Post-Stroke Depression Therapy: Where are we Now?

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Post-stroke Depression Therapy: Where are we now?

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Abstract: Post-stroke depression is an important psychological consequence of ischemic stroke, and affects around one third of stroke patients at any time post-stroke. It has a negative impact on patient morbidity and mortality, and as such development of effective post-stroke recognition and treatment strategies are very important. There are several therapeutic strategies for post-stroke depression, including both pharmacological and non-pharmacological approaches. In this review, we present evidence regarding the underlying biology of post-stroke depression, commonalities between post-stroke depression and Major Depressive Disorder and explore several treatment approaches, including antidepressant therapy, psychotherapy, surgical therapy, electroconvulsive therapy, acupuncture, music therapy and natural products. Further experimental and clinical studies are required, particularly in emerging fields such as the role of nutraceuticals in the treatment of stroke

Keywords: Acupuncture, antidepressant, nutraceutical, post-stroke depression, psychotherapy, stroke.

INTRODUCTION

Stroke (or cerebrovascular accident), a cardiovascular disorder, is the fourth most common cause of death in the United States, and is a leading cause of serious long term disability [1]. Established risk factors for stroke include; high blood pressure, race, high plasma cholesterol, aging, diabetes, genetic tendency of stroke, atrial fibrillation and smoking [2]. Rates of ischemic stroke increase markedly with increasing age [2], and about 75% of stroke patients are older than 65 years [3]. This is especially relevant to the development of psychiatric symptoms as both ischemic stroke and ageing both lead to increased oxidative stress, a factor central to the pathophysiology of many psychiatric disorders.

Stroke is generally classified into two main groups: hemorrhagic stroke and ischemic stroke [4]. It has been reported that more than 87% of strokes are acute ischemic stroke, caused by an interruption of the blood supply to the brain by a blood clot forming around atherosclerotic plaques (thrombotic stroke), arterial embolus (embolic stroke) or systemic hypoperfusion [1]. Neurons are highly sensitive to ischemia (due to their high oxygen requirement), which induces a series of reactions that may lead to cell death [5]. Following ischemic stroke neurons of certain brain regions may be more vulnerable and susceptible to post-ischemia cell death, specifically CA1 pyramidal neurons [6]. Yasuno *et al.* [7] also reported that stroke induced axonal damages in the bilateral anterior limbs of the internal capsule may disrupt neuroanatomical pathways of frontal-subcortical neuronal circuits.

Several pathological processes have been identified at a molecular level, including alterations in energy-dependent-processes (such as apoptosis), release of the excitatory neurotransmitter glutamate, lose of ion homeostasis in the cells, influx of calcium into the cells, leukocytes infiltration, glial cells activation, arachidonic acid production, blood-brain barrier disruption, excitotoxicity, increase acidity in the cell, and cytotoxicity induced by cytokines [8-10]. These pathological processes lead to cell death [9]. Ischemic stroke also generates reactive oxygen and nitrogen species and consequently induces oxidative stress [11].

POST-STROKE DEPRESSION

There are several neuropsychiatric complications which may occur after stroke, including depression, anxiety, dementia, apathy, psychosis and fatigue (Fig. **1**) [12]. Post-stroke depression is the most frequent neuropsychiatric consequence of stroke, occurring in one-third of stroke

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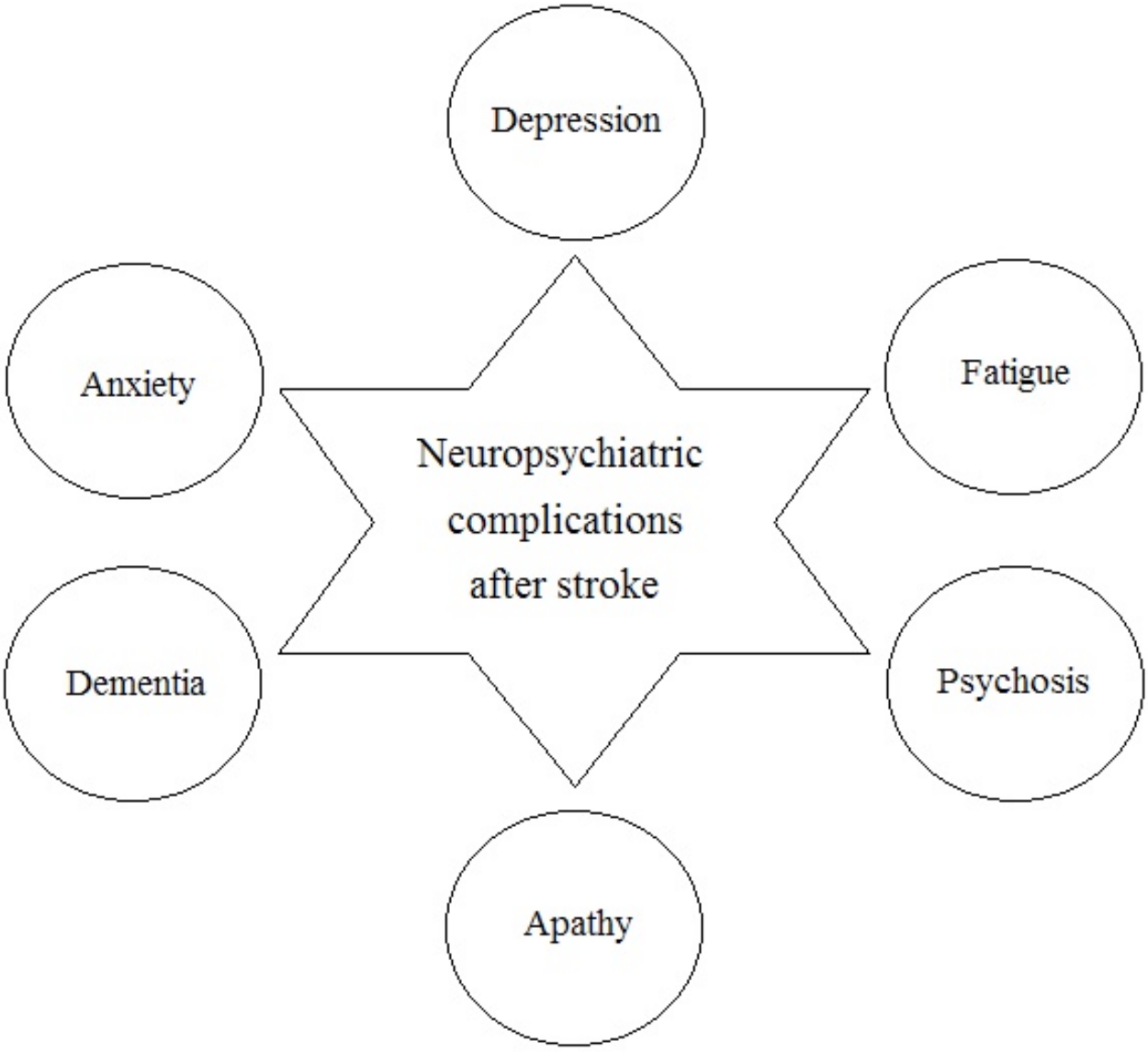

Fig. (1). Most common neuropsychiatric complications that occur following stroke.

survivors [13]. It has detrimental effects on cognitive function, social activity, and stroke rehabilitation [15] and is associated with increased mortality [15].

The major symptoms of early post-stroke depression (within the first 3 months post-stroke) [16] are melancholia and dysphoria, and vegetative signs [17]. Some studies suggest that vegetative signs, such as disturbances of sleep, and reduced libido and energy levels, are more common than dysphoria in post-stroke depression patients, particularly in those who suffer from right hemisphere injury [18].

A meta- analysis by Hackett et al [13] suggests the risk of depression following stroke is similar across the early, medium and late periods post-stroke [19]. Long-term studies have demonstrated that stroke patients are at higher risk of depression than community samples even years after the event [20]. Post-stroke depressive symptoms have been diagnosed in 18-30% of stroke patients even at 3 to 5 years after stroke event [21]. As in the general population, post-stroke depression appears to be more common in women than men [22, 23]. Lökk and Delbari [24] found in an elderly stroke population, the prevalence of depression in men was 42.9% and for women it was 64.1%.

Post-stroke depression is associated with greater levels of physical disability and cognitive impairment, and stroke severity [25]. It has also been reported that being in a nursing home or intermediate care facility significantly increases the incidence of post stroke depression [26]. A meta-analysis by Tenev *et al.* [27] demonstrated that a family history of psychiatric disorders was associated with an increased risk of depression in stroke patients. However, when compared to elderly patients with depression but without evidence of vascular diseases the contribution of family history to risk of depression is reduced [28]. Additional research is required to determine the relationship between stroke, specific psychiatric disorders and exploration of predictors of post-stroke depression to enable identification of those patients who may be at risk.

The focus of the present review is to provide an overview of current treatments in the context of recent evidence regarding available therapeutic procedures for treatment of

post-stroke depression, including pharmacological and non-pharmacological approaches treatment options and advances regarding proposed mechanisms of post-stroke depression.

BIOLOGICAL UNDERPINNING OF POST-STROKE DEPRESSION

There is an abundance of evidence demonstrating relationships between brain oxidant-antioxidant balance systems and post-stroke depression severity [29, 30]. Disruptions in the balance of antioxidants are also a feature of non-organic-related depression [31]. Additionally, the induction of inflammatory factors following stroke events may be similar to those seen in psychiatric patients with Major Depressive Disorder (MDD). Taken together the commonalities between post-stroke events and the pathophysiology of MDD may assist in explaining the development of depression following a stroke-event. However, given that not all individuals who experience an ischemic stroke event develop depression, further research is required to elucidate these differences. It may be postulated that higher levels of oxidative stress or inflammation may incur higher risks of developing post-stroke depression. The following sections will explore similarities between stroke and MDD to provide further evidence of these links and explain the factors that may lead to post-stroke depression. There is a plethora of reports which show that ischemic stroke causes alterations in the level of neurotransmitters and neurotransmitter receptors, including the accumulation of dopamine, noradrenaline, serotonin, as well as excitatory amino acids and g-amino-butyric acid (GABA) in the extracellular matrix [32-34]. It is believed that the neurotransmitter system and their receptors play crucial role in experience-dependent and restoration plasticity which is important for stroke rehabilitation. There is a close correlation between increasing the levels of biogenic amines in the brain, improving the neurotransmitter system, and rehabilitation of stroke-induced motor and verbal impairment [35]. Further, Spalletta *et al.* [36] argued that depletions of neurotransmitters and abnormalities in the cytokine expression, induced by an ischemic attack, are two main molecular mechanisms of post-stroke depression. Given that both serotonin and inflammatory cytokines are considered key to the pathology of MDD, it is not surprising that post-stoke depression is common. When compared with non-depressed stroke patients, post-stroke patients with depression have significantly lower cerebrospinal fluid concentrations of 5-hydroxyindoleacetic acid, the main metabolite of serotonin [37]. Fang and Cheng [37] reported that there is a close correlation between serotonin transporter gene-linked promoter region short variant genotype and post-stroke depression. Moller *et al.* [38] also reported that in the early phase of ischemic stroke, a change in serotonin neurotransmission occurs, suggesting that serotonin reuptake inhibitors can be used for treatment of post-stroke depression and provide further evidence for similarities between post-stroke depression and MDD.

In addition, some of the pro-inflammatory cytokines such as interleukin-1, tumor necrosis factor alpha, interleukin-6, interleukin-8 and interleukin-18 appear to have an important role in etiology of post-stroke depression [36, 39]. Cytokine activation causes depressive-like behaviors *via* increases in hypothalamus-pituitary-adrenal axis activity and changes to biogenic amine neurotransmission in different hypothalamic nuclei and also in limbic structures [36, 39]. Furthermore, certain cytokines decrease production of 5-hydroxytryptamine through up-regulation of indoleamine 2, 3-dioxygenase (Fig. **2**) [40]. In fact, in the ischemic lesion, abnormalities in the biogenic amine-containing axons cause decreases in serotonin and norepinephrine generation in the limbic systems of the temporal and frontal lobes and basal ganglia [41]. Starkstein and Robinson [42] also reported that decreases in biogenic amines such as serotonin have an important role in the pathogenesis of post-stroke depression.

Brain derived neurotrophic factor (BDNF) is also believed to significantly contribute to the pathophysiology of MDD. Altered neurogenesis is believed to be key to MDD and similar changes in BDNF levels have been reported in post-stroke depression [43]. According to their study findings, decreases in the levels of BDNF may be considered as a predictive biomarker for the development post-stroke depression [43]. Zhou *et al.* [44] have found decreased BDNF levels in post stroke depression patients (3-6 months after stroke). It has been proposed that a regulator and/or inhibitor of DNA promoter methylation could be used to improve the efficacy of antidepressant therapy [43].

THERAPEUTIC APPROACHES TO POST-STROKE DEPRESSION

Several strategies have been evaluated as potential treatments of post-stroke depression, including antidepressant therapy, psychotherapy, surgical therapy, electroconvulsive therapy, acupuncture, music therapy and natural products (Fig. **3**).

Antidepressants

Numerous clinical studies support the use of antidepressant treatment for post-stroke depression. A meta-analysis demonstrated an overall benefit of pharmacotherapy for post-stroke depression, with regard to both depression remission and symptom reduction (Table **1**) [45]. Antidepressant treatments explored in stroke patients include citalopram [46], escitalopram [47], nortriptyline [48], milnacipran [49], mirtazapine [50], methylphenidate [51], maprotiline [52], venlafaxine [53], mianserin, desipramine, imipramine [54], indeloxazine [55], piracetam [56], and fluoxetine [57]. Trazodone was found to be more effective than placebo, and reboxetine superior to citalopram in the reduction of depressive symptoms [58]. Narushima and Robinson [59] reported that nortriptyline and/or fluoxetine treatment was associated with improved activities of daily living (ADL) in patients who suffer from post-stroke depression. A mortality study by Jorge *et al.* [60] found that 12 weeks of treatment, with nortriptyline or fluoxetine, during the first six months following a stroke decreased mortality (at 9-year follow-up) in both depressed and non-depressed patients. Rasmussen *et al.* [61] showed that one year treatment with sertraline has superior preventive role

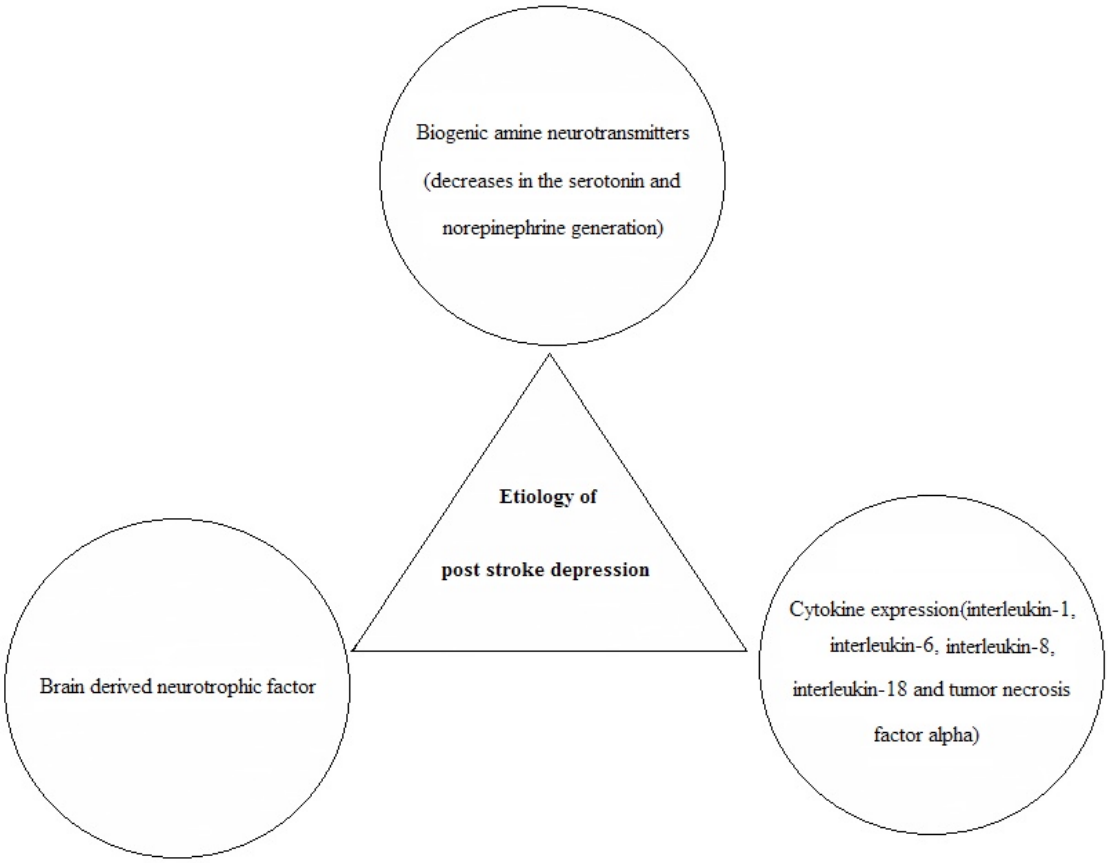

Fig. (2). Etiopathogenesis of post-stroke depression shows pivotal role of cytokines, TNF-α, BDNF and biogenic amines.

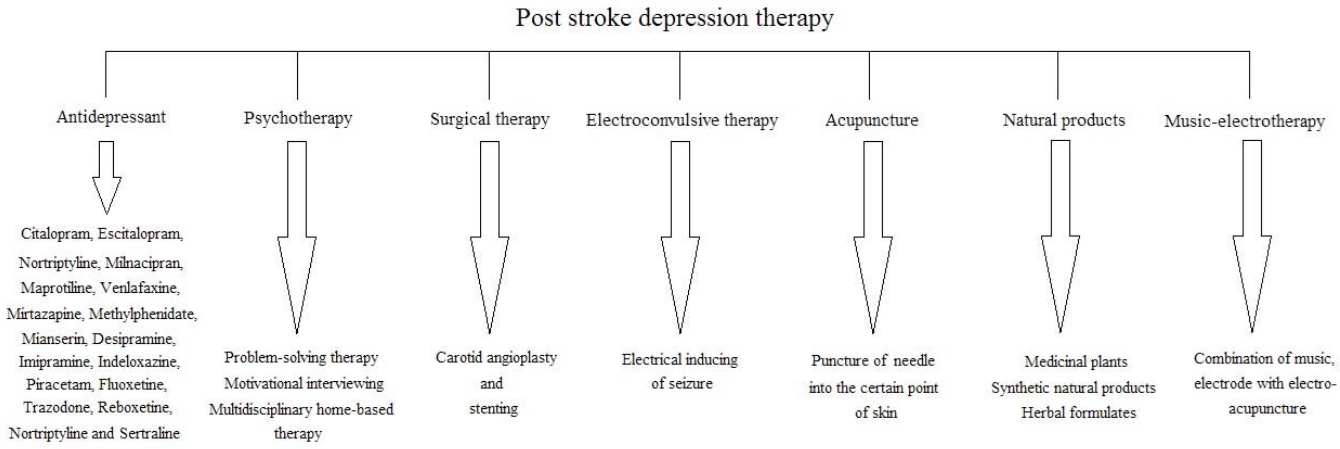

Fig. (3). Strategies for treatment of post-stroke depression including antidepressant, psychotherapy, surgery based therapy, electroconvulsive therapy, acupuncture, natural product andmusic electrotherapy.

Table 1. Summary of the numbers of studies on available antidepressants therapies for post stroke depression, table includes study characteristics, and overall results.

Study	Drug	Drug Dose	Treatment Period	Population Entered the Trial	Methods	Follow-up	Outcomes
Lauritzen *et al.*, [54]	Imipramine and mianserin	imipramine (75 mg daily), mianserin (25 mg daily)	6 weeks	10 patients	Controlled clinical study	2 weeks after treatment	Efficacy approach on the Melancholia scale at the end of treatment was 81%

Table 1. contd…

Study	Drug	Drug Dose	Treatment Period	Population Entered the Trial	Methods	Follow-up	Outcomes
	Desipramine and mianserin	desipramine (66 mg daily), mianserin (27 mg daily)	6 weeks	10 patients	Controlled clinical study	2 weeks after treatment	Efficacy approach on the Melancholia scale at the end of treatment was 12.6 %
Andersen et al., [46]	Citalopram	10 to 40 mg/d	6 weeks	28 patients	double-blind, placebo-controlled trial	52 weeks after stroke	Selective serotonin reuptake inhibitor citalopram is both safe and effective
Robinson *et al.*, [47]	Escitalopram	10 mg/d for patients <65 years and 5 mg/d for patients ≥65years	12 months	176 patients	Randomized Controlled Trial	12 months	Escitalopram significantly decrease incidence of depression over 12 months in comparison with placebo group
Narushima *et al.*, [63]	Nortriptyline	25 mg/day (first week), 50 mg/ day (weeks 2 and 3), 75 mg/day (weeks 4–6) and 100 mg/day for (final 6 weeks)	12 weeks	47 patients (11 patients Nortriptyline; 19 patients Fluoxetine; 17 patients placebo)	double-blind placebo-controlled trial	21 months after treatment	Antidepressant therapy associated with long-term improvement of executive function
	Fluoxetine	10 mg/day (first 3 weeks), 20 mg/day (weeks 4–6), 30 mg/day (weeks 7–9) and 40 mg/day (final 3 weeks)	12 weeks	47 patients (11 patients Nortriptyline; 19 patients Fluoxetine; 17 patients placebo)	double-blind placebo-controlled trial	21 months after treatment	
Lipsey *et al.* [48]	nortriptyline	20 mg /day (first week), 50 mg /day (weeks 2-3), 70 mg /day (week 4), 100 mg /day (weeks 5-6).	6 weeks	39 patients	double-blind, placebo-controlled trial	6 weeks	Nortriptyline decrease Hamilton depression scores, Zung depression scores, present state exam scores, and overall depression scores in comparison with placebo
		50 mg /day (first week), 70 mg /day (weeks 2-3), 100 mg /day (weeks 4).	4 weeks			4 weeks	
Kimura *et al.* [49]	milnacipran	30-75 mg b.i.d	6 weeks	12 patients	Randomized Controlled Trial	6 weeks	Near 58.3% (7/12) completing the study were in remission
Grade *et al.* [51]	Methylphenidate	started at 5mg /day and increased gradually to 30mg /day	3 weeks	21 patients	Double-blind, placebo-controlled study.	4 weeks	Methylphenidate was safe and effective in early poststroke rehabilitation in comparison with placebo geoup.

Table 1. contd…

Study	Drug	Drug Dose	Treatment Period	Population Entered the Trial	Methods	Follow-up	Outcomes
Dam *et al.*, [52]	Maprotiline	150 mg/d	3 months	52 patients (17 patients placebo, 17 patients Maprotiline, and 18 patient sFluoxetine)	Double-blind, placebo-controlled study.	3 months	Fluoxetine facilitated or, maprotiline may hinder recovery in undergoing rehabilitation of post stroke patient
	Fluoxetine	20 mg/d	3 months	52 patients (17 patients placebo, 17 patients Maprotiline, and 18 patients Fluoxetine)	Double-blind, placebo-controlled study.	3 months	
Fruehwald *et al.*, [57]	Fluoxetine	20 mg/d	3 months	54 patients	Double-blind, randomized placebo-controlled study	18 months	The beneficial actions of fluoxetine were obvious at the 18 months follow-up. They concluded fluoxetine was effective and safe strategy.
Jorge *et al.*, [60]	Nortriptyline	25 mg/day (first week), 50 mg/day (weeks 2 and 3), 75 mg/day (weeks 3–6), and 100 mg/day (final 6 weeks)	12 weeks	104 patients (40 patients receiving fluoxetine, 31 patients receiving nortriptyline, and 33 patients receiving placebo)	Placebo-controlled trial	9 years	Treatment with fluoxetine or nortriptyline cause significant increases in the survival of both depressed and non-depressed patients
	Fluoxetine	10 mg/day (first 3 weeks), 20 mg/day (weeks 4–6), 30 mg/day (weeks 7–9), and 40 mg/day (final 3 weeks)	12 weeks	104 patients (40 patients receiving fluoxetine, 31 patients receiving nortriptyline, and 33 patients receiving placebo)	Placebo-controlled trial	9 years	

against post-stroke depression in comparison with placebo group, however a meta-analysis found no clear effect for pharmacotherapy in the prevention of post-stroke depression [62].

In addition to treatment of depression, antidepressant therapy may also act to improve brain executive function following stroke. This is thought to occur two ways; via modulation of cortico-striato-pallido-thalamo-cortical pathways and also via changes to brain-derived neurotrophic factor (BDNF) and reorganization of neural circuitry [63]. The monoaminergic nuclei activities (raphe nuclei, the locus ceruleus and the ventral tegmental area) are desirable sites for antidepressants treatment, by modulating orbital frontal, dorsolateral prefrontal and anterior cingulated pathways which are involved in both executive [63, 64] and affective functions [63, 65]. Another therapeutic mechanism of antidepressant administration is neurogenesis which is restricted to germinal centers in the subventricular zone and the hippocampal/dentate gyrus in adult brain [66]. Long-term antidepressant treatment may improve the development of immature neurons, promote adult neuronal functioning and induce mood recovery and behavioral effects through enhancing of the secretion BDNF and its receptor TrkB [67]. BDNF and other neurotrophins appear to regulate neurite outgrowth, synaptic plasticity and organize connection in the CNS [68-69]. Long-term treatment with antidepressants may also inhibit stress-induced decreases of BDNF [70]. Therefore BDNF- dependent signaling pathways play an important role in antidepressant-induced brain recovery [63]. Antidepressants (specifically SSRIs) have also been shown to have properties that reduce oxidative stress [31] and decrease serum level of inflammatory cytokines [71]. However, the routine use of antidepressants in stroke patients is not generally accepted due to little evidence on their effectiveness in the prevention of PSD [62, 71] and the increased risk of adverse events [45].

Psychotherapy

There are a number of studies that have examined the effectiveness of psychotherapy for both the treatment and prevention of post-stroke depression. In a 2008 Cochrane review evaluating the efficacy of psychotherapy for the treatment of depression [45], four RCT's with 445 patients were included. Psychotherapy interventions included cognitive behavioral therapy [73], a social work intervention utilizing problem solving, advice on services and counseling [74], motivational interviewing [75] and a supportive intervention including education [76]. No treatment effects were found on any of the outcomes measured, however there were methodological limitations in the included studies. Since that review, at least one RCT has been published with promising results. For stroke survivors with aphasia, behavior therapy (9 one hour sessions delivered by a supervised psychologist and focusing on education, activity monitoring and scheduling and graded task assignments; n=51) was found to be superior to usual care alone (n=54) with regard to improvements in observer rated mood, with improvements maintained at 6 months [77].

Further, promising results have been found with regard to the use of psychotherapy in the prevention of post stroke depression, with six published RCTs to date evaluating home based therapy [78, 79], motivational interviewing [75] and problem solving therapy [47, 80, 81]. A 2008 Cochrane review [62] included four RCTs with 902 patients and found a small significant effect for psychotherapy in the prevention of post stroke depression.

Two randomized, controlled trials have evaluated home-based care of those who had experienced a stroke. Goldberg et al. [78] examined the effects of a system of home-based, case-managed care in older (aged 65 and above) stroke survivors returning to the community after inpatient rehabilitation with the assistance of a primary caregiver. Stroke patients with serious residual cognitive or language abnormalities were excluded. Improvements were seen in the intervention group with regard to daily living and social activities at the 6-month follow-up. Another study by Burton and Gibbon [79] examined the effect of a specialist nurse outreach education and support program for stroke patients and their carers following discharge from hospital. They randomized 87 patients to receive the intervention, and 89 patients to receive usual care. While change in severity of depressive symptoms was not significantly different between groups over time, the intervention was associated with improvements at the 12-month follow-up in perceived general health, emotional reactivity and social isolation in stroke survivors as well as reduced carer strain. Watkins et al [82] evaluated motivational interviewing by randomizing 411 stroke patients, 5 to 28 days post-stroke, to receive either ≤4 sessions of motivational interviewing or usual care. At 3 and 12 month follow-up, a benefit of motivational interviewing over usual care was found for mood, while at 12 months a benefit was also found for mortality.

Several randomized controlled trials have been conducted evaluating the effectiveness of problem-solving therapy in preventing post-stroke depression. Forster and Young [80] found that stroke survivors randomized to a specialist nurse delivered intervention did not demonstrate lower rates of depression over 12 month follow-up than those randomized to usual care. However, those with more mild post-stroke disability in the intervention group demonstrated small improvements social activity levels. In a more recent study comparing escitalopram, problem solving therapy and placebo, both escitalopram and problem solving therapy were found to be superior to placebo in the prevention of post-stroke depression, although problem solving therapy was not superior to placebo in intention to treat analysis [47].

In a novel animal model studying the impact of social networks, Verma et al. [83] studied possible effect of pair housing on rehabilitation and neuronal damages in mice suffering from post-stroke depression. They found that pair housing significantly improved sociability, up-regulated peri-infarct microglia arginase-1 expression level, decreased IL-6 level and reversed post stroke depressive behaviors such as anhedonia and avolition. They concluded that pair housing activation of M2 microglia/macrophages plays pivotal role in recovery of post stroke depressive behavior [83].

Overall, psychological therapies show promise with regard to both prevention and treatment of post-stroke depression, and has been established as an effective treatment option in the general community and other clinical (e.g. post-myocardial infarction) populations. However, to date, the literature regarding efficacy of psychological therapy for post-stroke depression is limited and further well designed studies are required.

Surgical Therapy

Carotid endarterectomy is an accepted surgical protocol for treating the symptomatic carotid artery stenosis that is found in >70% of stroke patients [84]. Endovascular protocols include angioplasty and stent placement [85]. During the past two decades, carotid angioplasty and stenting have become an alternative protocol to carotid endarterectomy for prevention of stroke [86]. A controlled study on 182 ischemic stroke patients with high grade stenosis demonstrated that carotid angioplasty stent was associated with significantly lower depression scores and severity of neurologic abnormalities one month post-baseline than antidepressant treatment [86]. Huang et al. [87] reported that depression and neurological abnormality were more significantly improved at one month in the patients who received carotid angioplasty stenting than in the patients who were treated with selective SSRIs; however this effect was not maintained at 3 months.

Electroconvulsive Therapy

Electroconvulsive therapy (ECT) is commonly used for treatment-resistant MDD, and involves the electrical induction of seizures in patients [88]. It has been reported that ECT in depressed patients is associated with neurobiological mechanisms including inhibition of neurotransmitter systems as well as monoamine neurotransmitters, endocrinological pathways and neurogenesis [89]. However, the exact mechanism of ECT remains unclear. The American Psychiatric Association's Task Force Report stated that ECT can be used for post-stroke depression therapy [90]. At least five case reports of ECT for post-stroke depression have

been published, with three demonstrating positive results. De Quardo and Tandon [91] described a male with a right parietotemporal stroke complicated by major depression. Unilateral, non-dominant ECT produced therapeutically adequate seizure and excellent clinical response with no neurological or neuropsychological deficits reported. Weintraub and Lippmann [92] reported that ECT, 7 to 14 days after stroke, completely treated the depression in a case of post-stroke depression. They concluded that uncomplicated use of ECT (without combining with antidepressants) is a safe and effective protocol for treatment of post-stroke depression. In 2012, Harmandayan et al. [93] reported that ECT therapy in a 30-year-old woman with a post-stroke depression and suicidality, and antiphospholipid syndrome, lead to reduced depression and hopelessness and improved mood and mental health outcomes.

Two cohort studies have also been published in this area. Murray et al. [94] described 14 patients in which ECT was performed on stroke patients with depression, demonstrating both safety and efficacy for the procedure. In this cohort, depression developed during the first year after stroke in 9 patients and after the first year in 5 patients. They reported that ECT significantly improved depression in 13 patients. They reported that transitory cardiac arrhythmia developed in one patient; however none of the patients had a development and/or exacerbation of stroke or other neurological abnormalities [94].

Currier et al. [95] reported that ECT mitigated depression in 19 out of 20 elderly stroke patients. Among the 19 patients, 7 patients suffered from relapses, 5 patients suffered from ECT-related medical complications and 3 patients suffered from transient interictal confusion or amnesia, however there were no reports of exacerbations of neurologic deficits [95]. They concluded that ECT is an effective method for treatment depression in stroke patients.

Although case and cohort studies support ECT as an effective method for post-stroke depression, there are some reports of adverse effects. The most common systemic adverse effects of ECT are confusion, headache and nausea [96]. In addition, mania, cognitive dysfunctions, prolonged seizures, prolonged apnea and cardiovascular complications such as hypertension and arrhythmia have been reported [97].

Acupuncture

Acupuncture, a Chinese medicine, involves the use of fine needles to puncture into the certain points of skin [98]. Acupuncture is based on balancing of energy flow (Qi) in the meridians channels [99]. There are numerous clinical studies around the use of acupuncture in treatment of post-stroke depression. Two meta-analyses have found that acupuncture is a safe and effective treatment for post-stroke depression [100, 101] and may positively impact on additional rehabilitation and neurological outcomes which also play important role in reduction of depressive symptoms, such as post-stroke limb disabilities, dysphagia, aphasia, and inability in the control of urination and defecation [101].

In 2010, Wu [102] randomized 300 patients with post-stroke depression to be treated with either fluoxetine or post-stroke daily acupuncture into the Sishencong (EX-HN 1), Baihui (GV 20), Shenting (GV 24), for 2 months. The acupuncture group demonstrated significantly greater improvements in depression symptoms than the fluoxetine group post-treatment. Similarly post-stroke, He and Shen [103] found twice-daily needle puncture into the Neiguan (PC 6), Renzhong (GV 26), Baihui (GV 20), Yintang (EX-HN 3) and Sanyinjiao (SP 6, the affected side) for one month was superior to amitriptyline (a tricyclic antidepressant) in improving depressive symptoms in post-stroke depression patients. Two different studies have shown benefits of acupuncture compared to fluoxetine. First in 2010, Wang et al. [104] showed that scalp acupuncture plus body acupuncture has antidepressant actions in post-stroke patients similar to fluoxetine, but appears to improve symptoms more quickly than the standard antidepressant trial. Li *et al.* [105] performed a randomized, double-blind control study on 43 post-stroke depression patients. They showed that 6 week needle puncture into the Baihui (GV 20), Yintang (EX-HN 3), Sishencong (EX-HN 1), Taichong (LR 3), has antidepressant action similar to fluoxetine without any side effects, but acupuncture is faster than antidepressant therapy. In addition, Liu et al. [106] reported that acup-moxibustion at Sishencong (EX-HN 1), Anmian, Neiguan (PC 6), Shenmen (HT 7), Zusanli (ST 36), Sanyinjiao (SP 6), Taichong (LR 3), Zhaohai (KI 6), Shenmai (BL 62) showed antidepressant action in post-stroke depression patient similar to sertraline. In 2007, Dong *et al.* [107] performed a clinical study on 108 cases of post-stroke depression to examine the therapeutic effect of point-through-point electroacupuncture in patients with post-stroke depression in comparison with non point-through-point group and a Western medicine group. They concluded that point-through-point electroacupuncture is more effective in increasing of plasma 5-hydroxytryptamine and, consequently decreasing of depressive symptoms in post-stroke depression patients. However, more clinical studies are needed to determine the exact mechanism of acupuncture therapy in patients with post-stroke depression.

Music Therapy

Previous studies demonstrate that music has beneficial effects on different psychological disorders such as depression and anxiety [108]. In physiotherapy and speech therapy for stroke rehabilitation, music has been used for modifying of motor activity and speech ability [109]. Furthermore, useful effects of nonverbal auditory stimuli on left visual neglect have been reported in stroke patients [109, 110]. Studies of the long-term effects of daily music therapy on the rehabilitation, psychological disturbances, and cognitive impairment of stroke are limited.

Two randomized controlled trials have demonstrated positive effects of daily music listening therapy in rehabilitation of stroke patients. Regularly listening to music during stroke recovery was found to results in a greater improvement in mood, than listening to audiobooks, or receiving no listening material [109]. The music listening group also demonstrated greater recovery in cognitive functions, including verbal memory and focused attention, and less confusion. The investigators concluded that music listening at early stage of stroke is an effective protocol for decreasing the depression and increasing the rehabilitation

[109]. Another randomized controlled trial reported by Kim et al. [111] examined the positive roles of music therapy on improvement of depressive mood and anxiety in stroke patients and also evaluated satisfaction of both patients and their caregivers. Kim et al. [111] reported that depression and anxiety symptoms decreased following music therapy and suggested music therapy can be used as effective therapeutic procedure to improve daily living functions and/or increase motivation for rehabilitation. However further randomized controlled trials are needed to determine the impact of both passive (e.g. music listening) and interactive (e.g. singing) music therapy approaches on mood as well as other rehabilitation outcomes.

Nutraceuticals

There are some preclinical studies indicating the potential efficacy of natural products and medicinal plants with antidepressant action in treatment of post-stroke depression Liu *et al.* [112] reported that daily treatment with the flavones fraction of *Abelmoschus manihot* L. Medic for 24 days significantly reduces immobility time in the forced swim test (a standard screen for antidepressant efficacy) in mice, induced by middle cerebral artery occlusion. Liu et al. [112] demonstrated that the protective effect of *Abelmoschus manihot* L. Medic is result of decreasing lipid peroxidation (malondialdehyde levels), and increasing the activity of antioxidant enzymes (superoxide dismutase and glutathione peroxidase). Liu *et al.* [112] also demonstrated that *Abelmoschus manihot* L. Medic up-regulates of BDNF expression at both the mRNA and protein levels, as well as cAMP response element-binding protein mRNA levels in the hippocampus. Lan *et al.* [113] and Yan *et al.* [114] reported that *Radix puerariae* extract (from the root of the *Pueraria lobata*) increases sucrose preference (on the sucrose preference test, a test of anhedonic behavior) following a combined ischemia insult and induction of depressive-like behavior (through chronic mild stress). According to the results of Lan *et al.* [113] study, *Radix puerariae* administration ameliorates depression *via* improving the mRNA expression of hippocampus tyrosine hydroxylase. Yan *et al.* [114] showed that administration of *Radix puerariae* reduces depressive-like behaviors in animals exposed to cerebral ischemia reperfusion *via* increasing of hippocampal and striatum norepinephrine and dopamine level.

Nabavi *et al.* [115] reported that intracerebroventricular administration of bi-3-azaoxoisoaporphine derivatives reduces depressive-like behaviors in a mouse model of post-stroke depression. Nabavi et al. reported that 4,4'-dimethyl-7H,7'H-[6,6'-bibenzo[e]perimidine]-7,7'-dione has a greater antidepressant action than 7H,7'H-[6,6'-bibenzo[e]-perimidine]-7,7'-dione and 4,4'-dibromo-7H,7'H-[6,6'bibenzo[e]-perimidine]-7,7'-dione. Aggrawal *et al.* [116] reported that nitric oxide plays an important role in the protective effect of naringin (a flavanone glycoside) against post-stroke depression induced by bilateral common carotid artery occlusion. Zhang [117] indicated that Shugan Jiannao Tiaoyu tablets improve performance in the forced swim test and sucrose preference test and reduce hippocampal neuronal damage in rats who suffer from post-stroke depression *via* down-regulation of the hypothalamic corticotrophin releasing hormone gene expression.

Another study reported by Khan *et al.* [118] showed that pretreatment with N-acetylcysteine (NAC, 150 mg/kg, intraperitoneally) mitigated the cerebral ischemia-reperfusion injury in animal model of ischemic stroke (*via* middle cerebral artery occlusion). Khan *et al.* [118] demonstrated that pretreatment with NAC significantly ameliorated stroke induced neural damage, increased glutathione levels, diminished infarct volume, down-regulated the expression of proinflammatory cytokines (TNF-alpha and IL-1beta) and inducible nitric oxide synthase. They also found that pre-administration of NAC down-regulated the expression of activated macro-phage/microglia (ED1).

Another study by Jatana *et al.* [119] reported that combining of hypothermia (30 + 0.5 degrees C) and NAC (50 mg/kg, intraperitoneally) has beneficial effects on brain injury, neonatal reflexes and myelination in neonatal hypoxic-ischemic rats. Jatana *et al.* [119] reported that brain infarct volumes were significantly reduced and neonatal reflexes were also significantly improved by combination therapy. Also, they showed that combination therapy attenuated the abnormality in the myelin expression in the brain sections. They concluded that hypothermia plus NAC combination therapy attenuated hypoxic-ischemic brain injury *via* improving of infarct volume, myelin expression and functional outcomes in rats with focal hypoxic-ischemic injury.

Furthermore, Hicdonmez et al. [120] examined the beneficial role of NAC in a murine closed-head trauma model. Hicdonmez *et al.* [120] showed that administration of NAC (150 mg/kg) attenuated the traumatic injuries, reflected in the levels of malondialdehyde as well as significantly increasing in the activities of superoxide dismutase and glutathione peroxidase, but not catalase activity. Hicdonmez *et al.* [120] concluded that treatment with NAC has a beneficial role in mitigating trauma-mediated oxidative stress in brain tissues.

There are few studies of nutraceuticals that have been carried out in human post-stroke depression populations. Li *et al.* [121] performed a randomized placebo controlled clinical trial of 150 post-stroke patients who were depressed, reporting that 8 weeks of administration of Free and Easy Wanderer Plus (Jia-Wey Shiau-Yau San, a polyherbal preparation) reduces depressive-like symptoms in patients with post-stroke depression. Xu *et al.* [122] performed a three-arm randomized controlled trial on 108 patients examining the efficacy of Wuling Capsule (a Chinese herbal formula comprise of mycelia of precious Xylaria nigripes (Kl.) Sacc) in treatment of post-stroke depression. Xu et al found that treatment with Wuling Capsule, fluoxetine and combination of fluoxetine and Wuling Capsule improved patient neurological function and reduced both Hamilton Depression Ratin Scale scores and Scandinavian Stroke Scale scores. Additionally, increases in both Barthel index and Mini-mental State Examination scores were reported. The authors also found a synergistic effect between Wuling Capsule and fluoxetine in the treatment of post-stroke depression, evidenced by a larger reduction in Hamilton

Depression Rating Scale scores and increases in Barthel index scores, in the combination group compared with other groups. Fu *et al.* [123] performed another three-arm randomized controlled trial on 114 patients to investigate the efficacy of flupenthixol/melitracen (Deanxit), Wuling Capsule, and flupenthixol/melitracen combined with Wuling Capsule in treatment of post-stroke depression. They found that combination of flupenthixol/melitracen with Wuling Capsule had a greater antidepressant effect than mono-therapy alone based on Hamilton Depression Rating Scale scores.

More research is needed in order to understand the chemical structure of natural products, their side effects, long-term efficacy and their exact mechanism of antidepressant action in post-stroke depression patients.

CONCLUSION AND RECOMMENDATION

Depression is a frequent neuropsychiatric complication of stroke, occurring in over 30% of stroke patients, and is a major health issue due to its effects on stroke rehabilitation and recovery. Post-stroke depression increases stroke morbidity and mortality and therefore, identification and evaluation of the efficacy and safety of treatments of post-stroke depression are vital to decrease the health care burden and costs of related to this patient population. We have reviewed the evidence for a range of options for post-stroke depression management, including antidepressant therapy, psychotherapy, surgical therapy, electroconvulsive therapy, acupuncture, music therapy, natural products and herbal medicine. Indeed, in many cases those treatments that are effective in MDD have also been shown to be effective in post-stroke depression overlap in treatment efficacy may be explained by biological commonalities between stroke and MDD including oxidative stress and inflammation. Indeed, these two fields of research may inform each other in terms of underlying pathophysiology. Understanding post-stroke depression may assist in better understanding both stroke and MDD independently.

Further research is required to provide specific efficacy of the different approaches as well as identifying the sub-groups of stroke survivors that may be a target for each treatment strategies. The role of natural antidepressant drugs in the treatment of post-stroke is an emerging field of research, and holds potential for the identification of new adjunctive and monotherapeutic treatments.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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