

# A Narrative Review on the Non-Pharmacologic Interventions in Post-Stroke Depression

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**Abstract:** Stroke is a major cause of death and disability globally. Post-stroke depression (PSD) is a major driver for poor recovery and poor quality of life with extra burden for the patient and the caregiver. We have previously shown the inflammatory basis of PSD with associated bioenergetic failure, disruption of the blood-brain barrier, cell death, and persistent maladapted inflammation, making the PSD a norm rather than the exception, highlighting the unmet need for therapeutic intervention in PSD across the recovery trajectory. In this era, various interventions are focused on pharmacotherapy; however, non-pill-based medication should also be explored as post-stroke patients are likely to suffer from the adverse effects of polypharmacy. This narrated review explores the status of non-pharmacological interventions in managing PSD. We performed a PubMed search using pre-specified keywords looking at various non-pharmacologic approaches for the management of PSD. Worldwide, approaches such as non-invasive brain stimulation, behavioral and psychosocial therapy, as well as exercise, acupuncture, music, literature, and art therapies are available as monotherapy or adjunctive treatment for PSD. While current literature shows convincing results on the benefits of non-pharmacologic interventions, more robust studies are necessary to determine its utility in PSD.

**Keywords:** stroke, depression, non-pharmacological intervention, disability

## Introduction

The Global Burden of Disease Study reported a steady decline in stroke-related mortality over the past three decades.<sup>1</sup> However, cerebrovascular diseases remain to be one of the leading causes of morbidity worldwide with more than 80 million people being affected in 2016 alone.<sup>1</sup> With a steep decline in mortality rates, long-term sequelae are expected among stroke survivors with staggering costs both for patients and their caregivers. While physical disability and cognitive complications significantly impact on patients' well-being, studies suggest that persistent depression after stroke is predictive of poor quality of life in the long term.<sup>2</sup>

Post-stroke depression (PSD) is a growing burden worldwide. It is a common yet often unrecognized post-stroke complication. Sufferers feel hopelessness, increased levels of anxiety and general lack of interest, as well as experiencing sleep alteration.<sup>3</sup> It affects one-third of patients with a history of stroke and with incidences highest in the first six months post-stroke and a second peak notable at 18 months after.<sup>4-6</sup> In the first three months after a stroke, some of the risk factors identified which increase the risk of PSD include previous mental illness, female gender, age <70, neuroticism, family history, severity of stroke and the level of disability.<sup>7</sup> On the other hand, longitudinal studies demonstrated that functional dependence and persistent relationship problems due to the antecedent stroke are the strongest predictors of PSD at 18 months.<sup>6</sup>

PSD is attributable to various neurochemical and anatomical alterations to their brain, regardless of the severity of the original stroke, and in association with various psychosocial influences.<sup>8</sup> Depending on which vascular territory is affected, various cortical and subcortical structures have been noted to manifest mood disorders post-stroke.<sup>8</sup> The

biological hypothesis is thought to result from a cascade of processes activating the hypothalamic-pituitary axis, leading to altered responses of the neurogenic system and altered energy metabolism.<sup>9</sup> Disruption of the glutaminergic system resulting in excitotoxicity may also contribute to the development of PSD, particularly coupled with the chronic, low grade neuroinflammatory state brought on by the patient's stroke.<sup>10,11</sup> Psychosocial variables such as baseline social ties and emotional support along with individual characteristics such as helplessness, passive coping, less acceptance, and perceived benefits have also been shown to impact significantly on PSD etiology.<sup>12</sup>

Management of PSD is equally complex, necessitating a multi-pronged approach using both pharmacologic and non-pharmacologic measures. Inadequate interventions have been shown to contribute to poor functional outcomes, increased stroke recurrence and increased mortality rates among PSD patients.<sup>8</sup> Pharmacologic therapy with antidepressants such as noradrenaline reuptake inhibitors, tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) is undoubtedly a cornerstone of current PSD treatment.<sup>13</sup> However, post-stroke patients have been observed to be poorly adherent to pharmacotherapy.<sup>14</sup> In a large cohort study involving more than 12,000 patients, nearly half of all PSD patients involved were either poorly adherent to antidepressant regimens or not adherent at all, leading to poor clinical outcomes.<sup>14</sup> Polypharmacy is likely a key factor contributing to this poor adherence,<sup>15</sup> thus non-pharmacologic approaches are well worth exploring as alternatives.

In a recent Cochrane review of interventions for post-stroke depression, it has been determined that there is no strong evidence to suggest that pharmacologic interventions are effective in reducing depressive symptoms post-stroke.<sup>16</sup> These conclusions, however, were drawn based on low-certainty evidence because of various forms of biases and high attrition rates noted in several studies.<sup>16</sup> While more robust data are necessary to assess the efficacy of pharmacologic management, the need to evaluate non-pill-based management is likewise imperative which can be utilized as monotherapy or adjunct to the former. This is particularly useful for stroke patients who are prescribed with several medications and may be at a high risk for interactions with antidepressants.<sup>17</sup> Its utility is further highlighted in special populations such as the elderly who may have a slightly increased risk for falls with anti-depressant therapy.<sup>18</sup> In this narrative review, we discuss various non-pharmacologic approaches for the management of post-stroke depression.

## Methodology

A PubMed literature search was performed from September to November 2021. The following topics were included: post-stroke depression; non-invasive brain stimulation; behavioral therapy; psychosocial interventions; acupuncture; exercise therapy; light therapy; music therapy and art therapy. Only literature in English and published in the past 25 years were included in this review. Outcomes of studies included should be various objective measures for the assessment of post-stroke depression. Summary of studies included in this review is outlined in [Table 1](#).

## Non-Invasive Brain Stimulation

Non-invasive brain stimulation is an established non-pharmacologic treatment for patients with major depressive disorder. However, its utility in PSD still needs further investigation. Transcranial Direct Current Stimulation (tDCS) is one of the techniques that has been explored in this regard. The earliest reports suggesting tDCS may be potentially beneficial for PSD were published by Bueno et al.<sup>19</sup> They reported a significant improvement in the mood and cognition of a post-stroke patient following 30-minute anodal stimulation of the left dorsal prefrontal cortex (DLFPC) for ten days.<sup>19</sup> However, immediate relapse was noted three weeks after discontinuation, necessitating the need for further maintenance sessions.<sup>19</sup> This regimen was also evaluated among aphasic patients with concomitant depression and bilateral DLFPC stimulation showed more than 50% improvement in their depressive scores.<sup>20</sup> Following this, 48 PSD patients were randomised to tDCS and sham treatment over six weeks for a total of 14 sessions.<sup>21</sup> This RCT proved that the former was significantly more effective in averting PSD with a number needed to treat of three.<sup>21</sup> However, no long-term follow-up was established in this study, and previous studies on non-stroke patients have noted more than 50% relapse following discontinuation of treatment.<sup>22</sup> Clearly, more studies on this intervention still need to be done, ideally performed using a larger population and with a longer follow-up period.

Repetitive Transcranial Magnetic Stimulation (rTMS) is another novel intervention in the field of neurorehabilitation. This involves stimulation or inhibition of various neural structures by application of electromagnetic impulses aimed at

**Table I** Summary of Studies on the Non-Pharmacologic Interventions for PSD

Author	Year	Study Design	N	Intervention	Comparator	Depression Outcome Measures	Outcome
Bueno et al	2011	Case report	1	Transcranial Direct Current Stimulation			Improvement in mood and cognitive impairment
Valiengo et al	2016	Case series	4	Transcranial Direct Current Stimulation		Stroke Aphasic Depression Score, Aphasic Depression Rating Scale	Improvement in mood among aphasic and depressed patients sustained for 4 weeks
Valiengo et al	2016	RCT	48	Transcranial Direct Current Stimulation	Sham control	Hamilton Depression Scale	Active TDCS superior to sham in the improvement of PSD
Valiengo et al	2013	RCT	Phase II-25 Phase II-42	Transcranial Direct Current Stimulation	Sertraline	Montgomery-Asberg Depression Rating Scale	tDCS should be optimized in treatment resistant depression
Gu et al	2017	RCT	24	Transcranial Magnetic Stimulation	Sham control	Hamilton Depression Scale 17 Beck Depression Inventory	rTMS decreased depression scores compared to sham
Frey et al	2020	Prospective Cohort	6	Transcranial Magnetic Stimulation		Hamilton Depression Scale	Accelerated rTMS protocol is a safe adjunct/ alternative for PSD
Hordacore et al	2021	RCT	11	Transcranial Magnetic Stimulation	Sham control	Beck Depression Index	Active rTMS improved depression and is well tolerated
Shao et al	2021	Meta-Analysis	7 RCTs, 351 patients	Transcranial Magnetic Stimulation	Various	Hamilton Depression Scale, clinical remission of depression	rTMS could be an effective treatment for PSD and more effective in Asians
Lincoln et al	1997	RCT	136	Cognitive Behavioral Therapy (CBT)		Hamilton Depression Scale 17 Beck Depression Inventory	CBT improved depression among PSD patients
Lincoln et al	2003	RCT	123	Cognitive Behavioral Therapy (CBT)		Beck Depression Inventory Wakefield Depression Inventory	CBT was ineffective in the treatment of PSD
Ward et al	2016		48	Cognitive Behavioral Therapy (CBT)		Beck Depression Inventory Hospital Anxiety Depression Scale	CBT was effective in the treatment of PSD

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Table I (Continued).

Author	Year	Study Design	N	Intervention	Comparator	Depression Outcome Measures	Outcome
Olukalde et al	2017		30	Cognitive Behavioral Therapy (CBT)	Psychoeducation, Standard care	Beck Depression Index	CBT improved depression among PSD patients
Simblette et al	2017	RCT	134	Computerized CBT (cCBT)	Computerized cognitive remediation therapy (cCRT)	Beck Depression Inventory-II (BDI-II) Beck Anxiety Inventory (BAI)	Both cCBT and cCRT are equally useful for PSD
Kootker et al	2017	RCT	61	Augmented CBT	Computerized Cognitive Training (CCT)	Hospital Anxiety and Depression Scale	CBT intervention was not superior to CCT for PSD
Wang et al	2018	Meta-Analysis	23 studies 1972 patients	Cognitive Behavioral Therapy (CBT)	Various	Various	CBT has positive effects on PSD
Lai et al	2006	RCT	100	Therapeutic exercise	Standard care	Geriatric Depression Scale Stroke Impact Scale Medical Outcomes Study 36-Item Short Form.	Exercise may help improve PSD and the quality of life of patients post stroke
Smith et al	2008	RCT	22	Treadmill training	Weekly phone call	Beck Depression Index Stroke Impact Scale	Task specific intervention to improve gait may secondarily improve PSD
Aguiar et al	2020	RCT	20	Treadmill training	Standard care	Patient Health Questionnaire	Aerobic treadmill improved PSD
Sims et al	2009	RCT	22	Community-based progressive resistance training (PRT) program	Wait-list comparison group	Centre for Epidemiologic Studies for Depression Scale Short Form-12 Health Survey Questionnaire (SF-12) Satisfaction with Life Scale (SWLS)	Trend to benefit in the PRT group but not significant difference compared to controls
Eng et al	2014	Meta-Analysis	13 RCT, N=1022	Exercise training	Various	Various	Exercise may be a potential treatment to improve PSD in the subacute to chronic period
Aidar et al	2018	RCT	36	Aquatic Exercise Program	Not described	State-Trait Anxiety Inventory Beck Depression Inventory	Aquatic training improved depression and anxiety in PSD
Dela Cruz et al	2020	RCT	45	Aquatic Therapy Program and land-based physiotherapy	Land-based physiotherapy	SF-36 quality of life scale Resilience scale	Aquatic exercises have positive effects on mood and QOL

Chan et al	2012	RCT	14	Yoga and exercise	Exercise only	Geriatric Depression Scale (GDS15) State Trait Anxiety Inventory (STAI)	No differences in depression and anxiety between intervention group and control
Immink et al	2014	RCT	22	Yoga	No treatment	Geriatric Depression Scale (GDS15) State Trait Anxiety Inventory (STAI)	Yoga improved QOL and anxiety among PSD patients.
Piliae	2014	RCT	145	Tai-chi (Yang style)	Strength exercises and usual care	Short-Form Health Survey Center for Epidemiologic Studies Depression Scale	Tai-chi improved physical function and QOL among post-stroke patients
Kim et al	2015	RCT	22	Ta-chi and general physiotherapy	General physiotherapy	SF-36 survey	Tai-chi improved QOL of of PSD patients
Lyu et al	2021	RCT	11 RCTs, N=723	Tai-chi	Conventional rehabilitation	Various depression scores	Tai-chi improved depression in stroke survivors
Zhang et al	2005	RCT	45	Brain resuscitation acupuncture	Fluoxetine	Hamilton Depression Rating Scale	Brain resuscitation acupuncture improves depression in patients with PSD with quick effects
Liu et al	2006	RCT	560	Acupuncture-moxibustion	Fluoxetine	Hamilton Depression Scale	Acupuncture-moxibustion resulted in significant improvement of depression with similar therapeutic effect as medical treatment
He et al	2007	Cross-sectional study	256	Acupuncture	Amitriptyline	Self-Rating Depression Scale (SDS) and Hamilton Rating Scale for Depression (HRSD)	Acupuncture significantly improves depression and is superior to medical treatment
Guo et al	2009	Cross-sectional study	120	Linggui Bafa acupuncture	Sertraline and no treatment	Hamilton Depression Scale, SF36, Function Independent Measure (FIM)	Acupuncture significantly improves depression and QOL and is superior to medical treatment
Wu et al	2010	Cross-sectional study	300	Acupuncture	Fluoxetine	Hamilton Depression Scale	Acupuncture is effective in improving PSD
Nie et al	2011		63	Acupuncture and Moxibustion	Fluoxetine	Hamilton Depression Scale	Acupuncture is effective in improving PSD

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Table 1 (Continued).

Author	Year	Study Design	N	Intervention	Comparator	Depression Outcome Measures	Outcome
Youn et al	2013	Cross-sectional study	28	Electro-acupuncture		Hamilton Depression Scale, Beck Depression Index	Electro-acupuncture can improve PSD
Li et al	2016	Meta-Analysis	813	Electro-acupuncture	Anti-depressants	Hamilton Depression Scale	No difference in electroacupuncture and medical treatment
Sun et al	2015	RCT	93	Acupuncture and Fluoxetine	Acupuncture or Fluoxetine	Hamilton Depression Scale	Acupuncture and Fluoxetine are superior to either Fluoxetine or acupuncture alone
Sun et al	2015	RCT	63	Acupuncture (Governor vessel) and Fluoxetine	Fluoxetine	Hamilton Depression Scale	Acupuncture and Fluoxetine is effective in PSD after 4 weeks of treatment
You et al	2020	RCT	99	Acupuncture (wrist ankle) and Fluoxetine	Sham needle + Fluoxetine	Hamilton Depression Scale, Self-rating Depression scale	Acupuncture (wrist ankle) and Fluoxetine can relieve PSD
Man et al	2014	RCT	43	Dense cranial electro-acupuncture stimulation (DCEAS) and body acupuncture and SSRI	Non-invasive cranial electro-acupuncture and body acupuncture and SSRI	Hamilton Depression Scale Clinical Global Impression - Severity scale (CGI-S)	Dense cranial electro-acupuncture stimulation (DCEAS) is effective in reducing depressive symptoms among stroke patients
Zhang et al	2017	Meta-Analysis	13 RCT 904 patients	Acupuncture and anti-depressants	Anti-depressants	Change in Hamilton Depression Scale	Combined acupuncture and antidepressant is more favorable than antidepressant alone in PSD
Zhang et al	2019	Meta-Analysis	7 studies	Acupuncture	Anti-depressants	Change in Hamilton Depression Scale	Acupuncture is better than drug therapy in PSD
Sondergaard et al	2006	RCT	63	Light therapy and Citalopram	Various intensities of light therapy	Hamilton Depression Scale	High intensity light treatment is effective in the treatment of PSD
West et al	2017	RCT	90	Circadian light	Standard light	Hamilton Depression Scale, Major Depression Inventory scale (MDI)	Circadian light is effective in the long term in the management of PSD
Wang et al	2020	RCT	46	Sunlight	Standard care	Taiwanese Depression Scale	Light therapy improves PSD
Xiao et al	2021	RCT	106	Bright light therapy and Escitalopram	Escitalopram	Hamilton Depression Scale	Bright light therapy and Escitalopram are effective in improvement in PSD

Sarkamo et al	2008	RCT	60	Self-selected music or audio books	Standard care	Profile of Mood States	Music listening during the early post-stroke stage can enhance cognitive recovery and prevent negative mood.
Jun et al	2013	Quasi experimental design	30	Music movement therapy	Standard care	Center for Epidemiologic Studies Depression Scale (CES-D)	Music therapy improved mood in the first 2 weeks of stroke improved patients' mood
Van Vugt	2014		28	Music therapy played in synchrony	Music therapy played individually	Profile of Mood States (POMS).	Music therapy improved mood regardless of whether performed individually or in synchrony
Kim et al	2011	RCT	18	Music therapy	Standard care	Beck Depression Inventory	Music therapy improved depression of PSD patients
Sumakul	2020		59	Music therapy	Standard care	Hamilton Depression Scale	Music therapy improved depression of PSD patients
Baylan et al	2020	RCT	72	Mindful music listening	Standard music listening or audiobook listening	Hospital Anxiety and Depression Scale	Mindful music therapy did not significantly improve mood among PSD patients
Lin et al	2017		92	Five phases in Traditional Chinese Medicine	Sertraline and/or acupuncture	Hamilton Depression Scale	Music therapy plus acupuncture improved PSD
Kongkasuwan	2016	RCT	118	Creative Art therapy	Conventional Physical therapy	Hospital Anxiety and Depression Scale	Creative art therapy combined with conventional physical therapy can significantly decrease depression
Kim et al	2013		28	Color therapy	Standard care	Purpose in life questionnaire	Color therapy improved the purpose in life among stroke patients
Ali et al	2014		6	Art therapy		Hospital Anxiety and Depression Scale	No difference in depression scores before and after treatment
Minshall et al	2020	RCT	173	Personalized psychosocial intervention	Standard care	Hospital Anxiety and Depression Scale	Personalized psychosocial intervention did not impact PSD at 6 months
Watkins et al	2007	RCT	207	Motivational interviewing	Standard care	General Health Questionnaire	Motivational interviewing leads to an improvement in patients' mood 3 months after stroke.
Mitchell et al	2009	RCT	101	Brief behavioral intervention and antidepressant	Standard care	Hamilton Depression Scale	A brief psychosocial-behavioral intervention is highly effective in reducing depression in both the short and long term.

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**Table I** (Continued).

Author	Year	Study Design	N	Intervention	Comparator	Depression Outcome Measures	Outcome
Watkins et al	2011	RCT	411	Motivational interviewing	Standard care	General Health Questionnaire	Motivational interviewing improves patients' mood and reduces mortality 12 months poststroke.
Chalmers et al	2019	Prospective Cohort	28	Problem solving	Wait-list comparison group	Center for Epidemiologic Studies Depression Scale (CES-D)	Younger stroke survivors may benefit from age appropriate psychological support
Hadidi et al	2014	RCT (feasibility)	22	Problem solving	Standard care	Center for Epidemiologic Studies Depression Scale (CES-D)	Problem solving therapy may be feasible for PSD
Fang et al et al	2017	Pilot trial	42	Constructive integrative psychosocial intervention (CIPI)	Standard care	Hospital Anxiety and Depression Scale	CIPI appears to be of incremental value in treating depression as well as anxiety in subacute care
Ostwald et al	2014	RCT	159	Psychoeducational program (home-based) in dyads	Mailed program	Geriatric Depression Scale	Intervention done in dyads are effective in PSD
Smith et al et al	2016	Mixed-methods pilot study	20	Psychoeducational program (home-based) in dyads	Standard care	Center for Epidemiologic Studies Depression Scale (CES-D)	Nurse-initiated cognitive coping intervention was supported by experimental group's elements.
Minshall et al	2019	Meta-Analysis	31 RCTs 5715 patients	Psychosocial interventions	Standard care	Various measures of depression	Psychosocial interventions reduced depressive symptoms in stroke survivors and their carers.

optimizing neuroplasticity to maintain residual neural function while also acquiring new skills.<sup>23</sup> Repetitive Transcranial Magnetic Stimulation targeting the left dorsolateral prefrontal cortex has been beneficial in the management of patients with PSD. In a randomized control trial comparing patients who received ten sessions of 10Hz rTMS to those receiving sham controls, significant decreases in depression scale scores were noted in the former.<sup>24</sup> In the Novel TMS for Stroke and Depression (NoTSAD) trial, an accelerated TMS protocol for PSD was employed, consisting of five sessions per day for four consecutive days within the subacute stroke period and likewise revealing beneficial results.<sup>25</sup> Another RCT done in Australia provided evidence for the efficacy of high-frequency TMS in the reduction of Beck Depression Scores among PSD patients compared to sham controls.<sup>26</sup> In this study, the authors also performed EEG to assess neurophysiologic correlation and noted enhanced theta frequency in the treatment group.<sup>26</sup> This is suggestive of improved connectivity between the dorsolateral prefrontal cortex and the parietal cortex, areas potentially compromised in PSD.<sup>26</sup> However, this remains speculative due to the small population size of this study. While the benefits of rTMS have likewise been replicated in a meta-analysis of 7 RCTs with 351 patients, its effects are likely limited to a short period.<sup>27</sup> Furthermore, subgroup analysis suggests that it may be more effective in Asian subjects, although unblinded techniques in the former may be prohibitive of its generalizability.<sup>27</sup> More studies involving more heterogeneous populations are needed to assess the efficacy and safety of non-invasive brain stimulation among post-stroke patients developing depression.

## Behavioral Therapy

Individualized behavioral therapies are also at the forefront of non-pharmacologic management of PSD. Cognitive behavioral therapy (CBT) is an established intervention rooted on the principle that psychological dilemmas are anchored on maladaptive patterns of thinking and unhelpful behavior.<sup>28,29</sup> Techniques employed include distraction, activity scheduling and modification, graded task assignments and others that seek to defy this negative mentality.<sup>28</sup>

The first study to assess the efficacy of CBT to treat PSD was performed more than two decades ago in the United Kingdom. In this observational study, the authors noted that there might be a likelihood of symptom improvement following 10 CBT sessions for three months.<sup>28</sup> However, they also noted that cognitive dysfunction after a stroke may be a limitation to its applicability.<sup>28</sup> A randomized control trial initiated in the same institution was done a few years later involving CBT compared with attention placebo intervention and standard care, concluding no differences in depression and functional outcomes.<sup>29</sup> Observational and small-scale RCTs, however, showed beneficial results<sup>30–33</sup> The effects of a group cognitive behavioral therapy called Brainstorm were evaluated in a group of post-stroke survivors in Australia manifesting depressive symptoms.<sup>30</sup> This tool kit involved monitoring of mood and activity and psychoeducation, as well as challenging negative thoughts.<sup>30</sup> Depression scores significantly improved from baseline to one month after, however its effects were not sustainable at the end of six months.<sup>30</sup> A prospective observational study in Nigeria also showed that, after nine sessions of CBT focused on activity stimulation, negative thoughts and people contacts, patients with PSD had better emotional well-being compared to controls.<sup>31</sup> Computerized CBT has also been explored in the past but did not prove superior over conventional CBT although only feasibility trials and studies with small population are available to date.<sup>32,33</sup> There is also an ongoing RCT on the use of an CBT-based iPad application promoting self-reinforcement and positivity being performed among Japanese patients.<sup>34</sup> Overall, it appears that CBT showed more improvement and higher remission and response rates with concomitant improvement in anxiety and functional neurological outcomes.<sup>35</sup> To date, recent clinical guidelines in stroke rehabilitation recommend CBT as monotherapy or adjuvant to standard medical therapy among patients with PSD.<sup>36</sup>

## Psychosocial Interventions

Psychosocial interventions prove to be an essential component for the management of PSD. As patients and their caregivers have a marked reduction in social participation and functioning after a stroke, approaches that involve motivational interviewing, transitional care, social support, and psychoeducation should be integral in stroke rehabilitation.<sup>37</sup> On an individual patient level, exploration of their respective needs, assessment of the potential barriers and supporting the skills and networks needed to achieve this has been suggested as an essential framework for recovery.<sup>38</sup> These strategies should eventually aim to achieve self-efficacy, a factor which has been shown to be negatively associated with PSD.<sup>39,40</sup>

Various studies have provided evidence on the value of motivational interviewing and comprehensive psychosocial interventions for the improvement of post-stroke mood disorders.<sup>41,42</sup> Motivational interviewing, described as patient-centered and talk-based therapy has been shown to improve PSD at three months and one year.<sup>41,43</sup> The Living Well with Stroke study also showed that a brief psychosocial-behavioral intervention over a period of eight weeks in conjunction with antidepressant medication has sustained benefits for PSD until two years.<sup>42</sup> A trend towards more beneficial effect has also been seen in problem-solving therapy to reduce post-stroke emotional distress in young and elderly stroke survivors.<sup>44,45</sup> A more comprehensive approach called constructive integrative psychosocial intervention has been proposed by Fang et al. This method reinforces positive construction of experiences by the patient regarding his or her illness by incorporating psychoeducation, sharing of experiences in relation to previous illnesses, crisis management and activity participation.<sup>46</sup>

A dyadic approach which involves psycho-intervention for both caregivers and stroke patients has also been shown to be useful in the management of PSD in the latter.<sup>47,48</sup> A home-based psycho-educational program over a six-month period for both the stroke patient and their spouses has demonstrated positive impact in the dyad's depressive symptoms.<sup>47</sup> Similar conclusions were drawn in another study where psychoeducational interventions were provided for stroke survivors and their spouses.<sup>48</sup> A meta-analysis of 11 studies highlighted that psychosocial interventions focusing on the patients, caregivers or both have ameliorating effects in PSD.<sup>49</sup> It is in this reason that authors emphasize the need to shift psycho-intervention for PSD towards a dyad approach in which the patient and the caregiver is considered a solitary unit.<sup>50</sup> Guidelines have also stressed the need for psychosocial interventions such as motivation interviewing and problem-solving therapy before commencing anti-depressant medications for PSD.<sup>51</sup> While the beneficial effects of this are promising, its main limitation is that it is largely human-resource intensive and that it can be time consuming. However, the evolving concepts of post-stroke neurorehabilitation post-stroke should focus on a wholistic and a biopsychosocial approach to reduce the improvement in the quality of life afflicted by post-stroke depression.

## Exercise Therapy

Exercise is an important cornerstone in neurorehabilitation as it promotes neural alterations at the structural and biochemical level. Even if not structurally altered by the stroke process, there is evidence that alterations to the neuroplasticity of the hippocampus play an essential role in post-stroke depression.<sup>52,53</sup> Accumulating evidence from biochemical studies show that exercise increases the mBDNF/proBDNF ratio, which is one of the key biomarkers involved in the promotion of hippocampal neuroplasticity.<sup>52</sup> Another neurochemical involved in PSD is phosphatase and tensin homologue (PTEN), a known tumor suppressor. Upregulation of this leads to neuronal apoptosis in the hippocampus.<sup>53</sup> Experimental studies have shown that in mice models exercise induces PTEN downregulation, which results in reduced levels of the inflammatory neurochemicals TLR4, NF- $\kappa$ B and NLRP3, all ameliorating PSD.<sup>54</sup>

Clinical studies also show substantial evidence that exercise promotes improvement in mood disorders post-stroke. One of the first randomised clinical trials examining the effect of a three-month structured exercise program on the occurrence of PSD among 100 stroke survivors was conducted in 2006.<sup>55</sup> In this study, Lai et al noted that after three months PSD occurred in 14% of the subjects in the intervention group and 35% in controls ( $p = 0.03$ ).<sup>55</sup> After nine months percentages were still numerically lower in the experimental group, albeit not to statistically significant levels.<sup>55</sup> Whilst aerobic exercises have been shown to be useful in improving gait and mobility after a stroke, clinical studies likewise confirm their secondary effect on PSD.<sup>56</sup> Targeting aerobic training to achieve 60–80% of the heart rate reserve has been shown to be beneficial not only for the alleviation of PSD but also for overall quality of life.<sup>56</sup> Apart from aerobic training, other exercise programs such as functional and resistance programs are also thought beneficial for PSD.<sup>57</sup> Resistance training has the advantage of lesser incidence of falls, particularly critical for post stroke patients with balance and mobility issues.<sup>58</sup> A study involving a community-based progressive resistance training regimen consisting of moderate-intensity exercises using machine weights documented reduced depression scores in the intervention group.<sup>58</sup> Corollary to this, a meta-analysis of 13 studies involving more than 1700 stroke patients reported a beneficial effect among those undergoing structured exercises, with notable effects in the first six months post stroke.<sup>59</sup> The same

study also concludes that those involved in high-intensity programs, defined as at least 150 minutes of cardiorespiratory, resistance and aerobic activities, achieved the greatest benefit.<sup>59</sup>

Other forms of exercises have likewise been helpful for mood-related disorders after a stroke. Regular aquatic exercise consisting of two sessions per week each lasting for 45–60 minutes over a 12-week period has been shown to improve depression measures among PSD patients.<sup>60</sup> The authors argued that improvement in mood seems to be correlated with improvement of mobility.<sup>60</sup> A novel form of aquatic therapy known as Ai Chi has also been shown to be beneficial. This form of therapy integrates body coordination and involves specific breathing exercises.<sup>61</sup> A study performed in 45 patients who underwent alternating Ai Chi and usual physiotherapy had the advantage over controls, showing better mood and improved quality of life.<sup>61</sup> Aquatic therapy has the additional advantage of providing additional external stimulation such as buoyancy and viscosity, which may impact neuroplasticity.<sup>62</sup> While this form of therapy is largely trainer and resource dependent, it is generally deemed to be a safe and effective means of treatment in the motor and non-motor aspects of post-stroke rehabilitation.

Mind-body exercises also seem to be a promising form of neurorehabilitation among depressed post-stroke patients. This form of therapy integrates the body, spirit, and the external environment to promote a holistic sense of well-being.<sup>63</sup> A complementary type of medicine which has originated in South Asia, yoga is a form of mind-body exercise which has demonstrated positive effects among patients with stroke. While yoga involves dynamic body positions, it has been proposed that yoga asana can be useful among post-stroke patients with significant limitations in their mobility.<sup>64</sup> One of the first clinical trials looking at the impact of yoga in depression and anxiety post stroke was performed by Chan et al.<sup>65</sup> In this small-scale randomized control trial performed in Australia, patients undergoing yoga in combination with usual post-stroke rehabilitation exercise had greater improvement in terms of anxiety and depression, although not statistically significant differences compared to controls.<sup>65</sup> A few years later, another study provided evidence on the benefit of yoga asana in the mood-related complications of stroke with persistent hemiparesis.<sup>66</sup> Tai Chi is another form of mind-body exercise which integrates martial arts and relaxation techniques. After a 12-week period of regular Yang tai chi exercises, a randomised control trial involving 145 patients with stroke demonstrated significant improvement in their physical function, fall rates and quality of life.<sup>67</sup> The majority of studies looking at the effect of Tai Chi on PSD were performed in Asia and showed positive results,<sup>68–70</sup> and its beneficial effect has also been confirmed in a meta-analysis of 11 RCTs.<sup>70</sup> While the exact mechanism by which Tai Chi promotes emotional well-being in acute stroke is uncertain, it has been hypothesized that it largely impacts the prefrontal cortex, which modulates inputs from neural structures involved in mood stabilization.<sup>71</sup> While most of these studies suggest mind-body exercises have beneficial effects regarding PSD, high-quality evidence is needed to substantiate these claims. As side effects are minimal, it is regardless not unreasonable to integrate these regimens in standard neurorehabilitative techniques.

## Acupuncture

Acupuncture is an old yet fundamental aspect of Chinese traditional medicine. Various observational studies and clinical trials validate its use in PSD. Experimental studies in rat models show that the effectiveness of acupuncture in PSD lies in its effects in the PI3K/Akt/mTOR signaling pathway and its inhibition of hippocampal neuronal cell death.<sup>72</sup> In addition to this, it may also be helpful in restoring the equilibrium of various hippocampal neurotransmitters such as norepinephrine, serotonin and dopamine.<sup>72,73</sup>

The first randomised clinical trial to evaluate the efficacy of Acupuncture in PSD was done in 2005 and compared it to Fluoxetine.<sup>74</sup> Compared to controls receiving Fluoxetine, acupuncture showed no significant difference as measured by the HAM-D scores.<sup>74</sup> However, the same study showed that onset of antidepressant effect was faster in the experimental group and free of side effects.<sup>74</sup> Other studies have likewise shown no difference in treatment effects between medical and acupuncture groups.<sup>75</sup> On the other hand, some literature has instead shown the superiority of acupuncture among PSD patients compared to Fluoxetine.<sup>76</sup> In a randomized control trial of more than 270 patients, He et al noted a superior therapeutic effect of acupuncture performed twice a day for one month, with a notable improvement in Self-Rating Depression Hamilton Depression scales.<sup>76</sup> Nie et al also observed that the onset of the therapeutic effect of Acupuncture Moxibustion is notable as early as the 2nd week of treatment and is superior to Paroxetine.<sup>79</sup> Observational and randomized control trials also prove the superiority of Acupuncture over Fluoxetine and Sertraline after two and six

months of intervention, respectively.<sup>77,78</sup> Furthermore, it has also been suggested that patients with good motor function at onset who have received acupuncture for at least a month show a greater degree of improvement in their scores in the Beck Depression and HRDS compared to those with severe motor disability.<sup>81</sup> Overall, a meta-analysis of randomized control trials involving more than 1500 patients did not show any significant difference in treatment effects in the acupuncture group compared to controls receiving antidepressants such as Fluoxetine, Citalopram and Sertraline, however, lesser adverse effects were noted in the former.<sup>82</sup>

It appears that combination therapy consisting of acupuncture and medical therapy is more effective than medical therapy alone in the management of PSD. Sun et al performed an RCT comparing patients receiving acupuncture and Fluoxetine versus acupuncture alone.<sup>83</sup> Anchored on the midnight-noon ebb-flow theory, the *ziwuliuzhu* technique in combination with an antidepressant was more effective at alleviating mood symptoms than acupuncture alone.<sup>84</sup> The same trend was observed in a single-blinded randomized control trial comparing PSD patients undergoing wrist-ankle acupuncture in combination with fluoxetine therapy versus sham control and fluoxetine treatment.<sup>85</sup> Using depression and quality of life scales as outcome measures, the treatment group demonstrated greater improvement in depressive symptoms compared to controls.<sup>85</sup> Another novel acupuncture technique that has been explored is the dense cranial electroacupuncture stimulation (DCEAS).<sup>86</sup> This involves the principle of deep brain stimulation and delivers electrical activity at forehead acupoints, directly activating the sensory afferent pathways of the trigeminal nerves.<sup>86</sup> Patients who received DCEAS in combination with SSRI and body electroacupuncture had better outcomes as measured by the Hamilton Depression Rating Scale (HAM-D-17) and the Clinical Global Impression-Severity scale (CGI-S), and improvements have been noted as early as one week post treatment.<sup>86</sup> Two recent meta-analyses in 2019 and 2020 corroborate these findings, concluding that acupuncture combined with conventional drug therapy is more effective versus standard antidepressant alone.<sup>87,88</sup> However, both studies recommend higher quality RCTs to increase confidence for recommendation. To date, the American Heart Association (AHA) recommends acupuncture as an add-on management for post-stroke complications such as dysphasia and shoulder pain, but not specifically for post-stroke depression.<sup>89</sup>

## Light Therapy

Light therapy is considered a traditional form of Western Medicine and has been extensively used in the 19th century in the management of various diseases.<sup>90</sup> In the modern day, this is otherwise known as brain photobiomodulation therapy and has been used in the management of various neuropsychiatric conditions.<sup>91,92</sup> The antidepressant effect of light therapy lies in its effect on the retino-geniculo-habenular pathway, circuitry likely involved in depression and other mood disorders.<sup>93</sup> At the molecular level, light therapy stimulates ATP synthesis via the mitochondrial respiratory chain and activates various pathways leading to neuronal and synaptic regeneration.<sup>94</sup> Sondergaard et al were the first to explore the utility of light therapy in PSD (Sondergaard). In a randomized, double-blind study, the effect of high versus medium intensity artificial light therapy was evaluated among PSD patients taking escitalopram.<sup>95</sup> Results showed that month-long high dose light therapy was more effective in the improvement of PSD symptoms than controls.<sup>95</sup> Among admitted stroke patients, researchers from a Danish hospital observed that those receiving circadian lighting or the blue light spectrum had significantly lower Hamilton Rating Scale for Depression (HAM-D6) and Major Depression Inventory scale (MDI) scores post treatment.<sup>96</sup> Alternatively, natural light exposure has also been shown to produce the same effects. Consistent sunlight exposure for at least 30 minutes per day for at least 14 days has been associated with improvement in the depression scores among Taiwanese patients.<sup>97</sup> Not only does it improve mood among PSD patients, but light therapy has also likewise been shown to ameliorate insomnia in the same subset of patients.<sup>98</sup> This is also very well tolerated with treatment-related adverse effects not significantly different from controls.<sup>98</sup> While it is a generally safe treatment regimen for a variety of affective disorder, its use in PSD to date remains exploratory.

## Music Therapy

Music therapy is another technique widely used in neurorehabilitation and is an accepted therapy for patients with mood disorders and other acquired brain injuries. It capitalizes on the principles of neuroplasticity by multisensory stimulation and consolidation of inputs from the frontal, parietal, temporal and occipital regions.<sup>99</sup> Music medicine interventions are distinct from recreational music as the former usually involves a professionally trained music trainer who implements

a specific type of music at the range of rhythmic auditory stimulation tailored to every patient's experiences and needs.<sup>100</sup>

There is considerable information on the beneficial effects of music therapy for PSD. Sarkamo et al looked at how music impacted the mood of patients with middle cerebral artery infarcts in the acute setting.<sup>101</sup> This single blind RCT reported that, among 60 patients involved in the study, there was a greater trend to improvement in depression in the intervention group than in controls at the end of three and six months, but this did not reach statistically significant differences.<sup>101</sup> It is likely that the concomitant improvement in physical function and fine motor skills of patients within the acute to subacute period after undergoing music therapy contributes to the improvement of their mood and their sense of well-being.<sup>102,103</sup> In the subacute to chronic post-stroke period, Korean stroke patients were likewise subjected to 40-minute structured music therapy in a four-week period.<sup>104</sup> Depression scores as measured by the Beck Depression Inventory were lower in those participating in these sessions.<sup>104</sup> The authors argued that this is likely related to how music also helps improve anxiety and pain perception.<sup>104</sup> It appears that other forms of music therapy are also equally effective. Among Indonesian PSD patients, 30 minutes of instrumental music therapy in combination with standard home-based therapy was found effective at PSD alleviation.<sup>105</sup> In the same way, mindfulness music, which integrates a brief period of mindfulness exercises, has also been shown to be beneficial.<sup>106</sup> Additionally, traditional Chinese music following a five-phase music therapy has also been evaluated regarding its impact on affective disorders post-stroke.<sup>107</sup> When combined with acupuncture, it provides more substantial reduction in depression scores among post-stroke patients.<sup>107</sup> While the results of these studies are promising, a systematic review found that these studies are underpowered to assess efficacy.<sup>108</sup> Furthermore, they reported significant heterogeneity between studies, which may preclude bias-free conclusions.<sup>108</sup> The same findings were documented in a Cochrane systematic review on the effect of music interventions in acquired brain injury including stroke.<sup>100</sup> Clearly, more well-controlled clinical trials are needed to allow unbiased conclusions to be formed.

## Art Therapy

Art therapies are unrecognized regimens which may regardless be useful for PSD patients. Art therapy has been deemed particularly helpful for post-stroke patients as it provides them a method of venting conflicts and emotions, thus alleviating their mental and emotional concerns.<sup>109</sup> Its utility in neurorehabilitation is based on the Hebbian principle of neuroplasticity, in which multimodal stimulation initiates neuronal activation leading to increased synaptogenesis.<sup>110</sup> Kongkasuwan et al demonstrated that creative art therapy provided in an inpatient group setting significantly improved post-stroke patients' mood, physical function and quality of life.<sup>111</sup> In addition, positive changes in concentration, emotion, self-confidence and motivation were also appreciable among patients subjected to art therapy.<sup>111</sup> Color therapy was also used in a cohort of Korean post-stroke patients in another study seeking to determine whether it impacted their "purpose in life".<sup>112</sup> In this study, a color transition was observed from monochromatic choices and colors of low tone early in the course of therapy to polychromatism and use of increased color tones towards the end of the rehabilitation period among patients with PSD.<sup>112</sup> This pattern of color transition seems to correlate with improvement in their purpose in life objective measures.<sup>112</sup> Interestingly, iPad art therapies seem to provide benefits as well regarding PSD. In a study by Ali et al, they demonstrated that art therapy supervised by psychotherapists over a six-week period provided some improvement in the Hospital and Anxiety Scores (HAD) of enrolled patients. While this exploratory study only involved six patients, the authors propose that this technique is feasible and should be further explored in a larger population.<sup>113</sup>

## Conclusion

Non-pharmacologic interventions are an essential adjuvant in the management of post-stroke depression. These regimes work by activating pre and postsynaptic connections in the juxta and regions remote from stroke lesions, facilitating neuroplasticity and neuronal reactivation. Interventions such as non-invasive brain stimulation, acupuncture, behavioral and psychosocial approaches have been incorporated in some clinical guidelines while exercise, music, light, and art therapy remain investigational. While the effects of non-pharmacologic interventions are promising, more robust, large-sample studies are necessary to evaluate its efficacy in the short or long term. There is also a need to explore further on whether these interventions are effective as monotherapy or adjunctive treatment to antidepressant medications.

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