Neuropsychiatric issues after stroke: Clinical significance and therapeutic implications

Shuo Zhang, Michael Xu, Zhi-Jun Liu, Juan Feng, Yan Ma

ORCID number: Shuo Zhang (0000-0002-4367-0026); Michael Xu (0000-0002-0248-6097); Zhi-Jun Liu (0000-0001-5533-3038); Juan Feng (0000-0002-1815-7036); Yan Ma (0000-0002-0900-0926).

Author contributions: Zhang S, Feng J and Liu ZJ conceived and designed the review; Xu M, Feng J, Ma Y and Zhang S reviewed and edited the manuscript; Zhang S and Liu ZJ wrote the paper.

Supported by the National Natural Science Foundation of China, No. 81801712, No. 81801710; the Science and Technology Project Funds from Education Department of Liaoning Province of China, No. LK2016022.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Received: December 30, 2019

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
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.

Citation: Zhang S, Xu M, Liu ZJ, Feng J, Ma Y. Neuropsychiatric issues after stroke: Clinical
significance and therapeutic implications. World J Psychiatr 2020; 10(6): 125-138
URL: https://www.wjgnet.com/2220-3206/full/v10/i6/125.htm
DOI: https://dx.doi.org/10.5498/wjp.v10.i6.125

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

Zhang S et al. Neuropsychiatric issues after stroke
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 variant allele genotype of the serotonin transporter-linked promoter region (5-HTTLPR) and post-stroke depression, whereas the homozygous long variant 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 \[^{[1]}\]. Although the 5-HTTLPR polymorphism was found to have a significant association with an antidepressant response and remission in Caucasians \[^{[2]}\], 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) \[^{[3]}\]. In addition, polymorphism in the tryptophan hydroxylase 2 gene were also found to be involved in PSA susceptibility \[^{[4]}\].

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) \[^{[5]}\].

A previous meta-analysis of 61 studies with 25488 patients indicated that the pooled frequency of PSD was 34% in 32 stroke cohorts \[^{[6]}\], consistent with a meta-analysis of 32 studies with 8938 patients receiving antidepressant therapy where the pooled frequency was 31\% \[^{[7]}\].

The proportional frequency of depression reported ranged from 5\% \[^{[8]}\] - 84\% \[^{[9]}\], 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 \[^{[10]}\].

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    | Center for epidemiological studies-depression scale; hospital anxiety depression  | According to the DSM-5 classification, PSD is defined as a depressive disorder due to TIA or     | SSRIs and SNRIs; psychological intervention; mental and physical exercise; neuromodulation      |
|                                        |                          | appetite/weight; insomnia or hypersomnia; psychomotor agitation/retardation; loss of energy/  | depression scale; Hamilton depression rating scale; beck depression inventory;    | stroke.                                                                                          |                                                                                                |
|                                        |                          | fatigue; feelings of worthlessness/inappropriate guilt; loss of concentration; appear          | geriatric depression scale; PHQ-9                                               |                                                                                                |                                                                                                |
|                                        |                          | pessimistic about health issues/recurrent thoughts of death or suicide                        |                                                                                  |                                                                                                |                                                                                                |
| Anxiety disorders after stroke         | 20-24                    | Prominent anxiety; excessive fear, worry, and concern about health issues; intense            | 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     | SSRIs; Tricyclic antidepressant; benzdiazepines; “Z-drugs” (zolpidem, zaleplon and             |
|                                        |                          | dread or uneasiness; panic attacks, or obsessions or compulsions predominat                    |                                                                                  | stroke.                                                                                          | eszopiclone); psychological interventions; mind-body interventions                           |
| PTSD after stroke                       | 8.3-29.6                 | Intrusive memories; alterations in physical reactions and arousal; avoidance; negative        | PTSD checklist for a stressor, TIA or stroke as stressor; clinician administered    | PTSD is related to TIA or stroke which creates psychological trauma in response to actual or     | Psychotherapeutic approach procedures; antidepressants, anxiolytics sympathtic inhibitor,     |
|                                        |                          | alterations in cognition and mood                                                             | PTSD scale; impact of events scale-revised; posttraumatic stress diagnostic       | threatened death, serious injury, and adverse life events.                                    | antipsychotics, anticonvulsants, and sedative drugs                                         |
| Psychosis and                         | 4.67-5.05                | Hallucinations or delusions; disorganized speech; catatonic or inappropriate motor behavior    | Neuropsychiatric inventory                                                      |                                                                                                |                                                                                                |
| psychotic disorders after stroke       |                          |                                                                                              |                                                                                  |                                                                                                |                                                                                                |

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.

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[3]. 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[4]. 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-


The TALOS study (the Efficacy of trial do not support the routine use of fluoxetine in prophylactic treatment for PSD or outcomes, and even increase the risk of bone fractures. The results from the FOCUS would enable the improvement of depression symptoms rather than clinical outcomes between the two groups, although results of the clinical trial indicated that fluoxetine the neuropsychological scale questionnaire showed statistically significant differences daily) or placebo for 6 mo. After an extended follow-up period of up to 12 mo, only (not patients with PSD) that were recruited and randomly allocated fluoxetine (20 mg the effect of fluoxetine on neurological functional outcomes after acute stroke. 103 hospitals through the National Health Service, United Kingdom, which focuses on neurological symptoms after stroke such as aphasia, alexia, or agnosia may lead to expressive or receptive dysfunction. Cognitive impairment such as loss of concern, anosognosia, abulia, or lack of insight may develop similar depressive symptoms. 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. 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.

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; 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. 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.

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 physotherapy promoted motor recovery after 3 mo. 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.

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. 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[49].

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[50]. 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[51].

Therefore, there are also growing concerns on the relationship of SSRIs with abnormal bleeding events[52]. Mortensen’s study demonstrated that prestroke SSRI exposure was significantly associated among the severity and mortality of patients with hemorrhagic stroke[53]. In a large collaborative study, the predmission use of SSRI alone and in combination with warfarin increased 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[54], 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[55].

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[56]. 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[57]. 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[58].

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\(^{[66]}\).

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\(^{[67]}\). 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\(^{[68]}\). This suggests that PSA subtypes\(^{[62]}\) and tailored therapeutic strategies are vital for future interventional studies.

### PTSD AFTER STROKE

#### Screening and identification
WJP

PTSD may have potential benefits for treating both PSA and PSD by improving the mood and quality of life of stroke survivors\(^{[67]}\). 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\(^{[68]}\). This suggests that PSA subtypes\(^{[62]}\) and tailored therapeutic strategies are vital for future interventional studies.
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[89]. 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[89].

Patients with post-stroke PTSD were likely to combine PSD and PSA[89]. A cross-sectional study showed that PSD, PSA, and post-stroke PTSD have a remarkably high degree of co-occurrence (approximately 40% patients with NDS comorbidity have the above three psychiatric disorders)[89]. However, the biological mechanism and clinical significance of overlap and comorbidity among these NDSs have yet to be well elucidated[89]. Studies report that the frequency of poststroke PTSD was varied, which depended on the type of stroke, assessment time-point, and morbidity condition[68,74,79]. 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[81]. 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[89]. 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[79]. PTSD after stroke might have a worse effect on the mental health of survivors and an undesirable functional prognosis[89]. Correspondingly, patients with PTSD also had a higher risk of developing stroke than control people without PTSD[89]. A similar association was also seen in veterans with PTSD[89], 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[89], 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[70,71,75,76,79], the clinician-administered PTSD scale[80], impact of events scale-revised[72], posttraumatic stress diagnostic scale[89], 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[89]. 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[89]. 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[89].

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\(^{[84]}\). 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\(^{[83]}\). 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\(^{[94]}\). 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\(^{[99-101]}\), 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 psychiatric 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\(^{[89-91]}\). 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\(^{[89]}\).

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\(^{[82,89]}\). 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\(^{[94]}\). 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\(^{[93]}\). 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. 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.

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 NSF. 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.

REFERENCES

1. Johnson W, Onuma O, Owolabi M, Sachdev S. Stroke: a global response is needed. Bull World Health Organ 2016; 94: 634-634A. [PMID: 27708461 DOI: 10.2471/BLT.16.181636]
2. Stein LA, Goldmann E, Zaman A, Luciano JM, Messé SR, Cucchiara BL, Kasner SE, Mullin MT. Association Between Anxiety, Depression, and Post-traumatic Stress Disorder and Outcomes After Ischemic Stroke. Front Neurol 2018; 9: 890 [PMID: 30450072 DOI: 10.3389/fneur.2018.00890]
3. Khan A, Chen L, GL Z, Guo X, Wu G, Wang H, You Y, Gu Y, Yunn M. Management of Poststroke Neuropsychiatric Disorders. Travel Neurosci Clin 2016; 2: 244-251 [DOI: 10.18679/CN11-6030/R.2016.031]
4. Bartoli F, Di Britta C, Crocamo C, Clerici M, Carrà G. Early Post-stroke Depression and Mortality: Meta-Analysis and Meta-Regression. Front Psychiatry 2018; 9: 530 [PMID: 30443225 DOI: 10.3389/fpsych.2018.00530]
5. Cai W, Mueller C, Li YJ, Shen WD, Stewart R. Post stroke depression and risk of stroke recurrence and mortality: A systematic review and meta-analysis. Ageing Res Rev 2019; 50: 102-109 [PMID: 30711712 DOI: 10.1016/j.arr.2019.01.013]
6. Ferro JM, Santos AC. Emotions after stroke: A narrative update. Int J Stroke 2020; 15: 256-267 [PMID: 31561930 DOI: 10.1111/ijst.13706]
7. Bongiovanni DM, Daunut GL, Gottesman RF, Faigle R. Patients with stroke and psychiatric comorbidities have lower carotid revascularization rates. Neurology 2019; 92: e2514-e2521 [PMID: 31055663 DOI: 10.1212/WNL.0000000000007565]
8. Hackett ML, Köhler S, O’Brien JT, Mead GE. Neuropsychiatric outcomes of stroke. Lancet Neurol 2014; 13: 525-534 [PMID: 2468279 DOI: 10.1016/S1474-4422(14)7016-X]
9. Ferro JM, Cairelo I, Figueira ML. Neuropsychiatric sequelae of stroke. Nat Rev Neurosci 2016; 12: 269-280 [PMID: 27063107 DOI: 10.1038/nrneurol.2016.46]
10. Tenev VT, Robinson RG, Jorge RE. Is family history of depression a risk factor for poststroke depression? Meta-analysis. Am J Geriatr Psychiatry 2009; 17: 276-280 [PMID: 19307856 DOI: 10.1097/JGP.0b013e3181953846]
11. Mak KK, Kong WY, Mak A, Sharma VK, Ho RC. Polymorphisms of the serotonin transporter gene gene and post-stroke depression: a meta-analysis. J Neurol Neurosurg Psychiatry 2013; 84: 322-328 [PMID: 23236014 DOI: 10.1136/jnnp-2012-30791]
12. Forcelli S, Fabbri C, Serretti A. Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with antidepressant efficacy. Eur Neuropsychopharmacol 2012; 22: 239-258 [PMID: 22137564 DOI: 10.1016/eunueropharm.2011.10.003]
13. Kim JM, Stewart R, Kang HJ, Kim SY, Kim SW, Shin IS, Park MS, Kim HR, Shin MG, Che KH, Yoon JS. A longitudinal study of BDNF promoter methylation and genotype with poststroke depression. J Affect Disord 2013; 149: 93-99 [PMID: 23393486 DOI: 10.1016/j.jad.2013.01.008]
14. Kang JJ, Kim KO, Kim JW, Kim SW, Park MS, Kim HR, Shin MG, Cho KH, Kim JM. A longitudinal study of the associations of BDNF genotype and methylation with poststroke anxiety. Int J Geriatr Psychiatry 2019; 34: 1706-1714 [PMID: 31368178 DOI: 10.1002/gps.5185]
15. Chi S, Teng L, Song JH, Zhou C, Pan WH, Zhao RL, Zhang C. Tryptophan hydroxylase 2 gene polymorphisms and poststroke anxiety disorders. J Affect Disord 2013; 144: 179-182 [PMID: 22835848 DOI: 10.1016/j.jad.2012.05.017]
16. Shi Y, Yang D, Zeng Y, Wu W. Risk Factors for Post-stroke Depression: A Meta-analysis. Front Aging Neurosci 2017; 9: 218 [PMID: 28744213 DOI: 10.3389/fnagi.2017.00218]
17. Babkair LA. Risk Factors for Poststroke Depression: An Integrative Review. J Neurol Surg 2017; 49: 73-84 [PMID: 28777449 DOI: 10.1055/jnns.0000000000000821]
18. Sanner Beauchamp JE, Casamini Montiel T, Cai C, Tallavajhula S, Hinojosa E, Okpala MN, Vahidy FS, Savitz SI, Sharriff AZ. A Retrospective Study to Identify Novel Factors Associated with Post-stroke Anxiety. J Stroke Cerebrovas Dis 2020; 19: 104582 [PMID: 31859033 DOI: 10.1016/j.jstrokecerebrovasdis.2019.104582]
19. Park EY, Kim JH. An analysis of depressive symptoms in stroke survivors: verification of a moderating effect of demographic characteristics. BMC Psychiatry 2017; 17: 132 [PMID: 28390402 DOI: 10.1186/s12888-017-1292-4]
20. Lin FH, Yih DN, Shih FM, Chu CM. Effect of social support and health education on depression scale
De Ryck A, Fransen E, Bruyneel M, Peij D, Marien P, De Deyn PP, Engelenburgs S. Poststroke depression and its multifactorial nature: results from a prospective longitudinal study. *J Neurol Sci* 2014; 347: 159-166 [PMID: 25451004 DOI: 10.1016/j.jns.2014.09.038]

Hackett ML, Pickles K. Part I: frequency of depression after stroke: an updated systematic review and meta-analysis of observational studies. *Int J Stroke* 2014; 9: 1017-1025 [PMID: 25117911 DOI: 10.1111/jis.12354]

Lancet Neurol. 2011; 10: 747-755 [PMID: 21216670 DOI: 10.1016/S1474-4422(10)70314-8]

J Stroke Cerebrovasc Dis. 2019; 28: S172-S172 [DOI: 10.1016/S0022-510X(09)70659-4]

*Front Neurol* 2018; 9: 301-303 [PMID: 29392603 DOI: 10.1016/STR.000000000000113]

*J Neurol Neurosurg Psychiatry* 2014; 85: 198-216 [PMID: 23385649 DOI: 10.1136/jnnp-2013-304194]

*M. J Stroke Cerebrovasc Dis* 2019; 28: e30-e43 [PMID: 27932603 DOI: 10.1016/STR.00000000000000001]

*J Neurol Neurosurg Psychiatry* 2018; 89: 25-37 [PMID: 31593971 DOI: 10.1136/mjnl-2019-050229]

*M. J Stroke Cerebrovasc Dis* 2018; 27: 262-277 [PMID: 27284119 DOI: 10.1016/jjocn.2006.01.025]

*J Neurol Neurosurg Psychiatry* 2014; 85: 93-101 [PMID: 24841903 DOI: 10.1136/jnnp-2013-304191]

*JAMA Psychiatry* 2016; 73: 1032-1040 [PMID: 27603000 DOI: 10.1001/jamapsychiatry.2016.1932]

*Int J Stroke* 2019; 1-12 [PMID: 31180740 DOI: 10.1111/ijs.12357]

*Ann Intern Med* 2019; 151: 25-37 [PMID: 31058767 DOI: 10.1097/JNN.000000000000442]

*Disabil Rehabil* 2019; 1-12 [PMID: 31100740 DOI: 10.1080/09638288.2019.1621394]

*Disabil Rehabil* 2018; 40: 301-303 [PMID: 29325929 DOI: 10.1080/09638288.2016.123517]

*Front Neurol* 2019; 10: 926 [PMID: 31907525 DOI: 10.3389/neur.2019.00926]

*J Stroke Cerebrovasc Dis* 2013; 22: 1243-1251 [PMID: 22554569 DOI: 10.1016/j.jstrokecerebrovasdis.2013.03.013]

*J Stroke Cerebrovasc Dis* 2012; 21: 159-166 [PMID: 25451004 DOI: 10.1016/j.jstrokecerebrovasdis.2013.03.013]

*J Stroke Cerebrovasc Dis* 2018; 27: 2905-2918 [PMID: 30201439 DOI: 10.1016/j.jstrokecerebrovasdis.2018.07.027]

*J Stroke Cerebrovasc Dis* 2018; 27: 1243-1251 [PMID: 22554569 DOI: 10.1016/j.jstrokecerebrovasdis.2012.03.013]

*J Stroke Cerebrovasc Dis* 2013; 22: 1243-1251 [PMID: 22554569 DOI: 10.1016/j.jstrokecerebrovasdis.2012.03.013]

*J Stroke Cerebrovasc Dis* 2018; 27: 2905-2918 [PMID: 30201439 DOI: 10.1016/j.jstrokecerebrovasdis.2018.07.027]

*J Stroke Cerebrovasc Dis* 2018; 27: 1243-1251 [PMID: 22554569 DOI: 10.1016/j.jstrokecerebrovasdis.2012.03.013]

*J Stroke Cerebrovasc Dis* 2018; 27: 2905-2918 [PMID: 30201439 DOI: 10.1016/j.jstrokecerebrovasdis.2018.07.027]

*J Stroke Cerebrovasc Dis* 2018; 27: 1243-1251 [PMID: 22554569 DOI: 10.1016/j.jstrokecerebrovasdis.2012.03.013]

*J Stroke Cerebrovasc Dis* 2018; 27: 1243-1251 [PMID: 22554569 DOI: 10.1016/j.jstrokecerebrovasdis.2012.03.013]
Analysis and Trial Sequential Analysis. J Stroke Cerebrovasc Dis 2018; 27: 1178-1189 [PMID: 29276014 DOI: 10.1016/j.jstrokecerebrovasdis.2017.11.031]

Mead GE, Hsieh CF, Lee R, Kutlubay MA, Claxton A, Hankey GJ, Hackett ML. Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery. Cochrane Database Syst Rev 2012; 11: CD009286 [PMID: 23152272 DOI: 10.1002/14651858.CD009286.pub2]

Yi ZM, Liu F, Zhai SD. Fluoxetine for the prophylaxis of poststroke depression in patients with stroke: a meta-analysis. Int J Clin Pract 2010; 64: 1310-1317 [PMID: 20653802 DOI: 10.1111/j.1742-1241.2010.02437.x]

FOCUS Trial Collaboration. Effects of fluoxetine on functional outcomes after acute stroke (FOCUS): a pragmatic, double-blind, randomised, controlled trial. Lancet 2019; 393: 265-274 [PMID: 30528472 DOI: 10.1016/S0140-6736(18)32833-X]

Kraglund KL, Mortensen JK, Damsbo AG, Modbra D, Simonsen SA, Iversen HK, Madsen M, Grove EL, Johnsen SP, Andersen G. Neuroregeneration and Vascular Protection by Ciluplatin in Acute Ischemic Stroke (TALOS) Stroke 2018; 49: 2568-2576 [PMID: 30355209 DOI: 10.1161/STROKEAHA.117.020067]

Legg LA, Tilney R, Hsieh CF, Wu S, Lundstrøm E, Rudberg AS, Kutlubay MA, Dennis M, Soleimani B, Barugh A, Hackett ML, Hankey GJ, Mead GE. Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery. Cochrane Database Syst Rev 2019; 2019 [PMID: 31769878 DOI: 10.1002/14651858.CD009286.pub3]

Mead GE, Legg L, Tilney R, Hsieh CF, Wu S, Lundstrøm E, Rudberg AS, Kutlubay M, Dennis MS, Soleimani B, Barugh A, Hackett ML, Hankey GJ. Fluoxetine for stroke recovery: Meta-analysis of randomized controlled trials. Int J Stroke 2019; 1474493019879655 [PMID: 31619317 DOI: 10.1177/1747493019879655]

Sahe L, Balestrieri A, Serra A, Garau R, Politi C, Lucatelli P, Murgia A, Suri JS, Mannelli L. FOCUS trial: results, potentialities and limits. Ann Transl Med 2019; 7: S152 [PMID: 31576359 DOI: 10.21037/atm.2019.09.37]

Bykov K, Schneeweiss S, Glynn RJ, Mittelman MA, Bates DW, Gagne J. Updating the Evidence of the Interaction Between Clopidoigrel and CYPC19-Inhibiting Selective Serotonin Reuptake Inhibitors: A Cohort Study and Meta-Analysis. Drug Saf 2017; 40: 923-932 [PMID: 28623527 DOI: 10.1007/s40264-017-0556-8]

Juurlink DN. Antidepressants, antiplatelets and bleeding: one more thing to worry about? CMAJ 2011; 183: 1819-1820 [PMID: 21969407 DOI: 10.1503/cmaj.110576]

Andrade C, Sharma E. Serotonin Reuptake Inhibitors and Risk of Abnormal Bleeding. Psychiatric Clin North Am 2016; 39: 413-426 [PMID: 27514297 DOI: 10.1016/j.psc.2016.04.010]

Mortensen JK, Larsson H, Johnsen SP, Andersen G. Impact of prestroke selective serotonin reuptake inhibitor treatment on stroke severity and mortality. Stroke 2014; 45: 2121-2123 [PMID: 24893612 DOI: 10.1161/STROKEAHA.114.005302]

Scheit JF, Ture G, Kujala L, Polymeris AA, Heldner MR, Zomeveld TP, Erdur H, Curte S, Traenca C, Bremiere C, Wiest R, Rocco A, Sibolt G, Gensicke H, Endres M, Martinez-Majander N, Béjot Y, Nederkoorn PJ, Oppenheim C, Arnold M, Engelst H, Srbnian D, Nolte CH, TRISP Collaboration. Intracerebral Hemorrhage and Outcome After Thrombolysis in Stroke Patients Using Selective Serotonin-Reuptake Inhibitors. Stroke 2017; 48: 3239-3244 [PMID: 29127249 DOI: 10.1161/STROKEAHA.117.018377]

Sansone RA, Sansone LA. Warfarin and Antidepressants: Happiness without Hemorrhaging. Psychiatry Edgmont 2009; 6: 24-29 [PMID: 19724766]

Jensen MF, Ziff OJ, Banerjee G, Ambler G, Werring DJ. The impact of selective serotonin reuptake inhibitors on the risk of intracranial haemorrhage: A systematic review and meta-analysis. Eur J Stroke 2019; 4: 144-152 [PMID: 31299262 DOI: 10.1161/STROKEAHA.119.027211]

Wang SB, Wang YY, Zhang QE, Wu SL, Ng CH, Ungvari GS, Chen L, Wang CX, Jia FJ, Xiang YT. Fluoxetine for the prophylaxis of poststroke depression in patients with stroke: a meta-analysis. J Affect Disord. 2019; 273: 589-596 [PMID: 30748554 DOI: 10.1016/j.jad.2018.04.011]

Starkstein SE, Hayhow ID. Treatment of Post-Stroke Depression. Curr Treat Options Neurol 2019; 21: 31 [PMID: 31236751 DOI: 10.1007/s11940-019-0570-5]

Craske MG, Stein MB. Anxiety. Lancet 2016; 388: 3048-3059 [PMID: 27349358 DOI: 10.1016/S0140-6736(16)30831-6]

Unsworth DJ, Mathias JL, Dotson DS. Preliminary Screening Recommendations for Patients at Risk of Depression and/or Anxiety more than 1 year Poststroke. J Stroke Cerebrovasc Dis 2019; 28: 1519-1528 [PMID: 30928216 DOI: 10.1016/j.jstrokecerebrovasdis.2019.03.014]

Cumming TB, Blomstrand C, Skoog I, Linden T. The High Prevalence of Anxiety Disorders After Stroke. Am J Geriatr Psychiatry 2016; 24: 154-160 [PMID: 26060173 DOI: 10.1016/j.jgp.2015.06.003]

Campbell Burton CA, Murray J, Holmes J, Astin F, Greenwood D, Knapp P. Frequency of anxiety after stroke: a systematic review and meta-analysis of observational studies. Int J Stroke 2013; 8: 545-559 [PMID: 23013268 DOI: 10.1111/j.1747-4949.2012.00906.x]

Chun HY, Whiteley WN, Dennis MS, Mead GE, Carson AJ. Anxiety After Stroke: The Importance of Subtyping. Stroke 2018; 49: 556-564 [PMID: 29437982 DOI: 10.1161/STROKEAHA.117.020078]

Lee EH, Kim JW, Kang HI, Kim SW, Kim JT, Park MS, Cho KH, Kim JM. Association between Anxiety and Functional Outcomes in Patients with Stroke: A 1-Year Longitudinal Study. Psychiatry Investig 2019; 16: 919-925 [PMID: 3169556 DOI: 10.30773/pit.2019.0188]

Knapp P, Campbell Burton CA, Holmes J, Murray J, Gillespie D, Lightbody CE, Watkins CL, Chun HY, Lewis SR. Interventions for treating anxiety after stroke. Cochrane Database Syst Rev 2017; 5: CD008860 [PMID: 2835532 DOI: 10.1002/14651858.CD008860.pub3]

Chun HY, Newman R, Whiteley WN, Dennis M, Mead GE, Carson AJ. A systematic review of anxiety interventions in stroke and acquired brain injury: Efficacy and trial design. J Psychosom Res 2018; 104: 65-75 [PMID: 29275788 DOI: 10.1016/j.jpsychores.2017.11.010]

Love MF, Sharrief A, Chaul A, Savitz S, Beauchamp JES. Mind-Body Interventions, Psychological Stresses, and Quality of Life in Stroke Survivors. Stroke 2019; 50: 834-840 [PMID: 30612536 DOI: 10.1161/STROKEAHA.118.021150]

Wang X, Smith C, Ashley L, Hyland ME. Tailoring Self-Help Mindfulness and Relaxation Techniques for Stroke Survivors: Examining Preferences, Feasibility and Acceptability. Front Psychol 2019; 10: 391 [PMID: 30866349 DOI: 10.3389/fpsyg.2019.00391]

Garton AL, Sisti JA, Gupta VP, Christophe BR, Connolly ES. Poststroke Post-Traumatic Stress Disorder.
Zhang S et al. Neuropsychiatric issues after stroke

A Review. Stroke 2017; 48: 507-512 [PMID: 27932604 DOI: 10.1161/STROKEAHA.116.015234]

Edmondson D, von Kanel R. Post-traumatic stress disorder and cardiovascular disease. Lancet Psychiatry 2017; 4: 320-329 [PMID: 28109846 DOI: 10.1016/S2215-0366(16)30377-7]

Kipphut IC, Utz KS, Noble AJ, Köhrlmann M, Schenk T. Increased prevalence of posttraumatic stress disorder in patients after transient ischemic attack. Stroke 2014; 45: 3360-3366 [PMID: 25278556 DOI: 10.1161/STROKEAHA.113.044549]

Rutovit S, Kadjoie D, Dikanovic M, Solic K, Malojbeic J. Prevalence and correlates of post-traumatic stress disorder after ischemic stroke. Acta Neuro Belg 2019 [PMID: 31452093 DOI: 10.1007/s13750-019-01209-9]

Favrole P, Jehel L, Levy P, Descombes S, Muresan IP, Manaficjer MJ, Alamowitch S. Frequency and predictors of post-traumatic stress disorder after stroke: a pilot study. J Neurol Sci 2013; 327: 35-40 [PMID: 23465907 DOI: 10.1016/j.jns.2013.02.001]

Noble AJ, Baisch S, Mendelow AD, Allen L, Kane P, Schenk T. Posttraumatic stress disorder explains reduced quality of life in subarachnoid hemorrhage patients in both the short and long term. Neurosurgery 2008; 63: 1095-104, discussion 1004-5 [PMID: 19057321 DOI: 10.1227/01.NEU.0000327580.91345.78]

Utz KS, Kipphut IC, Schenk T. Posttraumatic stress disorder in patients after transient ischemic attack: A one-year follow-up. J Psychosom Res 2019; 122: 36-38 [PMID: 31126409 DOI: 10.1016/j.jpsychires.2019.04.016]

Edmondson D, Richardson S, Fausett JK, Falzon L, Howard VJ, Kronish IM. Prevalence of PTSD in Survivors of Stroke and Transient Ischemic Attack: A Meta-Analytic Review. PLoS One 2013; 8: e66435 [PMID: 23840467 DOI: 10.1371/journal.pone.0066435]

Goldfinger JZ, Edmondson D, Kronish IM, Fei K, Balakrishnan R, Tuhrim S, Horowitz CR. Correlates of post-traumatic stress disorder in stroke survivors. J Stroke Cerebrovasc Dis 2014; 23: 1099-1105 [PMID: 24144593 DOI: 10.1016/j.jstrokecerebrovasdis.2013.09.019]

Chen MH, Pan TL, Li CT, Lin WC, Chen YS, Lee YC, Tsai SJ, Hsu JW, Huang KL, Tsai CF, Chang WH, Chen TJ, Su TP, Bai YM. Risk of stroke in patients with post-traumatic stress disorder: nationwide longitudinal study. Br J Psychiatry 2015; 206: 302-307 [PMID: 25987604 DOI: 10.1192/bjp.bp.113.145610]

Beristianos MH, Yaffe K, Cohen B, Byer AL. PTSD and Risk of Incident Cardiovascular Disease in Aging Veterans. Am J Geriatr Psychiatry 2016; 24: 192-200 [PMID: 25555625 DOI: 10.1016/j.jgp.2014.12.003]

Kronish IM, Edmondson D, Goldfinger JZ, Fei K, Horowitz CR. Posttraumatic stress disorder and adherence to medications in survivors of strokes and transient ischemic attacks. Stroke 2012; 43: 2192-2197 [PMID: 22618360 DOI: 10.1161/STROKEAHA.112.655209]

Semb S, Tarrier N, O'Neill P, Burns A, Faragher B. Does post-traumatic stress disorder occur after stroke: a preliminary study. Int J Geriatr Psychiatry 1998; 13: 315-322 [PMID: 9658264 DOI: 10.1002/(sici)1099-1166(199805)13:5<315::aid-gerps766>3.0.co;2-e]

Lee DJ, Schnitzlein CW, Wolf JP, Vythilingam M, Rasmusson AM, Hoge CW. Psychotherapy versus pharmacotherapy for posttraumatic stress disorder: systematic review and meta-analyses to determine first-line treatments. Depression Anxiety 2016; 33: 792-806 [PMID: 27126398 DOI: 10.1002/daua.22511]

Friedman MJ, Bernardy NC. Considering future pharmacotherapy for PTSD. Neurosci Lett 2017; 649: 181-185 [PMID: 27890743 DOI: 10.1016/j.neulet.2016.11.049]

Lieberman JA, First MB. Psychotic Disorders. N Engl J Med 2018; 379: 270-280 [PMID: 30021088 DOI: 10.1056/NEJMra1801490]

Ravins PV, Starkstein SE, Robinson RG. Risk factors for developing atypical (schizophreniform) psychosis following stroke. J Neuropsychiatry Clin Neurosci 1991; 3: 6-9 [PMID: 7580174 DOI: 10.1176/jnp.3.1.6]

Stangland H, Orgeta V, Bell V. Poststroke psychosis: a systematic review. J Neurol Neurosurg Psychiatry 2018; 89: 879-885 [PMID: 29323009 DOI: 10.1136/jnpp-2017-317327]

Almeida OP, Xiao J. Mortality associated with incident mental health disorders after stroke. Aust N Z J Psychiatry 2007; 41: 274-281 [PMID: 17464709 DOI: 10.1080/00048670601172772]

Gurin L, Blum S. Delusions and for the Right Hemisphere: A Review of the Right Hemisphere as a Mediator of Reality-Based Belief. J Neuropsychiatry Clin Neurosci 2017; 29: 225-235 [PMID: 28347214 DOI: 10.1176/jnp.16060118]

Devine MJ, Bentley P, Jones B, Hotton G, Greenwood RJ, Jenkins IH, Joyce EM, Malhotra PA. The role of the right inferior frontal gyrus in the pathogenesis of post-stroke psychosis. J Neurol 2014; 261: 600-603 [PMID: 24494063 DOI: 10.1007/s00415-014-7242-x]

Wong A, Cheng ST, Lo ES, Kwan PW, Law LS, Chan AY, Wong LK, Mok V. Validity and reliability of the neuropsychiatric inventory questionnaire version in patients with stroke or transient ischemic attack having cognitive impairment. J Geriatr Psychiatry Neurol 2014; 27: 247-252 [PMID: 24763069 DOI: 10.1177/0891988714532017]

van Almenkerk S, Depla MF, Smalbrugge M, Eefsting JA, Hertogh CM. Institutionalized stroke patients: status of functioning of an under researched population. J Am Med Dir Assoc 2012; 13: 634-639 [PMID: 22705032 DOI: 10.1016/j.jamda.2012.05.008]

Builjck BI, Zuidema SU, Spruit-van Eijk M, Geurts AC, Koopmans RT. Neuropsychiatric symptoms in geriatric patients admitted to skilled nursing facilities in nursing homes for rehabilitation after stroke: a longitudinal multicenter study. Int J Geriatr Psychiatry 2012; 27: 734-741 [PMID: 21932248 DOI: 10.1002/gps.2781]

Joyce EM. Organic psychosis: The pathobiology and treatment of delusions. CNS Neurol Ther 2018; 24: 598-603 [PMID: 29766655 DOI: 10.1111/cns.12973]

Pillingger T, McCutcheon RA, Vano L, Mizuno Y, Aramumah A, Hindley G, Beck K, Natesan S, Efthimiou O, Cipriani A, Howes OD. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. Lancet Psychiatry 2020; 7: 64-77 [PMID: 31804057 DOI: 10.1016/S2215-0366(19)30416-X]

Douglas JJ, Smeeth L. Exposure to antipsychotics and risk of stroke: self controlled case series study. BMJ 2008; 337: a1227 [PMID: 18755769 DOI: 10.1136/bmj.a1227]

Wang S, Linkletter C, Dore D, Mor V, Buka S, Maclure M. Age, antipsychotics, and the risk of ischemic stroke in the Veterans Health Administration. Stroke 2012; 43: 28-31 [PMID: 22033970 DOI: 10.1161/STROKEAHA.111.617911]

Zivkovic S, Koh CH, Kaza N, Jackson CA. Antipsychotic drug use and risk of stroke and myocardial
infarction: a systematic review and meta-analysis. *BMC Psychiatry* 2019; 19: 189 [PMID: 31221107 DOI: 10.1186/s12888-019-2177-5]

97 **Hsu WT**, Esmaily-Fard A, Lai CC, Zala D, Lee SH, Chang SS, Lee CC. Antipsychotics and the Risk of Cerebrovascular Accident: A Systematic Review and Meta-Analysis of Observational Studies. *J Am Med Dir Assoc* 2017; 18: 692-699 [PMID: 28431999 DOI: 10.1016/j.jamda.2017.02.020]

98 **Taylor LG**, Panucci G, Mosholder AD, Toh S, Huang TY. Antipsychotic Use and Stroke: A Retrospective Comparative Study in a Non-Elderly Population. *J Clin Psychiatry* 2019; 80 [PMID: 31163104 DOI: 10.4088/JCP.18m12636]

99 **Laws KR**, Conway W. Do adjunctive art therapies reduce symptomatology in schizophrenia? A meta-analysis. *World J Psychiatry* 2019; 9: 107-120 [PMID: 31911894 DOI: 10.5498/wjp.v9.i8.107]
