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Cerebrovascular Disorders (D Jamieson, Section Editor)

Treatment of Post-Stroke Depression

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Abstract

Purpose of review This review presents a critical appraisal of current therapeutic strategies for patients with post-stroke depression (PSD). We present the reader with the most recent evidence to support pharmacological, psychosocial, and neuromodulation interventions in PSD. We also discuss the relevance of using antidepressants and psychotherapy to prevent PSD and discuss evidence that antidepressant treatment may reduce mortality after stroke.
Recent findings Neuroinflammation and decrease neurogenesis and plasticity may play an important role in the mechanism of PSD. The strongest predictors of PSD are stroke severity, early physical disability, and severity of loss of functioning. Nevertheless, populations at risk for PSD are yet to be identified. Recent meta-analysis examined the efficacy of pharmacotherapy and psychotherapy. There is consensus that antidepressants such as escitalopram and paroxetine produce a significantly greater response and remission rate of PSD than placebo. Randomised controlled trials (RCTs) using psychotherapy are fewer, but recent meta-analysis tend to suggest efficacy for this treatment modality. Neuromodulation using repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS), as well as novel psychosocial interventions are potentially useful treatments in need of further research.
Summary Pharmacological therapy with antidepressants and psychotherapy should be considered as first line of treatment for PSD. The most effective antidepressants are the selective serotonin reuptake inhibitors escitalopram and paroxetine, whereas cognitive behavioural therapy is the most effective psychotherapeutic intervention.

Introduction

Stroke is the most frequent serious neurological condition worldwide and is the leading cause of long-term disability. Each year, there are 795,000 new or recurrent strokes in the USA with 142,000 stroke-related deaths [1, 2]. Stroke-related mortality has declined in the past 20–30 years, but this decline has led to an increased prevalence of stroke survivors. In the USA, estimated adult survivors were 1.5 million in 1973 and 7.0 million in 2019 [2]. There is a strong association between stroke and psychiatric disorders such as depression, anxiety, apathy, and fatigue [3].

Frequency of post-stroke depression (PSD)

The frequency of PSD has been examined in numerous studies of patients in acute settings, rehabilitation units, or living in the community. The first systematic review and meta-analysis conducted by Hacktett and co-workers in 2004 [4] showed a prevalence of PSD of 33% (95% CI, 26–36%). In 2014, the same group updated their work [5] and found the prevalence remained the same at 33% (95% CI, 26–39%).

Robinson and Jorge carried out a pooled analysis including RCTs published prior to 2003 [3], and included only those that used structured psychiatric interviews and standardised diagnostic criteria for major and minor depression. In community-based settings, the frequency of major and minor depression was 15% and 10%, respectively; in acute or rehabilitation settings, the frequencies were 22% and 20%, respectively, and at outpatient clinics, frequencies were 24% and 24%, respectively.

Ayerbe and co-workers [6] conducted a systematic review of studies published before August 2011 and reported a prevalence of PSD of 29% during the acute stroke period (95% CI, 25–32%). Another recent meta-analysis reported a prevalence of 18% for major depression, 13% for minor depression, and 3% for dysthymia [7].

Limitations for all the meta-analyses depend on important differences in the studies included, such as time since stroke, the method used to diagnose post-stroke depression (PSD) (e.g. use of standardised diagnostic criteria vs. cut-off scores on depression rating scales), the influence of depression before the stroke, exclusion of patients with severe strokes, aphasia or cognitive deficits, comorbidities such as anxiety, fatigue, and anosognosia, differences in lesion location, and inclusion of haemorrhagic strokes.

In conclusion, the prevalence of PSD is of no less than one third in acute settings and rehabilitation units. The prevalence of PSD among patients in the community is lower, perhaps related to less severe post-stroke impairments. There are no differences in the frequency of PSD between patients with either ischemic or hemorrhagic strokes [3].

Current treatments

Before discussing the efficacy of different therapeutic regimes, it is necessary to address the limitations of the studies to be reviewed. As discussed by Towfighi and co-workers [8], the number of RCTs that have examined the efficacy of

different therapies for the treatment of PSD remains few. Most of the RCTs that have been conducted are characterised by small sample size, short trial durations, variable diagnostic methods, and heterogeneous outcome measures [8]. This chapter will discuss recent findings in the management of depression related to ischemic or hemorrhagic strokes. Subarachnoid haemorrhage due to ruptured aneurysms will not be discussed given that this population is usually excluded from studies on PSD [3].

Pharmacological treatment

Given the large number of treatment studies for PSD, we shall discuss the results of structured reviews and meta-analyses, with reference to individual studies when necessary to illustrate important points.

The first meta-analysis on the treatment of PSD was carried out by Hackett and co-workers [9] and included 12 RCTs. They found benefits for antidepressants (mostly selective serotonin reuptake inhibitors (SSRIs) and tricyclics) for remission of PSD (OR = 0.47, 95% CI; 0.22–0.98) and benefits for response (defined as a reduction > 50% on depression rating scales) (OR 0.22, 95% CI, 0.09–0.52). The authors reported more frequent adverse events among subjects on active medication compared to patients on placebo in terms of neurological, gastrointestinal, and other less frequent side effects.

In one of the latest studies, Deng et al. [10] performed a network-meta-analysis to systematically assess and rank the efficacy and tolerability of antidepressants for PSD. The study included randomised controlled trials (RCTs) comparing 13 antidepressants published between 1984 and 2012. The authors found that paroxetine, imipramine, reboxetine, nortriptyline, and citalopram had significant efficacy over placebo, as manifested by a significant reduction on the Hamilton Depression Scale (HAM-D) scores. The authors considered paroxetine to have significant efficacy to treat PSD, with additional benefits on functional performance and quality of life (QoL) of patients. It is important to remark that antidepressant efficacy was similar for all the medications examined, with no significant differences between them. A single study [11] using duloxetine found higher efficacy during the first weeks of treatment compared to citalopram and sertraline, but whether reboxetine may result in early improvement of depression as compared to other antidepressants requires replication. Sexual dysfunction was identified as one of the main side effects of SSRIs. The authors also noted that their study could be biased in the selection of trials, the problem of small sample sizes in most trials, and the fact that to provide the meta-analysis with more consistency only selected studies using the HAM-D as the main outcome measure were selected.

Sun et al. [12] carried out a multiple-treatment meta-analysis on the efficacy and acceptability of antidepressant treatment in PSD. The authors pointed out the main limitations for the treatment of PSD, such as the high refusal of clinicians to recommend treatment with antidepressants to patients with PSD, given their belief that the efficacy of treatment is relatively minor compared to the risk of side effects [9].

This meta-analysis included 49 studies and 707 participants. The main finding was that all drugs included (especially reboxetine, paroxetine, doxepin, and duloxetine) showed a significantly higher efficacy than placebo. In terms of efficacy ranking, best results were obtained with reboxetine, followed by paroxetine, doxepin, duloxetine, trazodone, nortriptyline, and citalopram, whereas no significant differences against placebo were found for sertraline, nefiracetam, or fluoxetine. When acceptability was considered, reboxetine, paroxetine, and duloxetine had the highest therapeutic effectiveness, whereas trazodone, nortriptyline and citalopram were less effective. Given methodological shortcomings, such as small sample sizes, small number of studies for any given antidepressant, and methodological inconsistencies among studies, the authors cautioned that the ranking should be used as a reference only.

Cui et al. [13] carried out a meta-analysis including RTCs comparing citalopram with other SSRIs or selective norepinephrine reuptake inhibitors (SNRIs). The meta-analysis included 20 studies, and the main finding was that there was a similar efficacy for citalopram compared to other SSRIs or SNRIs. There were also no differences in the rate of the adverse events between citalopram and the comparison drugs. It is important to note that studies were selected based on (1) diagnosis of depression according to DSM-IV criteria or the Chinese Classification of Mental Disorders, (2) measuring the severity of depression using the HAM-D scale, and (3) the use of the Treatment Emergent Symptom Scale (Chinese) to evaluate adverse events. Efficacy was considered as a reduction of > 25% on the HAM-D. The study included nine trials, with an efficacy of 92.5% for citalopram and 89% for other SSRIs including sertraline, fluoxetine, and paroxetine. Remission of depression was calculated as a reduction on the Hamilton Depression Rating Scale (HDRS) > 75%. The remission rate for citalopram was 41%, and the same remission rate was found for the other SSRIs. Of note, all nine studies included in this meta-analysis were carried out in China. Four studies compared citalopram with the SNRI venlafaxine, and the remission rate was similar for both drugs (37% and 39%, respectively). There was a trend for citalopram to show a faster response compared to the other SSRIs and SNRIs, and there were no differences in the rate of adverse reactions between citalopram and the other antidepressants.

Robinson and Jorge [3] discussed the most relevant RCTs published before 2016. They agreed with Hackett et al. [9] that antidepressant medication has a beneficial effect in PSD. They also stressed the risks of using SSRIs, such as an increased risk of haemorrhagic complications, stroke, myocardial infarction, all-cause mortality, and falls [14].

Finally, the Guidelines for Healthcare Professionals from the American Heart and Stroke Associations (AHA/ASA) [8] recommend the use of antidepressants for PSD based on the Hackett et al. meta-analysis [9]. The authors stressed the need for further research to clarify the optimal timing and the most useful medications for the treatment of PSD.

In conclusion, and based on the above findings, treatment of PSD should be started with an SSRI (e.g. paroxetine or escitalopram) or SNRI (e.g. duloxetine or venlafaxine), and a tricyclic (e.g. nortriptyline) should be considered in case of lack of response to the first drug treatment. Before starting a tricyclic, contraindications and adverse effects of these drugs should be carefully considered. SSRI's but not tricyclic antidepressants are associated with a higher risk of

strokes in the elderly population [14]. These recommendations should also be considered tentative, given the methodological limitations of RCTs already discussed.

Psychotherapy

A meta-analysis by Hackett et al. [9] that included 12 studies using antidepressants and four studies assessing the efficacy of psychotherapy found a significant beneficial effect for antidepressants but not for psychotherapy. This meta-analysis was among the first to emphasise the relevance of psychoeducation, case management, and family support. These recommendations were recently structured as a specific type of therapy termed "ecosystem focused therapy" (EFT). Alexopoulos and co-workers [15] based the intervention on the "psychological storm" produced by acute disability, the sudden change in patient's needs, and its impact on family life (termed the "ecosystem"). The sudden functional deficits and the concomitant impact on motivation, fear of chronic emotional instability and death, and the demands of rehabilitation may result in hopelessness and helplessness ending in stress and depression. Based on these concepts, the authors designed EFT, to include five components: (1) a novel perspective about recovery and physical state, (2) helping the patient to follow a structured management plan, (3) providing a "problem solving structure" based on patients' values, (4) helping the family adapting to the patient's disabilities, and (5) coordinating the patient's care among the different specialists. The authors carried out a preliminary study on the efficacy of EFT as compared to a manualised intervention consisting of standard education on stroke and depression (ESD). Patients were randomly assigned to EFT or ESD and were provided with 12 weekly sessions. The study was single blinded, given that the same therapists provided EFT and ESD to the respective patients. They found that eight of the 12 patients (66%) in the EFT group achieved remission of depression compared to two of the 12 patients (17%) in the ESD group (OR = 10; 95% CI = 1.44–69.2). The efficacy of EFT needs to be properly assessed in RCTs, but could be a positive addition to other therapeutic modalities for PSD.

The "Living Well with Stroke" studies consisted of two psychosocial interventions. For the first study, patients were randomised to a brief psychosocial intervention (9 sessions of counselling) as compared to usual care [16]. The remission rate was 47% for the intervention arm as compared to 19% for the usual care group at 9 weeks, and 48% vs. 27% respectively at 1 year, both significantly favouring interventions. The second study consisted of six sessions that compared in person therapy vs. phone delivery of therapy vs. usual care. After six sessions, there was a 42% reduction on HDRS for the phone intervention, compared to 40% for the in person intervention and 30% for usual care, a difference that was not statistically significant. Future studies should examine the efficacy of Internet-delivered psychotherapy.

The Communication and Low Mood (CALM) trial [17] warrants special attention because it targeted aphasic patients. In this RCT, patients were allocated to receive 20 sessions of a specific behavioural therapy versus

usual care over a period of 3 months. The main outcome measure was the Stroke Aphasia Depression Questionnaire (SADQ). At 6 months, there was a 6-point decrease on the SADQ for the intervention group as compared to a 1.9-point decrease for the control group ($p < 0.01$).

One of the first meta-analyses on the efficacy of psychotherapy for PSD was carried out by Wang et al. [18], who selected 23 RCT. Nine studies compared the efficacy of cognitive behavioural therapy (CBT) versus routine rehabilitation treatment for PSD, while 14 trials used CBT in combination with antidepressants. It is important to note that 21 studies were carried out in China, whereas only two studies were carried out in Western countries. There was a significant benefit for CBT, with improvements not only in PSD, but also on anxiety, functional deficits, and neurological recovery. Nevertheless, as the authors pointed out, there was a high degree of heterogeneity and a low quality across the majority of the studies. Therefore, these findings should be only considered preliminary. The authors highlighted the fact that CBT should not be applied in a generic way but should be customised for PSD. Treatment duration and CBT sessions varied across studies, and none of the two studies conducted outside China showed improvements of CBT over placebo. The authors considered that sociocultural differences may account for the different outcome between the Chinese and the Western studies, as well as differences in the proportion of patients taking antidepressant medication. Given the methodological limitations and low quality of most RCTs, the authors concluded that the evidence for the benefit of CBT in PSD remains inconclusive.

Finally, Robinson and Jorge [3] suggested that brief psychosocial therapies focusing on care management, psycho-education, and family support may provide benefits to treat PSD when combined with antidepressant medication [16]. In our opinion, this remains the best therapeutic strategy.

Emerging therapies

Neuromodulation

Neuromodulation consists of stimulating brain regions using techniques such as repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS), which have demonstrated efficacy among patients with "primary" depression. An early study using rTMS in PSD suggested significant efficacy for this treatment among patients who do not respond to a trial with antidepressants [19••], a finding that led to subsequent RCTs.

A recent meta-analysis on the efficacy of rTMS [20] found this treatment to have positive effects on PSD. Nevertheless, there is still lack of clarity regarding optimal stimulation parameters, such as stimulation site, frequency, intensity, durations, and timing. Furthermore, most of the studies analysed are of low quality. Finally, this meta-analysis was only based on Chinese studies, and this literature is difficult to analyse in detail.

Another meta-analysis on neuromodulation by Bucur et al. [21] included seven studies (only three were RCTs) and a total of 157 patients with PSD. Once again, limitation was the heterogeneity of stimulation parameters, a criticism that is also valid for tDCS studies. While the authors found that stimulus intensity and duration were relatively homogeneous across

studies, there was considerable variation in the number of sessions, which ranged between 10 and 20. Outcome measures were the HAM-D in five studies, and the Montgomery-Asberg Depression Rating Scale (MADRS) and the Beck Depression Inventory (BDI) in the remaining studies. The authors made the important point that none of these scales were specifically designed for stroke patients.

All three RCTs showed significant improvements in depression with rTMS, irrespective of whether the same region (the left dorsolateral prefrontal cortex) was stimulated with an inhibitory or excitatory current. Three of the four tDCS studies were conducted in the same centre, and significant improvements were obtained at weeks 6 and 12. Nevertheless, all four studies had a non-randomised, experimental design with a low level of evidence. The authors also questioned the lack of ecological assessment and the possibility of publication bias toward positive findings. Moreover, important information such as lesion location, interval since stroke, and type of depression was not consistently included in the studies. Finally, differences in instruments used, cut-off points, and the exclusion of patients with severe strokes or language problems may also impact on the results of meta-analyses such as this one. The authors concluded that there is not enough data to support the efficacy of rTMS or tDCS in improving PSD, although both treatments may be considered safe with no major side effects when appropriate guidelines are followed.

Psychosocial interventions

Cheng et al. [22] designed and examined the efficacy of a comprehensive rehabilitation training program (CRT) which included both patients and family members. The CRT arm consisted of education, cognitive training and rehabilitation to treat PSD, anxiety, and cognitive impairment. The study used the Manual of Rehabilitation and Mental Health of Stroke for the education component, and an occupational therapist carried out the cognitive training component. Rehabilitation training consisted of one weekly session for 6 months, with a clinical assessment being conducted every 2 months. The "usual care" arm consisted of conventional physical training, prevention of complications, dietary instructions, and psychological nursing based on a Chinese Stroke Rehabilitation Therapy Guide. The main outcome measures were the Hospital Depression and Anxiety Scale (HADS) and the Zung Depression Scale (ZDS). Assessments were carried out at baseline, 3, 6, and 12 months later. The main finding was that CRT was associated with a significant decrease on depression and anxiety scores at all time points. The authors noted that while CRT is a "tailor-made" program consisting of goal setting and intervention, the study did not specify the method used to design the treating manual, how the intervention is adjusted to suit individual patients, or how the goal-setting process is conducted. The authors further stated that CRT may increase the awareness of patients and caregivers to potential complications allowing early intervention for psychiatric disorders, but this is not substantiated by the study.

Studies of other emerging non-pharmacological therapies such as ecosystem-focused therapy, life-review and problem-solving therapy, music

therapy, exercise, behavioural therapy, and robotic-assisted neuro-rehabilitation have reported positive results, but remain substandard in quality and in need of replication. Nevertheless, these therapies may be a good alternative for patients who reject or are unable to tolerate psychoactive medication.

Prevention of PSD

A number of studies have examined the efficacy of pharmacotherapy or psychotherapy to prevent PSD. The first RCT was carried out by Robinson and co-workers [23]. Acute stroke patients were randomised to treatment with escitalopram over 1 year, problem solving therapy, or placebo. The 1-year incidence of PSD for escitalopram was 8.5%, as compared to 11.9% for problem solving therapy and 22.4% for placebo. After controlling for age, gender, severity of stroke, and severity of impairment, the risk for developing PSD 1 year after stroke was four times higher for controls than for patients on escitalopram (adjusted HR = 4.5; 95% CI; 2.4–8.2), and two times higher for patients on problem-solving therapy (HR = 2.2; 95% CI; 1.4–3.5). While, a Cochrane review that included 12 RCTs [15] found no evidence that antidepressants prevent PSD; a later meta-analysis by Salter and co-workers [24] that included eight RCTs found that SSRIs significantly decreased the risk of developing PSD after 1 year of treatment (OR = 0.31; 95% CI; 0.18–0.56). There were no significant between-group defences on side effects. Based on this evidence, the AHA/ASA Scientific Statement [8] concluded that further studies are needed to determine the appropriate timing and duration of treatment.

The efficacy of psychosocial interventions to prevent PSD was assessed in a 2008 Cochrane review [9], which reported a small but significant effect for psychosocial interventions such as problem-solving therapy and motivational interviewing (OR = 0.64; 95% CI, 0.42–0.98) for preventing PSD.

Impact of antidepressants on post-stroke mortality

The first study to examine the mortality among patients with PSD and use of antidepressants was carried out by Robinson and co-workers [25•]. In a 9-year follow-up study of stroke, patients with or without depression who received treatment with either nortriptyline (100 mg/day) or fluoxetine (100 mg/day) for 12 weeks, patients receiving pharmacological treatment showed an increased probability of survival at the 9-year follow-up as compared to the placebo group. Moreover, this finding was independent of whether depression responded to treatment or whether the patient had depression prior to treatment.

Another relevant study conducted by Robinson and co-workers, included a pharmacological arm, a problem-solving therapy (PST) arm, and a placebo arm [26]. This study was a continuation of a RCT that demonstrated the efficacy of escitalopram for the treatment of PSD, but also showed a significant relapse to major depression in the 6 months after ceasing escitalopram [27]. The main finding was that after a mean follow-up of 8 years after stroke, the group that received PST had a significant delay in mortality as compared to the escitalopram and placebo groups. This was the first study to show that a psychological treatment had a significant impact in reducing post-stroke

mortality after controlling for important demographic and clinical factor, while escitalopram was not superior to placebo on delaying mortality.

Conclusion

Evidence from RCTs and meta-analyses suggests that PSD may respond to pharmacotherapy. The most recommended antidepressants are paroxetine and escitalopram, although there are no significant differences in effectiveness between these compounds and other SSRIs, SNRIs, or tricyclics. Tricyclics may be considered as second-line therapy given their contraindications and anticholinergic side effects. Psychotherapy, primarily CBT has also demonstrated effectiveness in the treatment of PSD, and may be adequate for patients who do not respond to antidepressants, experience intolerable side effects to antidepressants, or do not wish to take medication. Novel neuromodulation techniques such as rTMS or tDCS are promising alternatives for patients who are refractory to medical treatment, but have yet to demonstrate consistent efficacy. This is also the case for recently designed "ecological," psychosocial interventions, which aim to be both comprehensive and adaptive to the specific needs of each patient.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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