (P=0.001) at 9 weeks and 48% versus 27% (P=0.031) at 1 year, both favoring intervention.

A second Living Well With Stroke Study (N=100) included participants with ischemic and hemorrhagic stroke, had a shortened intervention (6 sessions), and compared in-person versus telephone delivery versus usual care. HDRS scores were reduced by 42% (telephone) and 40% (in person) immediately after intervention compared with 30% for usual care. Although this difference favored the intervention, it was not significant. By 12 months after intervention, there was no significant difference among the 3 conditions, with all 3 groups achieving a 40% reduction in scores.

The findings of the Living Well With Stroke Study RCTs were supported by a much smaller, multifaceted intervention, conducted during rehabilitation. Twenty-four patients with ischemic or hemorrhagic stroke in a rehabilitation hospital were randomly assigned to receive 12 weekly sessions of ecosystem-focused therapy (n=12), which emphasized a family-focused, problem-solving identification of valued activities and coordination of therapies. The comparison group (n=12) had 12 weekly sessions focused on education about stroke and depression and reviewed written materials. Participants were included in the trial based on the PHQ-9, with depression diagnosis confirmed by Diagnostic and Statistical Manual of Mental Disorders, 4th Edition criteria and depression severity measured by HDRS scores. At week 12, 66.7% of the ecosystem-focused therapy participants had achieved remission of depression (HDRS<10), which was significantly greater than the 16.7% achieving remission in the control group.

The CALM trial (Communication and Low Mood) (N=105) randomized stroke survivors with aphasia to receive up to 20 1-hour sessions of behavioral therapy over 3 months (n=51), delivered by an assistant psychologist supervised by a clinical psychologist and supported by an intervention manual developed from studies of cognitive behavioral therapy or usual care (n=54). Mean Stroke Aphasic Depression Questionnaire scores decreased from baseline to 6 months by 6 points in the intervention group compared with an increase of 1.9 points in the control group. When baseline values and communication impairment were controlled for, participants in the intervention group had improved mood compared with controls (P=0.002).

These 4 trials of 330 participants were relatively small, and 3 were conducted at single institutions, but the reduction in depression results were consistent with the exception of the second Living Well With Stroke Study.

**Implication for Clinical Practice**

In summary, 7 trials (n=775) suggest that brief psychosocial interventions may be useful and effective in treatment of PSD.
Whether antidepressant medication is a necessary or beneficial adjuvant cannot be established from these trials because of a lack of placebo controls.

Management: Stroke Liaison Workers
Stoke liaison workers provide services including education, information provision, social support, and liaison with other services. A systematic review of 15 interventions (2743 participants) in unselected groups of stroke survivors (ie, trials were not limited to people with or without depression) did not show any evidence of a beneficial effect from stroke liaison workers on depression, when compared with controls (standardized mean reduction in depression scores, −0.04; 95% CI, −0.12 to 0.04).91

Implication for Clinical Practice
In summary, 15 trials (n=2743) have not revealed a beneficial effect from stroke liaison workers on PSD; however, the trials included individuals without a diagnosis of PSD. Further studies are needed to determine the effect of liaison worker on those with established PSD.

Management: Information Provision
In a systematic review of studies assessing the effectiveness of information provision strategies in improving outcomes in stroke survivors (17 RCTs; n=2831), 12 trials evaluated the effect of passive or active information provision on depression. Dichotomous data were available for 956 of 1280 participants from 8 trials and revealed no significant difference on depression. Continuous data were available for 720 of 1016 participants in 7 trials and showed a small benefit of information provision on depression scores (weighted mean reduction in scores of −0.52; 95% CI, −0.93 to −0.10; P=0.01); however, the clinical significance of this improvement is unclear. Active information provision was significantly more effective than passive information for depression (P<0.02 for all trials), and anxiety (P<0.05 for trials reporting dichotomous data, P<0.01 for trials reporting continuous data).52 There was considerable variability in the interventions evaluated and quality of the trials.

Implication for Clinical Practice
In summary, 7 trials (n=720) suggest that information provision provides a small benefit in depression scores; however, the clinical significance of this improvement is unclear.

Management: Self-Management
The US Institute of Medicine has defined self-management as “the tasks that individuals must undertake to live with one or more chronic conditions. These tasks include having the confidence to deal with medical management, role management and emotional management of their conditions.”93 Self-efficacy, an individual’s confidence in their ability to carry out a specific task or behavior, is a mediator in the causal pathway between acquiring self-management skills and enactment of self-management behaviors. A systematic review without meta-analysis assessed the effectiveness of self-management strategies on depression, as a secondary end point, after stroke. No evidence of benefit was seen in 2 RCTs including 303 participants.94 Further research is needed to assess the effect of self-management teaching on PSD incidence and outcomes.

In summary, few studies have assessed the effectiveness of self-management strategies on PSD; further studies are needed to determine whether these strategies are beneficial.

Prevention of PSD Using Pharmacological Interventions
PSD is a disorder in which the ratio between recent incidence and prevalence is high (ie, high influx disorder).95 Given the high prevalence and association with functional impairment, poor QOL, and increased morbidity and mortality, PSD is an ideal target for selective prevention.

Salter et al performed a meta-analysis summarizing the findings of 8 RCTs (from 1990 through 2011) assessing the efficacy of preventive pharmacological interventions among 776 initially nondepressed stroke patients.96 Pooled analyses revealed that the likelihood of developing PSD was reduced among patients receiving active pharmacological treatment (OR, 0.34; 95% CI, 0.22–0.53), especially after a 1 year treatment (OR, 0.31; 95% CI, 0.18–0.56), and with the use of an SSRI (OR, 0.37; 95% CI, 0.22–0.61). The most commonly reported side effects were nausea, diarrhea, fatigue, and dizziness. There were no significant differences between the active treatment and placebo groups in the frequency of these symptoms. Only tremor was significantly associated with sertraline in 1 of the RCTs.96 This review included 2 publications from the same cohort and an open trial (drug vs usual care). These review results are contrary to an earlier 2008 Cochrane systematic review including 12 placebo-controlled trials of 611 individuals, finding no evidence that antidepressant drugs prevented depression after stroke.97 The Salter meta-analysis included 3 small trials of antidepressant medications published after the Cochrane review, and 1 other trial has since been published.98 All 4 trials (401 participants) showed benefit of their respective antidepressant (fluoxetine n=59, placebo n=59; milnacipran n=56, placebo n=46; paroxetine n=32, placebo n=32; and escitalopram n=59, placebo n=58) over placebo. With the exception of the single open label trial, the studies had satisfactory methodological quality; however, only 3 studies reported their mechanism for concealed allocation, and all studies excluded those with aphasia and/or significant cognitive impairment, limiting generalizability.

Implication for Clinical Practice
In summary, 8 trials (n=776) suggest that pharmacological treatment may be effective in preventing PSD; however, further studies are needed in more representative samples of stroke survivors, and additional study is required to determine the optimal timing and duration of treatment.

Prevention of PSD Using Psychosocial Interventions
A Cochrane review and meta-analysis first published in 2004, and updated in 2008 (4 trials including 902 participants), indicated a small but significant effect of psychosocial strategies (problem-solving therapy, a broad home-based therapy, motivational interviewing) to prevent PSD (OR, 0.64; 95% CI, 0.42–0.98).99 Limitations included considerable heterogeneity in design, analysis, and reporting of clinical trials, variable...
Depression is common after stroke, affecting up to one third of stroke survivors at any one time. The natural history of PSD is dynamic; however, symptoms most frequently develop in the first year. The pathophysiology of PSD is poorly understood; proposed mechanisms include psychosocial factors such as psychological response to new disability and social isolation, as well as biological factors such as genetic susceptibility, inflammation, alterations in neurotrophic factors, disruption of neural networks, and alterations in serotonergic, noradrenergic, and dopaminergic pathways. The most consistent predictors of PSD include physical disability, stroke severity, depression before stroke, and cognitive impairment. Individuals with PSD have higher healthcare use, poorer functional outcomes and QOL, and higher mortality. Numerous screening tools are reliable in identifying depression in stroke survivors; however, further studies are needed to determine the optimal timing, setting, and follow-up for screening. Clinical trials of antidepressants in individuals with PSD have shown a beneficial effect on depression remission and response, but trials were limited by small samples, variable criteria for PSD, and vague definitions for remission and response. Several recent trials have indicated a benefit of brief psychosocial therapies for treatment. The effect of information provision, collaborative care interventions, and clinical improvement teams on PSD require further study; however, preliminary data suggest a benefit of the latter 2. Pharmacological and psychosocial interventions have been shown to reduce the likelihood of developing PSD. The high prevalence and poor prognosis of depression in patients with stroke supports a strategy of increased awareness, timely screening, and prompt evidence-based management; however, further studies are needed to determine the optimal timing and method for screening, and ideal treatment strategy. This scientific statement aimed to draw attention to this underrecognized, underinvestigated, and undertreated problem with the goal of summarizing current knowledge, emphasizing implications for clinical practice, and recommending areas for future research.

Conclusions
### Disclosures

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*Modest.
†Significant.

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References


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