AHA/ASA Scientific Statement

Post-Stroke 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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I. Introduction

• Depression occurs in approximately 1/3 of stroke survivors at any one time and is associated with poor functional outcomes and higher mortality
• Few guidelines exist for recognition, treatment, and prevention of Poststroke Depression (PSD)
• Summarizes published evidence regarding causes, predisposing factors, epidemiology, screening, treatment, and prevention of PSD, illuminates gaps in the literature, and provides management implications for clinical practice.
II. Methods

• Writing group members included individuals from neurology, psychiatry, psychology, neurorehabilitation, primary care, epidemiology, biostatistics, and nursing
• Decided on 10 categories:
  – incidence, prevalence and natural history; pathophysiology; predictors; functional outcomes; quality of life; mortality; healthcare utilization; screening, and management and prevention
• Subcategory was led by a primary author, with 1-3 additional co-authors
• 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
II. Methods

• All English language articles regarding human subjects, published by February 2015
• Evidence was organized within the context of the AHA Framework
• Depression affects approximately 1/3 of stroke survivors at any one time post-stroke compared to 5-13% of adults without stroke, with a cumulative incidence of 55%

• 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% CI 29-36%)
  – All studies included ischemic stroke, most included intracerebral hemorrhage, and the majority excluded subarachnoid hemorrhage and transient ischemic attack
• Primary end-point was proportion of patients who met the diagnostic category of depression, which included
  – depressive disorder, depressive symptoms, or ‘psychological distress’, as defined by scores above a cut-point for abnormality on a standard scale
  – major depression, or minor depression (or dysthymia) according to DSM-IIIR, DSM-IV, DSM 5, or other standard diagnostic criteria using structured or semi-structured psychiatric interviews
• Ayerbe et al’s subsequent systematic review and meta-analysis of 43 cohorts published prior to August 2011 (n=20,293) revealed a similar pooled frequency of PSD of 29% (95% CI 25–32%)
III. Incidence, Prevalence, & Natural History of PSD

• Frequency remained fairly constant for the first year post-stroke and diminished slightly thereafter
  – 28%, 95% CI 23–34% within a month of stroke
  – 31%, 95% CI 24–39% at 1–6 months
  – 33%, 95% CI 23–43% at 6 months to 1 year
  – 25%, CI 19–32 beyond 1 year

• Five 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)
  – 15–50% of patients with PSD within 3 months of stroke recovered 1 year later
III. Incidence, Prevalence, & Natural History of PSD

• All longitudinal studies revealed a dynamic natural history, with new cases and recovery of depression occurring over time.
• Little is known about whether the natural course of PSD differs in those with a history of depression prior to stroke.
• Hackett et al updated their systematic review and meta-analysis in 2014 to include all published observational studies with prospective consecutive recruitment of stroke patients and assessment of depression or depressive symptoms at pre-specified time-points until May 2013—61 studies; n=25,488; 29 cohorts were also in Ayerbe et al review.
III. Incidence, Prevalence, & Natural History of PSD

- Depression present in 33% (95% CI 26-39%) at one year post stroke, with a decline beyond one year
- 25% (95% CI 16-33%) up to five years
- 23% (95% CI 14-31%) at five years
- Prevalence of PSD was lower beyond one year
- Subgroup analyses
  - 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 to 39%) for the 25 studies (n=19,218) including individuals with aphasia
  - 33% (95% CI 28 to 38%) for the 25 studies (n=5,658) of people with first-ever stroke
• In the meta-analyses by Hackett and Ayerbe the prevalence rates did not differ significantly over time during the first year post-stroke (within 1 month from stroke, 1-6 months, or 6-12 months) or by setting (hospital, rehabilitation, or population-based)
  – studies included in the reviews were heterogeneous in nature, using a variety of methods to diagnose depression and different thresholds for the same scale
  – 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 was poor in many studies
  – and important covariates (such as history of depression) were not included in multivariable models in most studies
• Approximately one third develop PSD at some point post-stroke
• Frequency is highest in the first year, at nearly one in three stroke survivors, and declines thereafter
IV. Pathophysiology of PSD

- Pathophysiology is poorly understood and likely multifactorial
- PSD due to biological causes could potentially respond better to pharmacologic therapy
- PSD due to psychosocial causes could possibly respond more favorably to psychotherapy and social support interventions
- Some studies suggest PSD may be a psychological reaction to the deficits
- Psychosocial risk factors for PSD are risk factors for depression without stroke
  - past psychiatric history, premorbid neurotic personality traits, and social isolation
Some studies suggest PSD has underlying biological causes and is not merely a psychological response to new disability or a life-threatening event

- one study showed that depression was more common after stroke than other physical illnesses with similar levels of physical disability
- PSD has been observed in individuals with anosognosia
- late-onset depression has been associated with white matter disease and small silent infarcts
- post-stroke depressive-like symptoms have been noted in several animal models
- depression has been reported after transient ischemic attack and minor stroke (NIHSS ≤5 at discharge)
IV. Pathophysiology of PSD

• Proposed biological factors contributing to PSD
  – 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

• Meta-analysis of 35 cohorts published prior to August 1999 and a subsequent systematic review and meta-analysis of 43 cohorts published prior to January 2014 (n= 5,507) 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 associated with lower odds of PSD (OR = 0.79, 95% CI 0.66–0.93).
• Meta-analysis of 52 studies published prior to July 2003 (n=3,668) 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)
  – When only high-quality studies, there was no relationship between PSD and lesion location
IV. Pathophysiology of PSD

• 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)

• Same cohort, a higher Brain Derived Neurotrophic Factor (BDNF) methylation status and the BDNF 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 hypothalamus-pituitary-adrenal axis and decreasing serotonin synthesis
IV. Pathophysiology of PSD

• Meta-analysis of the most studied biologic markers of PSD (cerebral blood flow, cortisol levels, inflammatory marker levels, BDNF levels, and brain volume/atrophy) including studies through June 2012 (33 studies; n=1,893 participants) showed associations between PSD and high post-dexamethasone cortisol levels (OR 3.28; 95% CI 1.28-8.39), lower serum BDNF levels (standardized mean difference [SMD] -0.52; 95% CI -0.84 to -0.21), smaller amygdala volumes (SMD -0.45; 95% CI -0.89 to -0.02), and overall brain perfusion reduction (SMD -0.35; 95% CI -0.64 to -0.06)
IV. Pathophysiology of PSD

• No significant associations between PSD and inflammatory markers such as C-reactive protein, IL-6, IL-18, or TNF-alpha
  – 7 studies; inflammation assessed within a mean of 35 days post-stroke
  – studies included individuals with TIA and silent stroke and apathy (without diagnosis of depression)
IV. Pathophysiology of PSD Summary

• 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.
V. Predictors of PSD

- Three independent systematic reviews of observational studies without corresponding meta-analyses (Hackett et al: 20 cohorts, n=17,934 and Kutlubaev et al: 23 cohorts, n=18,374; De Ryck et al: 24 cohorts, n=14,642; Ayerbe et al: 10 cohorts n=16,045) have identified consistent predictors of depression after stroke
  - 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 include lack of family and social support post-stroke and anxiety after stroke

- Older age, female sex, diabetes, stroke subtype, education level, living alone, and previous stroke have not shown a consistent association with the subsequent development of depression
V. Predictors of PSD

• People with TIAs and those with obvious speech disturbances or communication difficulties (e.g. aphasia, confusion, or dementia), impaired consciousness, severe cognitive decline or subarachnoid hemorrhage were excluded from most studies limiting our ability to generalize these findings

• 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
V. Predictors of PSD Summary

• Multitude of studies have evaluated predictors of PSD, but due to 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.
VI. Association Between PSD & Functional Outcomes

- PSD might conceivably influence functional outcome by limiting participation in rehabilitation, directly decreasing physical, social, and cognitive function, or perhaps affecting the biologic process of neuroplasticity.

- Systematic review of 14 studies prior to May 2013 with 4,498 participants assessing the association between PSD and stroke outcome (4 population-based including 2800 participants, 5 hospital-based including 800 participants, and 5 rehabilitation-based including 898 participants) revealed that PSD had a consistent adverse effect on outcomes.
VI. Association Between PSD & Functional Outcomes

• Six of eight studies, depression was associated with poor functional outcomes (3/5 with multivariable analyses)
• Two 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 one cohort study
VI. Association Between PSD & Functional Outcomes

• An RCT comparing fluoxetine to placebo within 5-10 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

• 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 SSRIs in general on neuroplasticity and motor recovery
VI. Association Between PSD & Functional Outcomes 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 one RCT
• Further research is needed to assess the impact of PSD on outcomes and to develop optimal strategies to counteract these effects
VII. Association Between PSD & Quality of Life

- Association between PSD and post-stroke quality of life (QOL) has not been explored in a systematic review or meta-analysis.

- Individual studies have found that post-stroke depressive symptoms are associated with reduced post-stroke QOL as measured by the Short-Form General Health Survey (SF-36), EuroQoL questionnaire and Assessment of Quality of Life.

- Stroke survivors’ cognitive and language impairments may necessitate proxy responses for self-reported outcomes.
  - Proxies tend to report worse QOL scores than stroke survivors themselves.
VII. Association Between PSD & Quality of Life Summary

• Few studies suggest that PSD adversely affects QOL
• Further research is needed to elucidate the independent impact of PSD on QOL and to determine how to improve QOL in individuals with or at risk for PSD
No systematic review has assessed the association between PSD and healthcare utilization.

Individual studies have shown that PSD is associated with higher rates of healthcare utilization post-stroke, including inpatient utilization and total healthcare utilization.

Two large Veterans Health Administration cohorts in the United States, those with PSD had longer lengths of stay and higher outpatient and inpatient utilization in the 12 months post-stroke.

Other mental health diagnoses post-stroke have also been associated with increased utilization.
Few studies, and none specifically in stroke patients, have assessed whether treatment of depression is associated with a decrease in utilization.

One study among patients 65 and older with prior thromboembolic event (including some with stroke) found that antidepressant use was not associated with an increase or decrease in utilization.

No large, high-quality studies of the relationship between depression treatment and subsequent healthcare utilization in patients with PSD have been published.
A few studies have shown an association between PSD and healthcare utilization.

Further studies are needed to evaluate the impact of treatment of PSD on subsequent healthcare utilization.
• Post-stroke depression has been associated with higher mortality rates after stroke.

• Systematic review and meta-analysis of studies published prior to November 2012 (13 studies; 59,598 individuals with stroke: 6,052 with PSD and 53,546 from comparison groups) revealed a pooled OR of 1.22 (95% CI 1.02-1.47) and pooled HR of 1.52 (95% CI 1.02-2.26) for increased/early mortality at follow-up for individuals with PSD.

• Ayerbe et al’s 2013 meta-analysis found an association between PSD and mortality in two out of three studies that investigated this association.
IX. Association Between PSD & Mortality

• Study of stroke survivors followed in the South London Stroke Register revealed individuals with PSD had a greater risk of mortality (HR 1.41, 95% CI 1.13-1.77)
• Association between PSD and mortality was strongest in individuals younger than 65 years of age
• 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)
  – should be interpreted with caution, as 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
• PSD is associated with higher mortality after stroke.
X. Screening for PSD

• Three key factors are important to consider when determining whether screening is useful for PSD
  – the validity and reliability of screening tools to detect PSD
  – whether treatment of PSD improves depressive symptoms, QOL, functional outcomes, and mortality
  – whether PSD screening improves outcomes
X. Screening for PSD

• Meader et al conducted a meta-analysis to determine which screening tools were most accurate for detecting PSD.
  – included studies through November 2012 (24 studies; n=2907 participants)
• 20-item Center of Epidemiological Studies-Depression Scale (CES-D) (sensitivity: 0.75; 95% CI 0.60-0.85; specificity: 0.88; 95% CI 0.71-0.95), 21-item HDRS (sensitivity: 0.84; 95% CI 0.75-0.90; specificity: 0.83; 95% CI 0.72-0.90), and 9-item PHQ-9 (sensitivity: 0.86; 95% CI 0.70-0.94; specificity: 0.79; 95% CI 0.60-0.90) appeared to be the optimal measures for screening
  – CES-D and HDRS had high sensitivity, they may not be feasible in a busy clinical practice, and PHQ-9 may be more pragmatic
X. Screening for PSD

• Limitations included
  – significant heterogeneity between studies, narrow inclusion and exclusion criteria, not reporting stroke type (ischemic vs. hemorrhagic), inadequate reporting of blinding of assessments, not reporting predefined cut-offs, rarely comparing multiple tools in the same population, not assessing scales in different languages, race/ethnic groups, and cultures, and lack of information concerning drop out

• PHQ-2 performed poorly (sensitivity 0.79, 95% CI 0.55-0.92; specificity 0.76, 95% CI 0.62-0.85)
  – Multiple choice version
• Two versions of the PHQ-2
  – yes/no version, developed in 1997, which has excellent sensitivity for diagnosing major depression in the general population
    ◆ screens positive if one or both of the two core symptoms (depressed mood and anhedonia) is present
    ◆ analysis of 1,024 participants with coronary heart disease enrolled in the Heart and Soul Study, of which 147 (14%) had a history of stroke, the yes/no PHQ-2 had sensitivity of 0.90 (95% CI 0.86-0.94) and specificity of 0.69 (95% CI 0.66-0.73
  – multiple-choice version, developed in 2003, has a 6-point scale and the cut point for a positive screen varies by population (≥2 or ≥3)
X. Screening for PSD

- Timing of Screening
- Meader et al performed subgroup analyses by timeframe post-stroke and found that 6 scales had sufficient data for meta-analysis in the acute (e.g. hospital setting and within 6 months of stroke) setting
  - Geriatric Depression Scale 15 (GDS 15), Montgomery Asberg Depression Rating Scale (MADRS), HDRS, Hospital Anxiety and Depression Scale (HADS-Total and HADS-D), and Beck Depression Inventory (BDI)
  - HDRS had the highest sensitivity and positive predictive value, while HADS-Total was most specific
X. Screening for PSD

• Four scales where meta-analysis was possible in post-acute (receiving outpatient or inpatient rehabilitation treatment) settings
  – HDRS, CES-D, HADS-D, and BDI
  – CES-D had the highest positive predictive value and the highest utility for screening, followed by the HDRS
X. Screening for PSD

• 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 multi-professional approach to patient care involving a structured patient management plan and interventions, scheduled patient follow-ups, and enhanced inter-professional communication) improved outcomes

• Collaborative care for depression
  – includes a variety of interventions from the simple (telephone calls to encourage medication compliance) to the complex (intensive follow-up including structured complex psychosocial interventions
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.

Non-stroke populations, collaborative care programs have resulted in improved control of depression and comorbid illness in a cost-effective manner.

- 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.
X. Screening for PSD

- Activate-Initiate-Monitor (AIM) RCT (N=188)
  - 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
  - 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% (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% vs 30% p=0.005, favoring the intervention group
X. Screening for PSD

• Consider costs associated with screening and whether treatment of depression in those who may have been missed without screening (i.e. milder cases) is effective
• Guidelines were not developed based upon RCT evidence showing that PSD screening improves outcomes
• Stroke-related neurological symptoms such as aprosodic speech, abulia, or flat affect may hinder health care practitioners’ identification of PSD while aphasia may lead to undiagnosed and inadequate treatment of depression
• High index of suspicion by all members of the interdisciplinary treatment team is necessary to accurately recognize depression
X. Screening for PSD

• Patients can experience emotional lability or a pseudobulbar affect after a stroke, often prompting the team to erroneously diagnose a patient to PSD

• Emotional lability typically decline over time and do not require treatment for depression

• Caregivers are also at particular risk for depression and declining health
  – Depression rates of stroke caregivers may even exceed that of stroke patients
  – 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
X. Screening for PSD Summary
Implication for Clinical Practice

• Twenty-four studies (n=2907 participants) showed that the CES-D, HDRS, and PHQ-9 had high sensitivity for detecting PSD
  – the studies had several limitations, including generalizability.

• Systematic screening for PSD with the 9-item PHQ-9 is pragmatic, has high sensitivity for detecting PSD, and 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.
• Few RCTs have examined the efficacy of antidepressants to treat PSD
  – 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
• RCT that enrolled the greatest number of PSD patients to date (n=285) did not use a rigorous operational diagnosis of depression to ascertain cases
• Most trials excluded individuals with aphasia, cognitive impairment and psychiatric comorbidity, limiting their generalizability
• PSD patients were enrolled at different times after an index stroke
XI. Management & Prevention of PSD
Pharmacotherapy to treat PSD

• Meta-analysis by Hackett et al of 12 RCTs studying the efficacy of antidepressant medication to treat PSD (n=1,121)
• Given above limitations the authors were mostly restricted to providing a narrative review of the available evidence
• 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 to those who received placebo
  – 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)
• Insufficient trials of each of the antidepressants to conduct meta-analyses by antidepressant
• Since the 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
• Evidence on the efficacy of psycho-stimulants is mostly limited to case reports and open label trials

• Small RCT (n= 21) of methylphenidate’s 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

• Given psycho-stimulants’ cardiovascular side effects and potential for inducing reversible vasoconstriction syndrome, larger, adequately powered RCTs, with long-term follow up are needed to determine if they are effective in improving outcomes after stroke
• Implication for Clinical Practice
• Twelve 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
• Preliminary evidence (n=92 patients) from a small RCT suggested that non-invasive 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
• No RCTs of ECT in stroke survivors with PSD
  – ECT has been used as a last resort to treat refractory PSD
• Treatment should be started at lowest effective energy levels, using pulsatile currents, increased spacing of treatments (2 to 5 days between treatments), and fewer treatments in an entire course (i.e., 4-6)
• Non-dominant unilateral ECT is the preferred technique
Further studies are needed to determine the efficacy of neuromodulation on treating PSD.
• 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’ over control conditions for treating PSD
• Four trials have been published since 2007
  – Three of these individual trials indicated a benefit of brief psychosocial therapies for established PSD and for prevention
Living Well with Stroke Study (N=101), ischemic stroke survivors were randomized to a brief psychosocial intervention (N=48) which comprised of 9 sessions of ‘counseling’ by psychosocial nurse practitioners about behavioral observation, information about adapting to stroke and mood, and problem-solving, vs. 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 one year). Remission ($\text{HDRS} \leq 9$) was 47% vs 19% ($p=0.001$) at 9 weeks and 48% vs 27% ($p=0.031$) at 1 year, both favoring intervention.
• 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 vs. telephone delivery vs. usual care.
• HDRS scores reduced by 42% (telephone) and 40% (in-person) immediately following intervention compared to 30% for usual care
  – not significant
• By 12 months following intervention there was no significant difference among the 3 conditions, with all three groups achieving a 40% reduction in scores
Multifaceted intervention, conducted on twenty-four patients with ischemic or hemorrhagic stroke in a rehabilitation hospital randomly assigned to
  – Receive 12 weekly sessions of ‘ecosystem focused therapy’ (N=12) which emphasized a family focus, problem-solving, identification of valued activities and coordination of therapies
  – Comparison group (N=12) had 12 weekly sessions focused on education on stroke and depression and reviewed written materials

Participants included in the trial based on the Patient Health Questionnaire (PHQ)-9, with depression diagnosis confirmed by DSM-IV criteria and depression severity was measured by HDRS scores

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 control group
• Communication and Low Mood (CALM) trial (N=105) randomized stroke survivors with aphasia to receive
  – Up to 20 one hour sessions of behavioral therapy over three 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
  – Usual care (N=54)
  – Mean Stroke Aphasic Depression Questionnaire scores decreased from baseline to six months by 6 points in the intervention group compared with an increase of 1.9 points in the control group
  – After baseline values and communication impairment were controlled for, participants in the intervention group had improved mood compared with controls (p=0.002)
XI. Management & Prevention of PSD
Psychosocial interventions to treat PSD

• **Implication for Clinical Practice**
• Seven 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 due to a lack of placebo-controls.
• Systematic review of 15 interventions (2,743 participants) in unselected groups of stroke survivors (i.e. 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 to controls (standardized mean reduction in depression scores -0.04, 95% CI -0.12 to 0.04)
XI. Management & Prevention of PSD

Stoke liaison workers

- **Implication for Clinical Practice**
- Fifteen trials (n=2743) have not revealed a beneficial effect from stroke liaison workers on PSD
  - 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
Systematic review of 17 RCTs (n=2831) assessing the effectiveness of information provision strategies in improving outcomes in stroke survivors, 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 revealed no significant difference on depression.
XI. Management & Prevention of PSD

Information Provision

- **Implication for Clinical Practice**
- Seven trials (n=720) suggest that information provision provides a small benefit in depression scores
  - clinical significance of this improvement is unclear
Self-management: “the tasks that individuals must undertake to live with one or more chronic conditions

- include having the confidence to deal with medical management, role management and emotional management of their conditions

Systematic review without meta-analysis assessed the effectiveness of self-management strategies on depression, as a secondary endpoint, after stroke

- No evidence of benefit was seen in two RCTs including 303 participants
• Few studies have assessed the effectiveness of self-management strategies on PSD
• Further studies are needed to determine if these strategies are beneficial
XI. Management & Prevention of PSD
Prevention of PSD using pharmacologic interventions

• Given the high prevalence and association with functional impairment, poor quality of life, and increased morbidity and mortality PSD is an ideal target for selective prevention

• Salter et al performed a meta-analysis summarizing findings of 8 RCTs (1990-2011) assessing the efficacy of preventive pharmacologic interventions among 776 initially non-depressed stroke patients.
  – Pooled analyses revealed the likelihood of developing PSD was reduced among subjects receiving active pharmacologic 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)
  – most commonly reported side effects: nausea, diarrhea, fatigue, and dizziness with no significant differences between active treatment and placebo groups in frequency of these symptoms
• Four of the trials (401 participants) showed benefit of their respective antidepressant over placebo
  – fluoxetine n=59, placebo n=59
  – milnacipran n=56, placebo n=46
  – paroxetine n=32, placebo n=32
  – escitalopram n=59, placebo n=58)
XI. Management & Prevention of PSD

Prevention of PSD using pharmacologic interventions

• Implication for Clinical Practice
  • Eight trials (n=776) suggest that pharmacologic treatment may be effective in preventing PSD
  • 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
• Cochrane review and meta-analysis first published in 2004, and updated in 2008 (four trials - 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)

• Results since 2008 review, one long term follow-up study of people with and without high depressive symptom burden at baseline (n=411)
  – group that received motivational interviewing sessions (n=204) was more likely to have normal mood (48% vs 38% control, OR 1.66, 95% CI 1.08-2.55) and to have survived at 12 months (6.5% died in intervention vs 12.8% control, OR 2.14; 95% CI 1.06-4.38)

• Formal diagnoses of depression were not made in this study
• Multi-site prevention trial included pharmacologic and psychosocial treatment for 176 non-depressed stroke survivors enrolled within 3 months of stroke

• Participants were randomized to one year of treatment either with a double blind trial of escitalopram (N=59) vs. placebo (N= 58) or a non-blinded problem solving therapy group (N=59)
  
  – placebo were more likely to report clinical depression (HR 4.5, 95% CI 2.4-8.2) than those who participated in the problem-solving treatment (HR 2.2, 95% CI 1.4-3.5) and than those taking escitalopram
  
  – four in the escitalopram group developed new symptoms of major depression when the drug was discontinued after one year, whereas no one in the placebo or problem-solving group developed new symptoms of depression
• **Implications for Clinical Practice**
• Five trials (n=1,078) suggest that psychosocial therapies may prevent the development of PSD
• Studies are not generalizable to all stroke survivors, given their narrow inclusion and exclusion criteria
• Further research with more rigorous methods are needed to assess the impact of psychotherapy on prevention of PSD
XII. Recommendations for Future Research

• Further elucidate pathophysiology of PSD, including relative contributions of biological and psychosocial factors in the development of PSD

• Determine if pathophysiology of early PSD differs from late-PSD

• Assess impact of PSD on outcomes and develop optimal strategies to counteract these effects

• Further elucidate the independent impact of PSD on QOL and to determine how to improve QOL in individuals with or at risk for PSD

• Evaluate the impact of treatment of PSD on subsequent healthcare utilization
XII. Recommendations for Future Research

• Assess risks and benefits of routine screening for PSD and determine optimal timing, frequency, setting, and method for screening

• Conduct large, multi-center, international RCTs to determine whether screening for PSD - in conjunction with collaborative care to ensure timely intervention, treatment, and follow up - improves outcomes

• Conduct large, multi-center, international RCTs to identify safe and effective treatments for PSD, optimal timing and thresholds for treatment, and to determine whether effective treatment of PSD improves survival and other outcomes after stroke

• Determine optimal strategies to prevent PSD
XIII. Conclusion

• Depression affects up to one third of stroke survivors at any one time, most frequently develop in the first year
• Pathophysiology of PSD is poorly understood
• Most consistent predictors of PSD include physical disability, stroke severity, depression prior to stroke, and cognitive impairment
• Individuals with PSD have higher healthcare utilization, poorer functional outcomes and quality of life, and higher mortality
• Numerous screening tools are reliable in identifying depression in stroke survivors but 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
• Impact of information provision, collaborative care interventions, and clinical improvement teams on PSD require further study
  – preliminary data suggest a benefit of the latter two
XIII. Conclusion

- Pharmacologic and psychosocial interventions have been shown to reduce the likelihood of developing PSD
- High prevalence and poor prognosis of depression in patients with stroke supports a strategy of increased awareness, timely screening, and prompt evidence-based management
  - 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 under-recognized, under-investigated and under-treated problem with the goal of summarizing current knowledge, emphasizing implications for clinical practice, and recommending areas for future research.
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