Stroke

TOPICAL REVIEW

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Depression, Anxiety, and Suicide After Stroke: A Narrative Review of the Best Available Evidence

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ABSTRACT: Depression and anxiety each affect around 1 in 3 people during the first year after a stroke. Suicide causes the death of about 3 to 4/1000 stroke survivors during the first 5 years. This narrative review describes the best available evidence for the epidemiology of depression, anxiety, and suicide; their prevention; and the treatment of anxiety and depression. We conclude with directions for future research.

Key Words: anxiety ■ depression ■ psychology ■ stroke ■ suicide

In June 2021, the Stroke Association (United Kingdom) James Lind Alliance Priority Setting Partnership reported that the mental and psychological problems after stroke were the top priorities for recovery and rehabilitation research.[1] Thus, it is timely to review current evidence to inform future research.

This narrative review focuses on anxiety and depression, which are associated with impaired quality of life and poorer functional outcomes after stroke.[2] We also discuss suicide—a devastating, though infrequent, possible consequence of stroke. We do not discuss symptoms of low mood and anxiety that are not severe enough to diagnose a mental disorder.

METHODS

We first searched for systematic review evidence about (1) the prevalence and incidence of anxiety, depression, and suicide and (2) interventions to treat and prevent anxiety, depression, and suicide-related behaviors. We then performed forward citation searches of recent systematic reviews (<5 years) to identify new studies. As this is a narrative review, we do not report the results of our search strategy, selection criteria, or the quality rating of studies reviewed.

Poststroke Anxiety

Anxiety as an Adaptive Response

Stroke threatens survival, independence, and people's ability to participate in occupational and social activities. Survivors with disabling strokes face uncertainties about recovery, while those with nondisabling strokes or transient ischemic attacks are made aware of the ongoing threat of recurrence, disability, or death. Dangers or threats trigger anxiety symptoms and behavioral reactions that seek to address the perceived threat. These behavioral reactions are learnt or innate and occur with or without our conscious control.

Definition of Anxiety Disorders

Maladaptive anxiety is when fear or anxiety becomes excessive, pervasive, or out of proportion to the threat. When symptoms interfere with occupational or social functioning, it is considered an anxiety disorder. Diagnosis relies on a detailed investigation of mental state and use of diagnostic criteria. The fifth edition of the Diagnostic Statistical Manual of Mental Disorders-5[3] lists the following conditions:

- Generalized anxiety disorder (GAD) is characterized by excessive worry about events or activities and difficulty controlling the worrying. Symptoms include restlessness, irritability, difficulty concentrating, fatigue, muscle tension, and sleep disturbance.

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- Agoraphobia, specific phobia, and social phobia are characterized by disproportionate fear or anxiety toward well-defined situations or stimuli, with exposure triggering unpleasant anxiety symptoms and avoidant behaviors.
- Panic disorder refers to recurrent unexpected attacks of overwhelming anxiety, occurring as an abrupt surge of intense fear and physiological symptoms, for example, palpitations, sweating, trembling, and shortness of breath.
- Post-traumatic stress disorder appears under the section of trauma and stress-related disorders. It requires 4 diagnostic clusters: reexperience of traumatic event, avoidance, negative cognitions and affect (eg, fear, guilt, shame), and increased arousal and reactivity after direct or indirect exposure to the traumatic event(s).

Assessing anxiety poststroke using a validated rating scale (eg, Hospital Anxiety and Depression Scale–Anxiety Subscale)[4] and 7-item GAD[5] is convenient and can help identify people's symptoms of anxiety that may be clinically significant despite not meeting criteria for an anxiety disorder.

Frequency, Predictors, and Time Course of Poststroke Anxiety

A systematic review of 97 studies (22 262 stroke survivors) published between 2009 and 2018 reported a cumulative proportion with an anxiety disorder of 15.5% (95% CI, 6.3–24.7) within the first month, 21.4% (95% CI, 19.2%–23.5%) between 1 and 5 months, and 31.8% (95% CI, 17.8%–45.7%) between 6 and 12 months.[6] Using rating scales, the frequency of clinically significant symptoms of anxiety was consistently above 20% across all time points up to 12 months, from 25.5% (95% CI, 18.6–32.3) within the first month to 23.6% (95% CI, 18.9%–28.2%) between 1 and 5 months and 21.5% (95% CI, 15.3%–27.8%) between 6 and 12 months.[6] Without individual participant-level data, it remains unclear whether poststroke anxiety improves in some with time, while other stroke survivors develop new or worsening anxiety at later time points. Most of these data were from European, Australasian, and North American populations, with little data from Asia, South America, and Africa.

Anxiety subtypes were reported using clinical interviews in a meta-analysis. Agoraphobia was present in 8.4% ([95% CI, 6.5%–10.4%] very high heterogeneity), social phobia in 2.3% (95% CI, 0.9%–3.7%), simple phobia in 2.1% ([95% CI, 1.5%–4.3%] high heterogeneity), and panic disorder in 3.7% ([95% CI, 2.4%–5.0%] very high heterogeneity).[6] Frequency of GAD could not be calculated due to the lack of supportive diagnostic information. A prospective cohort study using a structured clinical interview for anxiety subtypes (n=175) found that phobic disorders were the most prevalent anxiety disorder, with some cases overlapping with GAD (phobic disorder only, 10% [95% CI, 6%–16%]; phobic disorder and GAD, 7% [95% CI, 4%–12%]; GAD only, 4% [95% CI, 2–8]).[7] An older meta-analysis (1138 participants with prior stroke or transient ischemic attack) reported that post-traumatic stress disorder affected 13% ([95% CI, 11%–16%] very high heterogeneity).[8] The time between the stroke/transient ischemic attack and assessment varied across studies, and post-traumatic stress disorder diagnosis was mostly based on rating scales.

How Does Poststroke Anxiety Compare With Anxiety in the General Population?

The prevalence of anxiety disorders after stroke is slightly higher than in the general population, although direct contemporaneous comparisons are unavailable. In England, GAD is the most prevalent subtype: 6% to 7% for adults aged 16 to 64 years, 4% among those aged 65 to 74 years, and 2.5% for those aged >75 years.[9] Phobias affect 2% to 3% of those aged 16 to 64 years but only 0.5% of adults aged ≥65 years.[9]

Factors Associated With Poststroke Anxiety

A systematic review of 18 studies (8130 stroke survivors) published up to 2014 reported that prestroke depression, greater stroke severity, and cognitive impairment were associated with poststroke anxiety (Table S1).[10] In a longitudinal cohort of 2179 stroke survivors, clinically significant symptoms of anxiety were 3× as frequent at 3 months, 1 year, and 3 years among those <65 years of age compared with their older counterparts.[11] In a cross-sectional study (n=3831), age below 50 years was associated with a 4-fold increase in risk.[12] The association with sex is less clear; 3 of 6 observational studies reported an association between female sex and poststroke anxiety[11–13] but others did not. These data come from studies with ischemic stroke participants—little is known about associations with hemorrhagic strokes.

Living alone and socioeconomic hardship were associated with increased risk of anxiety in a systematic review.[10] Two of 3 studies found an association with stroke severity, but only 2 of 6 studies reported an association with disability.[10] Comorbidity between anxiety and depression poststroke is well established.[13] Both prestroke depression and prestroke anxiety have been associated with poststroke anxiety.[14]

Assessment of Anxiety After a Stroke

Anxiety rating scales are more frequently used in clinical practice than clinical interviews, for example, Structured Clinical Interview for Diagnostic Statistical Manual of Mental Disorders-5 and the Mini-International Neuropsychiatric Interview–Plus. The Hospital Anxiety and Depression Scale–Anxiety Subscale has been the most frequently used anxiety rating tool in stroke.[4] The GAD-7 is a sensitive and specific tool for GAD.[5] The self-rating Geriatric Anxiety Inventory[15] is internally valid, reliable, and has greater test accuracy than the Hospital Anxiety and Depression Scale–Anxiety Subscale.[16] The Behavioural Outcomes of Anxiety scale was designed to detect anxiety after stroke, including people with aphasia, using a set of anxiety descriptors rated by an observer who knows the patient well.[17] Data on the Behavioural Outcomes of Anxiety in clinical practice remain limited.

The choice of anxiety assessment instrument depends on clinical context (eg, the presence of aphasia), availability of trained staff, time, and familiarity with available instruments.

Interventions to Prevent Anxiety Poststroke

We found no trials of interventions to prevent anxiety after stroke.

Interventions to Treat Anxiety Poststroke

The 2017 Cochrane review included only 3 small trials (n=196; Table 1).[18] One study evaluated paroxetine or paroxetine plus psychotherapy or standard care, another, buspirone

Table 1. Interventions to Treat Anxiety After Stroke

Intervention	Summary of key evidence	Conclusion
Psychosocial	4 small trials • guided self-help[19] • relaxation compact disc[106] • psychotherapy plus paroxetine vs paroxetine alone[107]	Insufficient evidence to guide practice
Buspirone hydrochloride	1 small trial[108]	Insufficient evidence to guide practice

hydrochloride versus standard care, and the third study evaluated a relaxation compact disc against waitlist control. These studies were at high risk of methodological bias and so are insufficient to guide treatment. Forward citation search found one additional feasibility randomized controlled trial (RCT) evaluating a guided self-help cognitive behavioral therapy (CBT) intervention delivered via the internet and telephone. The preliminary results were promising but inconclusive.[19] Thus, large-scale, adequately powered, well-designed trials are needed to evaluate interventions to treat poststroke anxiety. Our anecdotal experience suggests that providing a realistic estimate of recurrent stroke risk (which is often overestimated) and addressing all stroke risk factors may decrease the perceived health threat. Situational phobias probably warrant exposure-based behavioral therapy though there are no stroke-specific trials. More RCTs are needed to evaluate pharmacological and nonpharmacological interventions for both management and prevention.

Poststroke Depression

Definition and Identification in Clinical Practice

Depression is the most frequent mental illness globally and the single highest contributor to mental health–related disease burden.[20] The *International Classification of Diseases, Eleventh Revision*, defines a depressive disorder as a period of at least 2 weeks of sustained depressed mood or diminished interest in activities accompanied by symptoms such as difficulty concentrating, feelings of worthlessness or guilt, hopelessness, recurrent thoughts of death or suicide, changes in appetite or sleep, psychomotor changes, and reduced energy or fatigue.[21] The clinical expression of depression can vary considerably, particularly in people with medical comorbidities, and this may contribute to variability in worldwide prevalence estimates.[22] Stroke-related disability, for example, dysphasia and sleep disturbances, fatigue, emotional lability, and apathy, may lead to misdiagnosis and render existing classification systems less effective.[23]

The Diagnostic Statistical Manual of Mental Disorders-5 lists poststroke depression (PSD) under depressive disorders due to another medical condition, specifying that the "disturbance is the direct pathophysiological consequence of another medical condition," although in practice this attribution is almost impossible to prove.[3] Therefore, the diagnosis of PSD relies on a careful exploration of presenting symptoms, including timing of onset, and may be assisted by the use of screening tools, especially those validated for use in stroke.[24]

Prevalence and Natural History

A systematic review of 51 observational studies (25 207 individuals) published between 1977 and 2002, using 10 different mood scales and 4 different psychiatric interview schedules, reported a pooled prevalence of PSD of 33% (95% CI, 29%–36%).[23] Prevalence estimates varied (30%–36%) according to the study setting (ie, population-, hospital-, or rehabilitation-based) and the method of case ascertainment (14%–41%), but not according to time frame (acute, <1 month poststroke; medium, 1–6 months poststroke; or long term, ≥6 months poststroke).

An updated systematic review and meta-analysis of 50 observational studies (43 data sets, 20 293 individual participants) published between 1983 and 2011 confirmed that time since stroke and case ascertainment varied (29 studies used validated scales, 12 used Diagnostic Statistical Manual of Mental Disorders criteria, and 2 used a validated question).[25] The pooled prevalence of PSD at any time was 29% (95% CI, 25%–32%).[25] PSD prevalence varied little according to time since stroke: 28% (95% CI, 23%–34%) within 1 month, 31% (95% CI, 24%–39%) at 1 to 6 months, 33% (95% CI, 23%–43%) at 6 months to 1 year, and 25% (95% CI, 19%–32%) after 1 year.[25] Studies that assessed patients more than once suggested that PSD incidence was highest shortly after the acute event (within 3 months) but many subsequently recovered. The cumulative incidence (5 studies) of PSD was up to 52% within 5 years of stroke. Statistical and clinical heterogeneity was high, and it was unclear whether data represented new cases of depression (ie, incidence) in addition to prevalent cases.[25] In a separate study of 4022 stroke survivors followed for 15 years poststroke, the cumulative incidence of PSD was 55% (95% CI, 53%–58%).[26] More recent systematic reviews and meta-analyses have reported similar results.[27–29]

Data on the worldwide distribution of PSD are limited, so that generalization of existing findings to different cultural and geographic contexts is difficult. The prevalence of PSD in Sub-Saharan Africa (17 studies, 1483 participants) was 31% (95% CI, 26%–36%).[30] Study heterogeneity and quality was of concern, and the timing of assessment of PSD was unclear. Six studies (641 participants) from Iran reported a pooled prevalence of 46% (95% CI, 30.1%–63.7%), but the studies were of variable quality.[31]

A large Danish cohort study, not yet included in systematic reviews, showed that 25% of 157 243 stroke patients experienced depression within 2 years of stroke compared with 7.8% in 160 236 controls.[32] The risk of depression was highest in the first 3 months.

These data suggest that depression is common among stroke survivors, particularly during the first 3 months, but most studies have used depression scales, so it is unclear whether symptoms fulfill diagnostic criteria for depression. Variations in how PSD is assessed and reported (ie, point prevalence versus cumulative prevalence), and the study settings introduce uncertainty about its true prevalence and incidence. Furthermore, participants with aphasia and significant cognitive impairment are frequently excluded from epidemiological studies, and the validity of depression scales in these populations is uncertain. Hence, existing epidemiological estimates may not be generalizable to all stroke survivors.

Risk Factors for PSD

PSD development seems to be mediated by multiple overlapping biological, functional, social, and psychological factors (Table S2). Risk factors include female sex, past depressive episodes, poor social support, family history of mood disorders,

and a personality style characterized by traits of neuroticism and obsessionality.[33–35] Associations with education, premorbid intelligence, age, and socioeconomic status are less clear.[36,37]

A 2005 systematic review of 20 observational studies (17 934 participants) found that physical disability, stroke severity, and poststroke cognitive impairment were associated with PSD.[38] These findings have been replicated, with the addition of poststroke anxiety and functional capacity as relevant risk factors.[25,33,34,37,39–41] Stroke location seems irrelevant for PSD despite early tentative evidence to the contrary.[33,37,42–44] Other studies have reported associations between PSD and neuroinflammation, disruption of the hypothalamic-pituitary axis, oxidative stress, abnormal glutamatergic neurotransmission, disrupted production of neurotrophic factors, lower levels of monoaminergic transmission, and genetic susceptibility. However, there is no consistent evidence linking a particular biomarker to PSD.[45,46]

Prevention of PSD

A Cochrane review included 19 RCTs of 21 interventions in 1771 participants (Table 2).[47] Pharmacological trials predominated (n=12 884 participants) and showed a modest benefit for active treatment compared with placebo in decreasing the prevalence of PSD. Interventions included antidepressants (sertraline, fluoxetine, paroxetine, maprotiline, mianserin, trazadone, nortriptyline, escitalopram, indeloxazine, and milnacipran) and other pharmacological agents (piracetam and methylphenidate).[47] Similar results from 2 trials have been reported for psychological treatments.[48,49]

The use of selective reuptake inhibitors in promoting functional recovery after stroke was summarized in a 2019 Cochrane review (63 trials, 9168 participants).[50] Selective reuptake inhibitors reduced the average depression score slightly (standardized mean difference [SMD], 0.11 lower [95% CI, 0.19–0.04]; 2 trials, 2861 participants) but increased gastrointestinal side effects (risk ratio [RR], 2.19 [95% CI, 1.00–4.76]).[50] Three large, randomized, placebo-controlled trials of fluoxetine for recovery following stroke have been completed: EFFECTS (Efficacy of Fluoxetine Randomised Controlled Trial in Stroke),[51] FOCUS (Fluoxetine or Control Under Supervision),[52] and AFFINITY (Assessment of Fluoxetine in Stroke Recovery).[53] Collectively, these trials found that daily treatment with 20 mg of fluoxetine for 6 months did not improve functional outcomes poststroke. FOCUS and EFFECTS reported less depression in those treated with fluoxetine than placebo (13.3% versus 17.2%, P=0.003 and 7% versus 11%, P=0.015) but not AFFINITY (5.1% versus 7.2%, respectively). A more detailed analysis of the AFFINITY trial showed that routine daily treatment with 20 mg of fluoxetine for 6 months does not decrease the prevalence of clinically significant symptoms of depression after a stroke (Patient Health Questionnaire-9, ≥9).[54]

Fluoxetine increased the risk of bone fractures in EFFECTS, FOCUS, and AFFINITY.[55] A subsequent post hoc analysis of all 3 trials showed an absolute risk increase for fractures of 1.8% (number needed to harm, 56).[56] These data suggest that the routine use of fluoxetine following a stroke cannot be recommended.

There is tentative evidence that poststroke rehabilitation may prevent PSD.[57] Data on the antidepressant effects of music, exercise, yoga, pilates, tai chi, Feldenkrais Method, qigong, acupuncture, and mindfulness for the prevention of PSD are limited and inconclusive.[58–63] A substudy from the VITATOPS trial (Vitamins to Prevent Stroke) suggested that vitamins B6, B12, and folic acid decreased the 7-year cumulative incidence of PSD,[64] although these findings are yet to be replicated.

Treatment of PSD

Treatment options for PSD can be broadly divided into psychosocial, nonspecific interventions, pharmacological, and neuromodulation (Table 3).[45]

Psychosocial

Various psychological techniques have been tested, either alone or in combination with pharmacotherapy. A meta-analysis[65] found that CBT reduced depressive symptom severity in adults with PSD (23 RCTs, 1972 participants) compared with waiting lists or control interventions (SMD, −0.83 [95% CI, −1.05 to −0.60]). This effect was apparent if CBT was delivered alone or with antidepressants. CBT improved response and remission rates

Table 2. Intervention for Prevention of Depression After Stroke

Intervention	Summary of key evidence	Conclusions
Psychosocial interventions	2020 Cochrane systematic review of 7 trials but only 2 trials suitable for meta-analysis (RR, 0.68 [95% CI, 0.49–0.94]; n=607).[47] Music therapy and mindfulness unlikely to reduce the risk of PSD.[58,60] Motivational interviewing may increase odds of having normal mood after stroke (OR, 1.60 [95% CI, 1.04–2.46]; n=411).[49] Problem-solving therapy may reduce depressive symptoms.[48,106]	Psychosocial interventions: generally safe and may reduce PSD risk. Evidence difficult to generalize.
Physical exercise	Exercise benefits are uncertain.[59,69]	Exercise provides multiple potential health benefits, but role in PSD prevention is unclear.
Others	Unclear evidence for yoga, tai chi, pilates, Feldenkrais method, qigong, and acupuncture.[59] B vitamins may reduce PSD, but trial data need replication.[64]	Insufficient data to guide practice.
Pharmacological	2020 Cochrane review: 8 RCTs showed modest effect of pharmacological treatments to decrease the prevalence of PSD (RR, 0.50 [95% CI, 0.37–0.68]; n=734).[47] 2019 Cochrane review of 63 trials (n=9168) showed SSRIs reduced the average depression score compared with placebo (SMD, 0.11 lower [95% CI, 0.19–0.04]).[50] This small effect was offset by more gastrointestinal side effects in the active treatment groups. Three large RCTs of fluoxetine for recovery following acute stroke reported mixed results: two trials reported less depression in those treated with fluoxetine,[51,52] but the third reported no effect of fluoxetine on depressive symptoms.[53,54] Fluoxetine increased the risk of bone fractures in all 3 trials: absolute risk increase, 1.8%; numbers needed to harm, 56.	Antidepressants may reduce PSD, but this is of uncertain clinical significance. Risk of adverse effects may outweigh the potential benefits, so not recommended in routine clinical care.

OR indicates odds ratio; PSD, poststroke depression; RCT, randomized controlled trial; RR, risk ratio; SMD, standardized mean difference; and SSRI, selective reuptake inhibitor.

Table 3. Interventions for Treatment of Depression After Stroke

Intervention	Summary of key evidence	Conclusion
Psychosocial	CBT with or without antidepressants decreased depressive symptoms in 23 RCTs.[65] Various forms of psychotherapy (CBT, motivational interviewing, supportive, group, or problem-solving therapy) decreased proportion with depression (RR, 0.77 [95% CI, 0.62–0.95]), but evidence quality is low.[66] Behavioral activation: uncertain.[67]	Psychological therapy: likely to be effective.
Exercise	Exercise brings many benefits, but its role in treating PSD is uncertain.[59,69,70]	Consider exercise as part of a comprehensive stroke rehabilitation program. Unclear if it reduces PSD.
Others	Lack of consistent evidence for acupuncture, Chinese herbal medicines, and hyperbaric therapy.[73–75]	Acupuncture and other nonspecific interventions not currently supported.
Pharmacological	Antidepressants reduce PSD (RR, 0.70 [95% CI, 0.55–0.88]) but with greater risk of adverse effects.[66]	Consider antidepressants as in the general population. Be mindful of side effects and drug interactions.
Neuromodulation	Limited data support rTMS and tDCS.[84,85]	No compelling evidence.

CBT indicates cognitive behavioral therapy; RCTs, randomized controlled trials; RR, risk ratio; rTMS, repetitive transcranial magnetic stimulation; and tDCS, transcranial direct current stimulation.

of PSD compared with controls. However, study quality varied and there was high heterogeneity. A 2020 Cochrane review and meta-analysis of 6 trials of psychotherapy for PSD showed that fewer people met criteria for depression at treatment end (RR, 0.77 [95% CI, 0.62–0.95]; n=521), but evidence was of very low certainty.[66] Interventions included CBT, motivational interviewing, various supportive in-person or via telehealth psychotherapies, group psychotherapy, and problem-solving. Further evidence about behavioral activation is required.[67]

Nonspecific Interventions

Exercise improves depression in nonstroke patients, but its role as a stand-alone treatment for PSD is uncertain.[68] A 2014 systematic review of 13 RCTs (n=1022) showed some promise in treating PSD (SMD, −0.13 [95% CI, −0.26 to −0.01]), but benefits were small, unsustained, and of uncertain clinical significance.[59] A 2020 Cochrane review (75 RCTs, 3017 participants) of cardiorespiratory or resistance training compared with usual care or a nonexercise intervention for stroke survivors found that training improved disability scores.[69] There was insufficient evidence about the effect of exercise on mood, but participants in the intervention groups experienced multiple benefits for physical fitness, walking speed, and balance, without evidence of significant adverse effects.[69] A 2021 meta-analysis of 4 trials (263 participants) failed to confirm the antidepressant effects of exercise for PSD (SMD, −0.24 [95% CI, −0.48 to 0.01]).[70] However, there was a positive effect of all available nonpharmacological interventions combined (complementary alternative therapy, exercise, psychosocial therapy, and multifactorial therapy) compared with a heterogeneous control group, suggesting the meta-analysis of exercise alone may have lacked statistical power. Notwithstanding the lack of compelling evidence about exercise as a PSD treatment, exercise has general health benefits and should be used whenever possible.

An overview of 10 systematic reviews of acupuncture reported favorable results when used with rehabilitation interventions or antidepressants.[71] A systematic review of electroacupuncture compared with antidepressant treatment for PSD (18 RCTs) reported a benefit of electroacupuncture and fewer adverse effects.[72] More recently, a systematic review and meta-analysis of 17 RCTs of acupuncture reported a beneficial effect for acupuncture in combination with antidepressants but not for acupuncture alone.[73] Traditional Chinese herbal medicines[74] and hyperbaric oxygen therapy[75] have also been trialed, but supportive data remain scant.

A systematic review of 45 studies did not find evidence of efficacy for various rehabilitation interventions to treat PSD.[57] Depression was a secondary outcome in most of these studies, many lacked a control arm and a reproducible description of the intervention, and there was uncertainty about the definition of depression.[57] These findings were consistent with a separate systematic review of occupational therapy activities on depressive symptoms among stroke survivors.[76] Supportive nurse-led interventions, including information about stroke recovery, and more specific interventions, such as motivational interviewing, life review, and music therapy, show promise, although the quality and quantity of existing evidence is not compelling.[77]

Pharmacological

Pharmacological options for PSD treatment are similar to those available for nonstroke adults with depression.[78] A 2020 Cochrane systematic review[66] showed that, compared with placebo, pharmacological interventions decrease the proportion of participants meeting criteria for depression (RR, 0.70 [95% CI, 0.55–0.88]; 8 trials, n=1025) and decrease the proportion of people who experience <50% reduction in depression scores at study end (RR, 0.47 [95% CI, 0.32–0.69]; 6 trials, n=511). The included trials all utilized antidepressants as the active intervention (citalopram, fluoxetine, nortriptyline, paroxetine, and sertraline) apart from one trial of a nootropic agent—aniracetam. Antidepressant treatment was associated with more frequent central nervous system and gastrointestinal side effects although the evidence was of very low certainty. These findings are consistent with earlier systematic reviews.[79–81]

Some trials have investigated the role of antidepressants in combination with psychological therapy or neuromodulation, but their results are difficult to interpret given the relative paucity of data.[66]

Neuromodulation

Electroconvulsive therapy is the traditional neuromodulation approach to treating depression. Results from an old case series suggested that electroconvulsive therapy is effective and safe in treating PSD, although good-quality trial data are lacking.[82] Other approaches such as repetitive transcranial magnetic stimulation, vagal nerve stimulation, magnetic seizure therapy, transcranial direct current stimulation, and deep brain stimulation have been

explored,[83] but supportive evidence for their use remains scarce and inconclusive.[66] A separate review on repetitive transcranial magnetic stimulation[84] (7 RCTs, 351 participants) suggested that repetitive transcranial magnetic stimulation decreases the severity of PSD (SMD, −1.15 [95% CI, −1.02 to −0.32]) and increases the odds of remission of symptoms (odds ratio, 3.46 [95% CI, 1.68–7.12]), but statistical and clinical heterogeneity was apparent. A small, sham-controlled RCT of transcranial direct current stimulation in 48 antidepressant-free patients with PSD showed benefit with active treatment (mean difference on Hamilton Depression Rating Scale, 4.7; SD, 9.21; $P<0.001$),[85] but these results were not replicated in a similar trial focusing on poststroke motor recovery.[86]

Summary and Recommendations for Future Research

Clinically significant symptoms of depression affect about 1/3 of stroke survivors. Despite extensive research, there is no compelling evidence to support the use of specific strategies to prevent PSD. The equivocal benefits of psychological and pharmacological interventions to treat PSD must be balanced against potential harms, particularly if spontaneous recovery is expected. These findings may be due to the heterogeneity of PSD and to the lack of specificity of the interventions trialed to date. Future studies of PSD should use semistructured or structured clinical interviews and well-established diagnostic criteria, not just scales for depressive symptoms. Participants must reflect the heterogeneity of stroke, including the severity of neurological deficits (including language), cognitive and functional impairments, and of depressive symptoms. Such a step up in research rigor is necessary to give certainty about what PSD is, its prevalence and incidence, its mediating factors, and the best prevention and treatment options.

Suicide Behaviors After Stroke

Definitions

Suicide is defined as the intentional self-perpetrated act that results in the end of one's own life. Suicide ideation indicates the presence of thoughts about engaging in behaviors to end one's own life. Suicide plan refers to the formulation of steps and methods required to end one's life. Suicide attempt is defined as self-injurious behaviors that may have had the intent of causing death.[87]

Suicide Ideation, Plans, Attempts, and Suicide After Stroke

Suicide ideation is reported by 12.2% of survivors according to a systematic review of 21 studies that included a total of 17 189 participants,[88] although the approaches used to define suicide ideation have uncertain validity (eg, "ever thinking that would be better off dead after a stroke" alongside "recurring thoughts about doing something to kill oneself"). Risk factors are summarized in Table S3. Suicide ideation is more prevalent among stroke survivors with moderate-to-severe disability, current or prior depression, stroke recurrence, and cognitive impairment and less frequent among those who are married, employed, or more highly educated.[89]

Suicide plans are frequent after stroke. An American cohort study from the mid-1990s identified suicide plans in 6.6% of participants at hospital admission and in 11.3% during 2 years of follow-up.[90,91] Suicide plans were associated with concurrent depression and history of cerebrovascular disease. Acute onset plans were associated with alcohol abuse and younger age, whereas later suicide plans were associated with physical disability.[90,91]

A systematic review and meta-analysis of 23 studies (>2 million stroke survivors) showed that suicide risk was 73% higher (pooled adjusted RR, 1.73 [1.53–1.96], I^2=93.5%) among cases than noncases but risk declined over time.[92] Meta-regression found no significant differences in the global geographic distribution of suicides. One longitudinal study found that suicide rates dropped from 381.9 per 100 000 person-years during the first 5 years poststroke to 20.4 per 100 000 person-years after 10 years.[93]

Two studies reported the use of highly lethal methods of self-harm, such as hanging, or in the United States, firearms.[94,95] Jumping from a height or self-poisoning seem to be less frequent self-harm methods.[95]

A population-wide cohort study found higher risk of suicide in younger (<50 years) than older stroke survivors.[96] Women may have a slightly greater risk than men.[94] Clinically significant symptoms of depression are associated with higher suicide risk.[91,97,98] There is also tentative evidence that poststroke, but not prestroke depression, increases the risk of suicide completion.[97] However, the difference between pre- and poststroke depression is not entirely clear because some depression after stroke could represent worsening of prestroke depression.[35]

Suicide risk is similar in patients with ischemic and hemorrhagic strokes.[89] Other risk factors include financial stress, living in less urbanized regions, manual labor, comparatively lower educational attainment, chronic morbidities,[96,98,99] and fatigue, pain, and insomnia independent of depression.[100–102] The quality of existing evidence is poor.

Prevention of Suicide

Suicide attempts or completion are uncommon even among stroke survivors considered high risk. Nonetheless, preventive strategies need to identify risk groups and modifiable risk factors. Stroke clinicians should identify, diagnose, and manage existing clinically significant symptoms of depression, rehabilitate and mitigate disabilities, and restrict access to means of self-harm. However, screening for depression with 1 or 2 questions will probably not reveal suicide thoughts, and so clinicians should consider asking questions about suicide thoughts regardless of a negative depression screen[103] or use a depression screening tool that includes questions about suicidal ideation; for example, the Patient Health Questionnaire-9.[104] Early engagement with support and rehabilitation services may help.

Stroke may adversely affect physical and mental health and lead to suicide ideation, plans, attempts, and completion. Being aware of the risk factors for suicide, identifying and treating mood disorders, and limiting access to the means of self-harm should be considered.

Recommendations for Future Research

Future research should seek to clarify what type of interventions would best decrease rates of poststroke suicide. Conclusive data on how best to prevent poststroke suicide will require collaborative multicenter studies involving a large number of participants.

FUTURE DIRECTIONS

Further research is needed about how to treat depression and anxiety after stroke. An international consensus could examine the most promising interventions to test and then consortia could investigate these approaches in multiple countries. Consideration should be given to whether RCTs are the most appropriate approaches for testing complex interventions or whether other types of evaluation would be preferable.[105] For suicide, we need better epidemiology about the cause of death, research to identify factors leading from suicidal ideation to death, and valid approaches to risk evaluation and prevention.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S3

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