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MINIREVIEWS

Neuropsychiatric issues after stroke: Clinical significance and therapeutic implications

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Abstract

A spectrum of neuropsychiatric disorders is a common complication from stroke. Neuropsychiatric disorders after stroke have negative effects on functional recovery, increasing the rate of mortality and disability of stroke survivors. Given the vital significance of maintaining physical and mental health in stroke patients, neuropsychiatric issues after stroke have raised concerns by clinicians and researchers. This mini-review focuses on the most common non-cognitive functional neuropsychiatric disorders seen after stroke, including depressive disorders, anxiety disorders, post-traumatic stress disorder, psychosis, and psychotic disorders. For each condition, the clinical performance, epidemiology, identification of the therapeutic implication, and strategies are reviewed and discussed; the main opinions and perspectives presented here are based on the latest controlled studies, meta-analysis, or updated systematic reviews. In the absence of data from controlled studies, consensus recommendations were provided accordingly.

Key words: Stroke; Neuropsychiatric disorders; Depression; Anxiety; Post-traumatic stress disorder; Psychosis

Core tip: The purpose of this mini-review is to summarize the research advance of neuropsychiatric disorders including depressive disorders after stroke, anxiety disorders after stroke, post-traumatic stress disorder after stroke, post-stroke psychosis, and psychotic disorders. Recent evidence showed that neuropsychiatric disorders after stroke are associated with worsened outcomes yet are still under-recognized. With the exception of depressive disorders after stroke, the other neuropsychiatric disorders lack

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reliable and high-quality evidence in clinical practice. Further studies should attempt to develop protocols or guidelines for the diagnosis, treatment, or prevention of neuropsychiatric disorders after stroke.

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INTRODUCTION

With the aging of the global population, stroke has become the second leading cause of death for people over age 60 and the fifth leading cause in people between the ages of 15 and 59 worldwide. Due to brain damage and loss of function, stroke is also a major cause of long-term disability in adults worldwide, which decreases the quality of life for patients and increases the global medical burden[1]. Recently, neuropsychiatric issues appearing after stroke have raised concerns for clinicians and researchers. Psychiatric disorders are common complications post-stroke and are associated with worsened outcomes, including low quality of life, increase in the burden of caregiving, and unfavorable functional status[2,3]. Even early neuropsychiatric disorders after stroke (NDS) may increase the risk of mortality and recurrence in patients with stroke[4,5]. The current management and treatment of the majority of NDS is not satisfactory, except for some antidepressants that show therapeutic benefit[3,6]. Patients with NDS do not even benefit from existing advanced medical intervention. A retrospective study showed patients with stroke and neuropsychiatric co-morbidities were slightly less likely to receive carotid revascularization intervention compared to those who did not have neuropsychiatric co-morbidities[7]. A lack of subjective intervention willingness from patients and inadequate social and family support may be the reason for the difference in intervention.

Neuropsychiatric impairment after stroke encompasses a wide spectrum of diseases, including neurocognitive disorders and non-cognitive disorders[8]. In this review, we will put an emphasis on discussing the most common non-cognitive NDS after stroke or transient ischemic attacks (TIA): Depressive disorders and anxiety disorders, as well as post-traumatic stress disorder (PTSD), psychosis and psychotic disorders after stroke. Uncommon conditions such as apathy, personality disorders, emotional lability, emotional incontinence, fatigue, mania, catastrophic reactions, and some manifestations of NDS will not be included in this review. These conditions were excluded because these disorders and their manifestations do not have widely acknowledged diagnostic criteria at present, have not established definitions, or are not regarded as standard neuropsychiatric diseases in the fifth edition of the diagnostic and statistical manual of mental disorders (DSM-5)[9]. Something particularly noteworthy is that some patients may suffer from co-occurring NDS (*i.e.*, depression and anxiety) after stroke. Although there exists substantial overlap of symptoms between these NDS, each issue will be reviewed separately.

This review will address the clinical significance for stroke, screening, and identification of each NDS. We then will focus on therapeutic implications and discuss strategies.

The purpose of this mini-review is to outline the current research in the field of NDS, including clinical presentation, epidemiology, therapeutic implications, and strategies to alleviate neuropsychiatric symptoms, to improve the well-being of patients, and to reinforce physical and mental status for stroke survivors. We focused on clinical significance and therapeutic strategies. Our opinions on management and treatment mainly depend on results from studies of evidence-based medicine and expert consensus.

Risk factors for NDS

Genetic background and family history are considered to be important potential susceptibility factors that can affect NDS. A meta-analysis showed that stroke patients with a family history of psychiatric disorders have an increased risk for developing post-stroke depression[10]. Several studies have also identified a number of potential candidate genes that may underlie susceptibility to depressive and anxiety disorders

after stroke. Serotonin transporter gene is the most common gene associated with depression. A meta-analysis of four studies with 641 individuals indicated that there was a positive association between the homozygous short variation allele genotype of the serotonin transporter-linked promoter region (5-HTTLPR) and post-stroke depression, whereas the homozygous long variation allele genotype of 5-HTTLPR showed a significant negative association with post-stroke depression. The heterozygous short and long allele genotypes for 5-HTTLPR or rs25531 and *STin2 VNTR* gene polymorphisms of the serotonin transporter gene have not been proven to be susceptibility genes for post-stroke depression[11]. Although the 5-HTTLPR polymorphism was found to have a significant association with an antidepressant response and remission in Caucasians[12], the relationship between the 5-HTTLPR polymorphism and the responsiveness of antidepressants for post-stroke depression remained not well-determined.

It was reported that stroke patients with brain-derived neurotrophic factor gene hypermethylation levels and brain-derived neurotrophic factor gene polymorphisms had a higher risk of developing post-stroke depression and post-stroke anxiety (PSA)[13,14]. In addition, polymorphism in the tryptophan hydroxylase 2 gene were also found to be involved in PSA susceptibility[15].

NDS is multifactorial and influenced by many other demographic and external factors. A meta-analysis published in 2017 with 36 studies analyzed the research status and emerging trends in regard to risk factors for post-stroke depression, and suggested that the correlation between a history of psychiatric disorders and post-stroke depression was highest among all factors; other demographic and external risk factors for post-stroke depression were female, age (< 70 years), stroke severity, functional impairments, and lack of social and family support[16]. However, one other meta-analysis also published in 2017 with 18 studies concluded that gender, age, and social factors were not reliable risk factors[17]. Moreover, a recent study confirmed that unmarried status and excessive fatigue were potential negative risk factors for PSA[18].

Medical conditions and socioeconomic status, such as time to access of health services, willingness to seek treatment, health insurance coverage, medical expenditure, and educational level may have a partial effect on NDS[19,20]. However,few prospective studies have focused on the above factors for the development and evolution of NDS. Features of neuropsychiatric disorders after stroke is shown in Table 1.

DEPRESSIVE DISORDERS AFTER STROKE

Screening and identification

Post-stroke depressive (PSD) disorders are the most commonly reported and widely investigated among all types of NDP in the literature. PSD is the most frequent treatable neuropsychiatric complication of stroke at any one time after onset. A prospective study showed PSD can occur from 1 to 18 mo after the onset of stroke, and prevalence of PSD was not found to vary considerably over time (the prevalence at 1, 3, 6, 12, and 18 mo were 24.5%, 27.1%, 28.3%, 19.8%, and 26.3% respectively)[21].

A previous meta-analysis of 61 studies with 25488 patients indicated that the pooled frequency of PSD was 34% in 32 stroke cohorts[22], consistent with a meta-analysis of 32 studies with 8938 patients receiving antidepressant therapy where the pooled frequency was 31%[23].

The proportional frequency of depression reported ranged from 5%[24]-84%[25], which varied considerably across studies because of different PSD identification criteria, threshold time points of assessment during follow-up, and clinical setting. A national register-based cohort study in Denmark consecutively recruited 157243 first-time hospitalized patients with new-onset PSD and 160236 local healthy residents as a reference population during 2 years of follow-up between 2001 and 2011. The total incidence of depressive disorders after stroke was 25.4%, compared with 7.8% in the control population[26].

Compared with orthopedic patients with similar degrees of motor disability[27], myocardial infarction, and similar predisposing factors of cardiovascular disease[23], patients with stroke are more likely to suffer from depressive disorders, suggesting that there is a more complex neurobiological mechanism for the etiology of PSD.

Generally, PSD occurs in the range from 25%-35% of stroke survivors with the frequency estimated to be the highest in the 1st year after onset, with gradually declining prevalence thereafter[28].

Optimal screening for and identification of PSD is vital for following treatment and management; however, there is currently no established diagnostic criterion for PSD. The DSM-5 classifies PSD as a "depressive disorder due to another medical

Table 1 Features of neuropsychiatric disorders after stroke

Disorders	Prevalence/ frequency, %	Main clinical manifestations	Screening tools	Identification	Management and treatment
Depressive disorders after stroke	5-84	Depressed mood; marked reduction in interest or pleasure in activities; decreased/increased appetite/weight; insomnia or hypersomnia; psychomotor agitation/retardation; loss of energy/fatigue; feelings of worthlessness/inappropriate guilt; loss of concentration; appear pessimistic about health issues/recurrent thoughts of death or suicide	Center for epidemiological studies-depression scale; hospital anxiety depression scale; Hamilton depression rating scale; beck depression inventory; geriatric depression scale; PHQ-9	According to the DSM-5 classification, PSD is defined as a depressive disorder due to TIA or stroke.	SSRIs and SNRIs; psychological intervention; mental and physical exercise; neuromodulation
Anxiety disorders after stroke	20-24	Prominent anxiety; excessive fear, worry, and concern about health issues; intense dread or uneasiness; panic attacks, or obsessions or compulsions predominate	Hamilton anxiety scale; hospital anxiety and depression scale-anxiety subscale	According to the DSM-5 classification, PSA is defined as an anxiety disorder due to TIA or stroke.	SSRIs; Tricyclic antidepressant; benzodiazepines; "Z-drugs" (zolpidem, zaleplon and eszopiclone); psychological interventions; mind-body interventions
PTSD after stroke	8.3-29.6	Intrusive memories; alterations in physical reactions and arousal; avoidance; negative alterations in cognition and mood	PTSD checklist for a stressor, TIA or stroke as stressor; clinician administered PTSD scale; impact of events scale-revised; posttraumatic stress diagnostic scale; structured clinical interview for DSM	PTSD is related to TIA or stroke which creates psychological trauma in response to actual or threatened death, serious injury, and adverse life events.	Psychotherapeutic approach procedures; antidepressants, anxiolytics sympathetic inhibitor, antipsychotics, anticonvulsants, and sedative drugs
Psychosis and psychotic disorders after stroke	4.67-5.05	Hallucinations or delusions; disorganized speech; catatonic or inappropriate motor behavior	Neuropsychiatric inventory	According to the DSM-5 classification post-stroke psychotic disorders are defined as psychotic disorders due to TIA or stroke.	Antipsychotic drugs; neuromodulation and psychosocial therapy; psychological intervention

TIA: Transient ischemic attacks; SSRIs: Selective serotonin reuptake inhibitors; SNRIs: Serotonin-norepinephrine reuptake inhibitors; PSD: Post-stroke depressive; PSA: Post-stroke anxiety; PTSD: Post-traumatic stress disorder; PHQ-9: 9-item patient health questionnaire; DSM-5: Diagnostic and statistical manual of mental disorders.

condition". The identification and diagnosis of PSD is usually based on the combination of detailed clinical assessment and screening scale tools in the clinical practice. For example, clinicians diagnose PSD using a structured clinical interview for DSM-5 combined with a screening scale before initiating PSD treatment. There is no universally accepted screening tool for PSD. The following psychiatric scales are frequently used to measure PSD symptoms in clinical study and practice: The center for epidemiological studies depression scale, hospital anxiety depression scale, Hamilton depression rating scale, beck depression inventory, geriatric depression scale, and nine-item patient health questionnaire (PHQ-9). In 2017, the American Heart Association and American Stroke Association jointly issued the first scientific consensus statement for healthcare, which comprehensively discussed the epidemiology, pathophysiology, screening, management, and prevention of PSD[28]. Based on the results of a meta-analysis with 2907 participants, the center for epidemiological studies depression scale, Hamilton depression rating scale, and PHQ-9 scores have proven to have higher sensitivities for identifying PSD, using the international classification of disease or DSM diagnosis of depression as the reference standard[29]. The PHQ-9 is one of the most commonly used tools for screening for PSD with high validity and reliability in primary care. One individual patient's data meta-

analysis showed that a cutoff of a score of 10 on the PHQ-9 yielded a maximum diagnostic performance[30]. Considering the structured interview for DSM as the reference standard for PSD, the sensitivity and specificity of PHQ-9 were 0.82 and 0.97, respectively. The overall diagnostic performance of the PHQ-9 was better than the hospital anxiety depression scale-D and geriatric depression scale[31]. Another individual participant's data meta-analysis of PHQ-9 reported the existence of selective cutoff reporting bias when estimating sensitivity in most studies[32]. In addition, a systematic review concluded that the results regarding the sensitivity and specificity of the PHQ-9 for PSD screening and identification were uncertain[33].

Remarkably, unlike depressive disorders caused by other diseases, screening for PSD faces many challenges; particular attention should be paid to the actual condition of patients with stroke. Neurological symptoms resulting from stroke such as aphasia, alexia, or agnosia may lead to expressive or receptive dysfunction[34]. Cognitive impairment such as loss of concern, anosognosia, abulia, or lack of insight may develop similar depressive symptoms[35]. The above adverse factors for screening could hinder the identification and diagnosis of PSD. Therefore, screening and identification procedures of PSD should be performed following protocols tailored to the individual.

Management and therapeutic implication

PSD is associated with worsened functional outcomes after stroke. A meta-analysis including 14 studies before May 2018 with 17609 PSD patients evaluating the association between PSD and the mortality of different follow-up times revealed that PSD showed a negative impact on survival rates; the effect of PSD on short-term mortality was slightly higher than its effect on long-term mortality[4]. A recent case-control study showed PSD increased disability severity in ischemic stroke survivors, whose Barthel index and Rivermead mobility index scores were both lower than stroke survivors without PSD at both admission and discharge[36].

In theory, the early and prophylactic use of PSD may reduce the risk of PSD in stroke survivors. A meta-analysis with eight prospective randomized controlled trials published from 1990 to 2011 revealed that antidepressant prophylaxis (mianserin, fluoxetine, nortriptyline, sertraline, escitalopram, milnacipran) reduced the odds of developing PSD, and pooled results uncovered the benefit of early initiation of pharmacotherapy in stroke patients[37]; however, the final conclusion of this review was based on eight studies with four classes of antidepressants [selective serotonin reuptake inhibitor (SSRI), tetracyclic antidepressant, tricyclic antidepressant, serotonin-norepinephrine reuptake inhibitor (SNRI)]. Therefore, there may be a high relative heterogeneity among the studies. A systematic review just published in November 2019, which retrieved data from 2009 to 2018, suggested that the use of SSRIs, psychological intervention [*e.g.*, cognitive behavioral therapy (CBT)], as well as mental and physical exercise could relieve most mood symptoms of PSD, but the level of evidence quality of the included studies were low to moderate[38]. A meta-analysis including 20 studies with 1485 patients indicated that both SSRIs and SNRIs had favorable therapeutic effects on PSD, and furthermore that citalopram may improve depressed moods faster than other SSRIs[39].

Fluoxetine for motor recovery after acute ischemic stroke is a randomized placebo-controlled trial conducted in France, which included 118 patients with ischemic stroke and moderate-to-severe motor deficits, found that the early use of fluoxetine with physiotherapy promoted motor recovery after 3 mo[40]. Similar to the conclusion of fluoxetine for motor recovery after acute ischemic stroke, most meta-analyses and systematic reviews published before 2019 supported that, if given early, fluoxetine could alleviate neurological deficits and disability and allow patients to recover independently through rehabilitation after stroke[41-43].

With the release in December 2018 of results on the effect of fluoxetine on functional outcomes after acute stroke (FOCUS), SSRI-modulated neuroplasticity that could enhance neurological recovery began to be questioned. The FOCUS trial is a multicenter randomized double blind and parallel control, collaborative study held at 103 hospitals through the National Health Service, United Kingdom, which focuses on the effect of fluoxetine on neurological functional outcomes after acute stroke.

In FOCUS, from 2 to 15 d after onset, there were 3,127 eligible patients with stroke (not patients with PSD) that were recruited and randomly allocated fluoxetine (20 mg daily) or placebo for 6 mo. After an extended follow-up period of up to 12 mo, only the neuropsychological scale questionnaire showed statistically significant differences between the two groups, although results of the clinical trial indicated that fluoxetine would enable the improvement of depression symptoms rather than clinical outcomes, and even increase the risk of bone fractures. The results from the FOCUS trial do not support the routine use of fluoxetine in prophylactic treatment for PSD or to promote the recovery of neurological function[44]. The TALOS study (the Efficacy of

Citalopram Treatment in Acute Stroke) was a placebo-controlled, randomized, double-blind study with 642 stroke patients in Denmark. Similarly to the FOCUS results, the TALOS study also did not show that citalopram could promote functional recovery, reduce the dependence on activities of daily living, or decrease the risk of recurrent cardiovascular events in acute ischemic stroke[45].

Since the FOCUS study has the largest number of patients among similar studies so far, the results from the FOCUS study undoubtedly carry a higher weight in the present meta-analysis. Both a recent systematic review[46] and a meta-analysis[47] that encompassed FOCUS data did not support the routine prescription of fluoxetine or other SSRIs to reduce and promote function recovery early after stroke without PSD. Instead, they suggested that fluoxetine or other SSRIs might be used to treat depressive disorders in patients with PSD. Nonetheless, the present result may not be the final conclusion, and the therapeutic effect of SSRIs and SNRIs for PSD functional rehabilitation remains controversial. Consequently, the two big ongoing trials, assessment of Fluoxetine in Stroke recovery (participants are being recruited from Australia, New Zealand and Vietnam), and efficacy of fluoxetine, a randomized Controlled Trial in Stroke (participants are being recruited from Sweden) will provide further information regarding fluoxetine for stroke recovery[48]. In addition, a meta-analysis using individual participant data will be needed[47].

SSRIs and antithrombotics are always simultaneously prescribed for patients with PSD in clinical practice. Clopidogrel is one of the commonly used anti-platelet medications that prevent and treat ischemic stroke. Clopidogrel can be metabolized into active products with therapeutic properties by cytochrome P450 (CYP) enzymes. A cohort study and meta-analysis (which included 72020 participants) have shown that CYP2C19-inhibiting SSRIs (fluoxetine and fluvoxamine) can decrease the therapeutic efficacy of clopidogrel. Patients using clopidogrel who were co-prescribed CYP2C19-inhibiting SSRIs had an 11% higher risk of developing ischemic disease than patients using clopidogrel who were treated with non-inhibiting SSRIs[49]. Serotonin could be released from platelets in the blood during the coagulation process. Aspirin is another important prescription medication for treating and preventing ischemic stroke and TIA. In theory, SSRI and SNRI reuptake serotonin in platelets as well as they do in the central nervous system, which reduce platelet serotonin and may be associated with aspirin-related bleeding[50].

Therefore, there are also growing concerns on the relationship of SSRIs with abnormal bleeding events[51]. Mortensen's study demonstrated that prestroke SSRI exposure was significantly associated among the severity and mortality of patients with hemorrhagic stroke[52]. In a large collaborative study, the preadmission use of SSRI alone did not increase the risk of spontaneous intracerebral hemorrhage after intravenous thrombolytic therapy for acute ischemic stroke. While there was a significant interaction between the concurrent preadmission use of SSRIs and oral anticoagulants on the occurrence of intracerebral hemorrhage related to thrombolysis[53], this condition can be seen in PSD patients with recurrent acute ischemic stroke that are treated with SSRIs. Moreover, fluoxetine and fluvoxamine are reported to have potential interactions with warfarin, and inhibit warfarin metabolism by competitively binding plasma protein and interfering with CYP isoenzymes, which are more likely to strengthen the anticoagulant effects of warfarin. Paroxetine also seems to have a low-to-moderate risk of enhancing the pharmacological effects of warfarin; however, other SSRIs and SNRIs do not appear to interact with warfarin[54].

A recent systematic review suggested that there is no high quality evidence to support that SSRIs used alone can increase the risk of spontaneous intracerebral hemorrhage. In addition, the association between SSRIs and intracerebral hemorrhage as previously reported was partly accounted for by biases and methodological limitations[55]. Neurologists and psychiatrists need to be well aware of the pharmacological interaction profiles when co-prescribing antidepressants and antithrombotics to patients with PSD and other NDS, monitor the possible adverse events during follow-up, and provide tailored therapeutic strategies for treating PSD and other NDS.

Psychotherapy is also an important intervention for PSD. CBT may be the most effective psychotherapeutic intervention. A meta-analysis on the efficacy of psychotherapy for PSD concluded that the evidence for the benefit of CBT in PSD remains inconclusive due to the high degree of heterogeneity and low quality across the majority of included studies[56]. Neuromodulation, such as transcranial magnetic stimulation and transcranial direct current stimulation, are promising adjunctive therapies. However, high quality randomized controlled trials using psychotherapy or neuromodulation are limited, and further research is needed[57].

In summary, antidepressant therapy should be used early once the definitive diagnosis of PSD has been made. SSRIs and SNRIs are recommended as a first-line

pharmacotherapy for mitigating depression. Other treatment approaches, *i.e.*, psychotherapy, neuromodulation, and psychosocial interventions, should also be considered. No reliable evidence exists to show that the use of SSRIs and other antidepressants can improve neurological function outcomes for patients with PSD.

ANXIETY DISORDERS AFTER STROKE

Screening and identification

PSA disorders are relatively common psychological problems and are the secondary NDS after depressive disorders. There are several distinct types of anxiety disorders: generalized anxiety disorder, phobias, selective mutism, agoraphobia, social anxiety disorder, and panic disorders. These disorders share similar core psychological symptoms, including feelings of uneasiness, excessive and persistent worry, and fear. Notably, anxiety disorders can also be accompanied by significant physical symptoms, some of which resemble neurological manifestations, such as tense muscles, dizziness, numb or tingling hands or feet, headache, chronic muscle or joint pain, and disturbed sleep[58]. Furthermore, unfavorable physical conditions due to brain damage caused by stroke, such as chronic pain, sleep disturbance, and communication difficulties, posed a high risk of developing PSA[59].

A case-control study conducted in Sweden revealed that the odds of PSA were predominantly higher than in the control population, which cannot be attributed to higher rates of comorbid depression. Remarkably, PSD did not show a significant independent association with PSA[60]. A meta-analysis reported that the frequency of PSA gradually rises over time, which ranged from 20% [95% confidence interval (CI): 13%-27%] within 1 mo, 23% (95%CI: 19%-27%) for one to five-mo after stroke, to 24% (95%CI: 19%-29%) for 6 mo or more after stroke[61]. The DSM-5 classifies PSA as an "anxiety disorder due to another medical condition". The prognosis of patients with PSA was markedly poor, as they likely suffered from persistent dependence with poorer quality of life and restricted social participation at 3 mo after stroke[62]. Similarity, a longitudinal study in South Korea found that PSA occurs within 2 wk after stroke, which may be an independent detrimental factor for long-term functional outcomes and daily life activities[63].

The Hamilton anxiety scale and the hospital anxiety and depression scale-anxiety subscale are the most commonly used to screen and measure the anxiety symptom severity of PSA. The cutoff score of possible and probable diagnosis of hospital anxiety and depression scale-anxiety subscale was the most widely considered identification criterion[59].

Management and therapeutic implication

There are no widely accepted guidelines that have been developed for the treatment of PSA. Several classes of pharmacotherapy were used to treat PSA in clinical practice, including SSRIs, tricyclic antidepressants, benzodiazepines and "Z-drugs"[64]. Likewise, various forms of psychological interventions, such as CBT, were frequently used for PSA, but few high-quality intervention studies have been shown.

In a study by Chun *et al*[62,64,65], meta-analysis including four pharmacotherapy comparisons studies (three studies published in Chinese journals) using paroxetine, imipramine, and buspirone, as well as eight psychotherapy comparisons studies showed an overall favorable pharmacotherapy and psychotherapy effect compared with control; however, the heterogeneity of the included studies of this meta-analysis was high and the quality of literature was relatively low. The positive conclusion may be driven by risk of bias[65]. In line with the study by Chun *et al*[64], a Cochrane review suggested that there was no high-quality clinical evidence to guide PSA management. Large-scale randomized double-blind controlled trials are required to determine the efficacy of pharmaceuticals and psychological therapies[64].

A systematic review revealed that mind-body interventions (*i.e.*, yoga, Tai Chi) may have potential benefits for treating both PSA and PSD by improving the mood and quality of life of stroke survivors[66]. Likewise, self-help mindfulness and relaxation techniques have been reported to be effective self-administered therapies to help alleviate symptoms, especially for patients with communication difficulties[67]. This suggests that PSA subtypes[62] and tailored therapeutic strategies are vital for future interventional studies.

PTSD AFTER STROKE

Screening and identification

PTSD is a mental health condition that develops following a traumatic event, including acute stroke and TIA. Under the DSM-5, PTSD is categorized as a subtype of anxiety disorder. The occurrence of PTSD is related to an event that creates psychological trauma in response to actual or threatened death, serious injury, and adverse life events. PTSD has four main hallmark characteristics: (1) Intrusive memories; (2) Alterations in physical reactions and arousal; (3) Avoidance; and (4) Negative alterations in cognition and mood[68]. As an unexpected "traumatic" event, acute stroke or TIA may be considered to be potentially life-threatening or as severe disability disorders by patients. A growing body of clinical evidence has highlighted PTSD as a common result of neuropsychiatric sequelae of stroke or TIA[69].

Patients with post-stroke PTSD were likely to combine PSD and PSA[70]. A cross-sectional study showed that PSD, PSA, and post-stoke PTSD have a remarkably high degree of co-occurrence (approximately 40% patients with NDS comorbidity have the above three psychiatric disorders)[2]. However, the biological mechanism and clinical significance of overlap and comorbidity among these NDSs have yet to be well elucidated[68]. Studies report that the frequency of poststroke PTSD was varied, which depended on the type of stroke, assessment time-point, and morbidity condition[71,72]. Notably, the incidence rate was even as high as 37% in survivors with spontaneous subarachnoid hemorrhage, which was disadvantageous to patient quality of life and outcome[73]. A retrospective study with 12 mo follow-up showed that the prevalence of probable PTSD was lower within 1-year than that within 3 mo (8.3% compared with 29.6%) after TIA, suggesting that the risk of PTSD declined gradually over time after onset, This improvement could be due to the reversibility and transience of TIA, and the trauma event and psychological distress might therefore be more likely to be temporary unless it progresses into ischemic stroke[74]. A meta-analysis with data collected before January 2013 also suggested that the prevalence of PTSD after stroke and TIA was 23% within 1 year of onset and 11% after 1 year[75]. PTSD after stroke might have a worse effect on the mental health of survivors and an undesirable functional prognosis[76]. Correspondingly, patients with PTSD also had a higher risk of developing stroke than control people without PTSD[77]. A similar association was also seen in veterans with PTSD[78], but whether PTSD treatment offset the risk of developing stroke or TIA is unknown. Additionally, the treatment adherence to medication prescribed by specialists of stroke or TIA survivors with PTSD was reported to be poor[79], which impeded the efficient management of mental and physical health.

In most studies, PTSD after stroke was identified by the combination of diagnostic interviews and self-rating scales and questionnaires. A variety of assessments was used for screening; more frequently used scales included the PTSD checklist for a stressor using the "stroke or TIA" as a stressor[71,76,79], the clinician-administered PTSD scale[80], impact of events scale-revised[72], posttraumatic stress diagnostic scale[70], as well as the structured clinical interview for DSM. As the most widely used scale at present, a cutoff score of 50 on the PTSD checklist for a stressor highly indicated probable PTSD diagnosis after stroke.

Management and therapeutic implications

To our knowledge, there is no high-quality randomized controlled trial evaluating the efficacy of pharmacotherapy or psychotherapy for the intervention of post-stroke PTSD[68,69]. The psychotherapeutic approach procedures, such as CBT, trauma-focused psychotherapies, and exposure therapy are useful for facilitating compliance for developing strategies, which look promising for post-stroke PTSD of which the efficacy needs to be tested in future studies[81]. It remains unclear whether post-stroke PTSD could benefit from pharmacotherapeutic interventions like PSD, such as SSRI antidepressants. Although antidepressants were usually administrated for patients with post-stroke PTSD with comorbid depressive disorders, evidence for the effectiveness of medication (antidepressants, anxiolytics sympathetic inhibitor, antipsychotics, anticonvulsants, and sedative drugs) has still been inconsistent[82].

PSYCHOSIS AND PSYCHOTIC DISORDERS AFTER STROKE

Screening and identification

Under DSM-5 classifications, post-stroke psychotic disorders may be categorized as psychotic disorders due to another medical condition. The main symptoms of post-stroke psychotic disorders are characterized by hallucinations or delusions, which may be accompanied by disorganized speech, catatonic or inappropriate motor behavior, typically followed by acute severe stroke. Post-stroke psychosis refers to a series of symptoms after stroke; psychosis can be a clinical syndrome embedded with

many medical conditions, including schizophrenia, bipolar disorder with psychotic properties, and other psychotic disorders. The most prominent symptoms of psychosis include delusions and hallucinations[83]. Psychosis may manifest within 1 wk after stroke and rapidly develop into psychotic disorders, but psychosis would also be delayed and occur several weeks after onset. Delusions and hallucinations may be permanent as an accompanying sequel, or temporary as a result of functional rehabilitation.

Post-stroke psychosis didn't appear to notably raise many clinical research concerns like PSD or PSA, resulting in the lack of robust consensus supported by evidence-based medicine. Previous studies have suggested that post-stroke psychotic disorders are a rare complication of stroke. A cohort study published in 1991 included 1191 stroke patients with a 9-year follow-up, of whom only five patients were identified to suffer psychosis[84]. Although single psychotic symptoms (psychosis) may not meet the criteria of strict psychotic disorders, delusions and hallucinations seem to be more frequent in stroke survivors. A recent meta-analysis reported that the estimated frequency from the eligible four studies with delusions symptom was 4.67%, and the estimated frequency from the three studies with hallucination symptoms was 5.05%, with a pooled prevalence rate of psychosis after stroke of 4.86%[85]. A retrospective study consecutively included 1,108 stroke survivors in Western Australia from 1990 to 2002, and reported the cumulative incidence of psychosis after stroke to be 6.7%, which is a significantly positive correlation with a 10-year mortality[86]. Structural lesions that were related to delusions were centered on the right frontal, temporal, and parietal lobes, as well as white matter lesions with connectivity to the above areas, in addition to the right caudate nucleus[87,88].

Although different versions of the neuropsychiatric inventory were administered to stroke survivors for detecting delusions and hallucinations in some studies[89-91], unfortunately neuropsychiatric assessment tools for psychosis and psychotic disorders after stroke were presented inconsistently in the current studies. Moreover, there is no structured assessment that is suitable for a quantitative evaluation of psychosis and psychotic disorders respectively. It is thus a challenge to represent standardization studies across different research endeavors about psychosis and psychotic disorders after stroke.

There is no widely acknowledged diagnostic criterion for psychosis and psychotic disorders after stroke, and most studies adopt the DSM and International Classification of Diseases as diagnostic criteria for psychotic disorders. Therefore, it is hard to yield consistent conclusions, or to stand in agreement with these promising study results. Such deficiencies have already been highlighted by the latest systematic reviews or meta-analyses on post-stroke psychosis[85,92]. Validated structured assessment tools of psychosis and acknowledged diagnostic criteria are needed to identify the presentation and estimate the severity of psychosis and psychotic disorders after stroke, which will facilitate the standardization of research in this field.

Management and therapeutic implication

Currently, there is no randomized controlled trial study that systematically investigates the therapeutic efficacy and safety of antipsychotic medication for post-stroke psychosis. Most studies applied the management and treatment for post-stroke psychosis in a similar manner with that used for primary psychotic disorders, indicating that they share the same clinical and etiology properties. In some case reports and case series studies, stroke survivors with psychosis or psychotic disorders were mostly treated with antipsychotic medications. Approximately two thirds of patients who were treated with antipsychotics attained complete or partial recovery[85].

Second-generation antipsychotic drugs, such as risperidone, quetiapine, and olanzapine, were the most commonly used antipsychotic medications for post-stroke psychoses. The safety of antipsychotics for patients with stroke is still highly controversial. Antipsychotic drugs appear to have undesirable side effects on glucose and lipid metabolism. Whereas different antipsychotics exhibited distinctly varying degrees of influence on metabolic side-effects, a meta-analysis suggested that olanzapine and clozapine showed the most unfavorable effects on metabolism[93]. Previous studies have concluded that either first or second generation antipsychotic drugs may increase the risk of stroke, especially for patients with vascular dementia[94,95]. A recent meta-analysis revealed that antipsychotic drug exposure may significantly increase the risk of developing a stroke, but the conclusion remains unproven due to the high heterogeneity of these included studies[96]. A meta-analysis indicated that the risk of developing stroke might be higher in patients who received first-generation antipsychotic drugs than in those who received second-generation antipsychotic drugs[97]. However, a large-scale case control study found that neither first nor second generation antipsychotic drugs increase the risk of stroke in elderly

subjects with non-cognitive decline[98]. Therefore, as an important complementary therapy, non-pharmaceutical approaches such as physical neuromodulation and psychosocial therapy are promising therapeutic options for psychosis and psychotic disorders after stroke. It has been shown that CBT might help mitigate the distress caused by hallucinations or delusional beliefs[99].

CONCLUSION

At present, more and more attention is paid to the screening, diagnosis, and management of NDS. There is still lack of a widely-acknowledged structured scale for screening and assessing each NDS. Pharmacotherapy by modulating neurotransmitters is the mainstay treatment modality for NDS. Except for PSD being studied extensively, large-scale randomized double-blind controlled trials are still required to determine the efficacy of pharmaceuticals and psychological therapies for other NDS. Further aim should attempt to develop protocols or guidelines for the diagnosis, treatment, or prevention of NSD. Current evidence reveals the limitations of our knowledge about NDS and may change as scientific research reflects that stroke is the pathological basis and cause of NDS.

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