Current Neuropharmacology, 2022, *20*, 738-750

REVIEW ARTICLE

Potential Mechanisms and Clinical Effectiveness of Acupuncture in Depression

Na-Na Yang[1], Lu-Lu Lin[1], Yue-Jie Li[1], Hong-Ping Li[1], Yan Cao[1], Chun-Xia Tan[1], Xiao-Wan Hao[1], Si-Ming Ma[1], Lu Wang[1] and Cun-Zhi Liu[1,*]

[1]*International Acupuncture and Moxibustion Innovation Institute, School of Acupuncture-Moxibustion and Tunia, Beijing University of Chinese Medicine, Beijing 100029, China*

ARTICLE HISTORY

Received: February 27, 2021
Revised: May 05, 2021
Accepted: May 10, 2021

DOI:
10.2174/1570159X19666210609162809

Abstract: Major depressive disorder is the most common mental disorder with significant economic burden and limited treatments. Acupuncture has emerged as a promising non-pharmacological treatment for reducing depressive symptoms. However, the potential mechanisms and clinical effectiveness of acupuncture are not fully understood. This review aimed to: (1) summarize the available evidence on the mechanisms and clinical effectiveness of acupuncture for depression, and then (2) compare with pharmacological interventions, guiding future studies. Studies with animal models of depression and patients have shown that acupuncture could increase hippocampal and network neuroplasticity and decrease brain inflammation, potentially to alleviating depressive disorders. Overall clinical studies indicated that acupuncture could relieve primary depression, particularly milder cases, and was helpful in the management of post-stroke depression, pain-related depression, and postpartum depression both as an isolated and adjunct treatment. It was emphasized that acupuncture combined with antidepressant pharmacological treatment not only enhanced the improvement of primary and secondary depressive symptoms but also reduced the side effects of the medical treatment, which is the main cause for high dropout rates with drug treatment. In summary, substantial evidence from animal and human researches supported the beneficial effect of acupuncture in depression. However, most clinical trials of acupuncture were small, and it is unclear whether their findings can be generalized, so more studies are needed.

Keywords: Depression, acupuncture, pharmacological treatments, neuroplasticity, inflammation, non-pharmacological treatment.

1. INTRODUCTION

As the most severe psychiatric disorder, depression is the primary cause of disability worldwide. The World Health Organization predicted that it would become the greatest cause of global disease burden by 2030 [1]. The clinical symptoms include anhedonia, fatigue, negative emotions [2, 3], and the vulnerability of physical illness, such as stroke, pain, cancer, and others [4, 5], which lead to the poor response to pharmacological treatments. The standard drug treatments (mainly selective serotonin reuptake inhibitors (SSRIs)) for depressive disorder are not entirely satisfactory due to undesirable side effects and delay the onset of action [6, 7]. Regardless of the high incidence of depressive disorder or the high rate of suicide and treatment-resistant that would draw public attention to depression, new strategies to enhance the efficacy of antidepressants in the early stage of treatment are greatly in need.

Acupuncture is a promising non-pharmacological treatment for reducing depressive symptoms, which can be alternatives to pharmacological treatment or complementary treatment to improve the outcomes [8]. Compared with pharmacological treatments, acupuncture has the advantages of low cost and minimal side effects [9]. In addition, growing evidence have indicated that acupuncture plus drug treatment is more effective than the drug alone, is safe, well-tolerated, and has an early onset of action, which embodied the potential benefits of combining acupuncture and pharmacological treatments for the depressive disorder [7]. Given the growing body of literature on the effectiveness and neurobiological pathways underlying acupuncture for major depressive disorder, it is time to synthesize and review the available evidence on the mechanism and clinical effectiveness of acupuncture for depression in comparison to pharmacological interventions consolidating its effectiveness and guiding future studies.

*Address correspondence to this author at the International Acupuncture and Moxibustion Innovation Institute, School of Acupuncture-Moxibustion and Tuina, Beijing University of Chinese Medicine, No. 11 Bei San Huan Dong Lu, Chaoyang District, Beijing 100029, China;
E-mail: lcz623780 @126.com

1875-6190/22 $65.00+.00

2. METHOD

We searched PubMed, Web of Science, and Embase. The searches identified English language papers published from the database establishment up to the present time. Keywords included "acupuncture" or "electroacupuncture" or "EA", and "depression" or "mental disorder" or "psychological disorder" or "emotional". After carefully evaluated, the information presented in the following studies was described and discussed.

3. IDENTIFYING ACUPOINTS AND STIMULATION

As an isolated and adjunct treatment, acupuncture has been emerging as a potential therapeutic regimen to treat depression with two main styles, acupuncture (manual) and electroacupuncture. Manual acupuncture, which is typically used in clinical practice, is the traditional method of penetrating a thin and metallic needle into acupoint through the skin and then manipulating by hands, such as lifting, thrusting, twisting, and others. The acupoint stimulation with the electrical current instead of manual manipulations is called electroacupuncture. Compared with manual acupuncture, electroacupuncture can generate more consistent and reproducible results. Therefore electroacupuncture is the most commonly used method in clinical trials and laboratory research.

With respect to the Yellow Emperor's Internal Classic, meridian and acupoint are the unique systems in the circulation of energy channels [10]. Governor Vessel was the most popular meridian in depressive disorder as it is the only meridian of the fourteen meridians to connect the head and brain directly [11,12]. In this meridian, Baihui (GV20), Yintang (GV29), and Shenting (GV24) are often used points to promote recovery of depressive disorder. Besides, Liver Qi stagnation contributed to the etiology of depression, causing symptoms like mental stress, down in spirits and activities, and low self-esteem [13]. Xingjian (LR2), Taichong (LR3), and Qimen (LR14) in Liver Meridian are the points of the standard acupuncture protocol to regulate Liver Qi movement. In summary, the application of meridians and acupoints for depression lays emphasis on the head acupoints (such as GV20, GV29, and GV24) and extremities (such as LR3 and LR2). It makes good use of superior-inferior acupoints matching.

4. PROPOSED MECHANISMS OF ACUPUNCTURE FOR DEPRESSION

Depression is a heterogeneous disease with multi-pathophysiological mechanisms, including neuroplasticity and inflammation that generated various symptom patterns [14]. Although different animal models of depression have been used for many years in experiments, a credible and reasonable animal model can perfectly reproduce the depression-like phenotype of human has yet to be found [15]. Different modeling methods produce different selectivity upon antidepressants with both advantages and disadvantages [16]. For example, the reserpine-induced model has low reliability but high efficiency [17]; meanwhile, the learned helplessness model, chronic mild stress model, and social defeat stress model are high specificity but easily affected by subjective impacts and environmental impacts with high mortality rate [16, 18]. Therefore, the underlying pathophysiology of depression may be multifactorial and involved several factors, which is difficult to predict the therapeutic effect using only a single model [14]. The current pharmacological treatment of depression, targeting a single point, is far from perfect. The changing of synaptic plasticity [19] and the imbalance of the immune system [20, 21] are gradually accepted as the key players in the pathogenesis of depression.

Acupuncture, as a comprehensive treatment in depression, has the potential to alleviate depressive symptoms by targeting neuronal and synaptic remodeling and immune response. Therefore, acupuncture may be a promising treatment for major depressive disorder arising from various mechanisms.

4.1. Targeting Neuroplasticity in Depression

Although the cause of depression is not yet clear, the brain played an important role in the pathogenesis of depression. The changes of neural circuits or chemical balance in the brain were thought to be the physiological abnormalities that directly caused depressive symptoms [22]. A multitude of neuroimaging studies found that there were abnormal structure and function in specific brain regions or connections, where they were associated with the process of cognition and emotion, including the hippocampus [23], medial prefrontal cortex (mPFC) [24], anterior cingulate cortex (ACC) [25], amygdala [26], and nucleus accumbens (NAc) [27]. Besides, the changing of these regions could affect the symptoms of depressive disorder [14, 28-31]. The reduction in hippocampal volume, which was related to the duration of depression (Fig. **1A**) and was inversely proportional to the length of treatment [32], was reversed by antidepressant treatment [33]. Changed structure and function of these specific brain regions had the potential to alter connectivity [34], such as default-mode network (DMN) [35], ACC-thalamus [36], prefrontal-limbic-thalamic [37], and others, which suggested that alterations in the connections of multiple neuronal circuits were risk factors for the development of depression pathologies.

Growing evidence implicated the importance of underlying cellular changes, which lead to the reduction of volume in brain regions. Neuroplasticity is probably especially pertinent in regulating the structure and function of neuronal networks *via* various pathways, including promoting neurogenesis and modulating the synapse connections [38, 39]. The decreased gene expression of glutamate was observed in both the PFC [40] and hippocampus [41] by microarray gene profiling, leading to the loss of excitatory synapses. Similarly, the size of the neuronal cell, but not cell numbers, was also decreased in PFC and hippocampus through postmortem studies [42], indicating that the synaptic contacts and processions between neurons were decreased in major depressive disorder.

Compared with sham acupuncture treatment, the acupuncture increased resting-state functional connectivity (rsFC) between the left amygdala and ACC or right amygdala and left hippocampus, which was positively correlated with corresponding clinical improvement, indicating that the

therapeutic effect of acupuncture was mediated by the limbic system, especially the amygdala and the ACC [43]. Similarly, another randomized controlled trial (RCT) also found that acupoint stimulation could decrease the clinical depressive scores after eight-week treatment, mainly through increasing the rsFC between the inferior ventral striatum and mPFC, ventral rostral putamen, and amygdala/para-hippocampus [7], indicating that acupuncture altered corticostriatal reward/motivation circuitry to play therapeutic effects in depressive disorder.

Acupuncture may act in a variety of ways, such as stimulating biochemical pathways and restoring neuronal structures in patients with depression. No matter developing neurons and mature neurons, the monoamine neurotransmitter of serotonin (5-HT) always has a powerful influence on synaptic plasticity. When altered, it could lead to neurodevelopmental and psychiatric disorders [44]. Therefore, significant focus has been placed on 5-HT in the pathophysiology and treatment of depression. Electroacupuncture could regulate the 5-HT receptor and restore hippocampus CA1 synaptic plasticity, in turn, ameliorate depressive-like behaviors [45, 46]. Similarly, acupoint electro-stimulation had antidepressant efficacy, mainly or partly *via* improving the 5-HT receptor and upregulating the 5-HT content in synaptic gaps of brain regions (Fig. **1B**) [47].

Brain-derived neurotrophic factor (BDNF) not only regulates neural structural plasticity by promoting the growth, reconstruction, and synaptic formation of axons and dendrites but also affects neural functional plasticity by altering synaptic transmission through presynaptic and postsynaptic mechanisms [38]. Electroacupuncture at GV20 and GV29 acupoints could ameliorate the depression-like behaviors and markedly promoted nerve regeneration by increasing BDNF expression in the hippocampus [48]. In addition, acupuncture at Shenmen (HT7) also upregulated the expression of BDNF in the PFC, suggesting that acupuncture has neuroprotective effects in depression *via* up-regulating BDNF (Fig. **1B**) [48-51].

4.2. Targeting Immune System and Inflammation in Depression

In the central nervous system (CNS), microglia is the main factor responsible for the physiology and pathology in the innate immune [52]. Microglia shifts from immune surveillance to an activated state under pathogen infection or synaptic and neuron damage in some diseases (Fig. **1C**). When active, microglia not only was the hyper-ramified phenotype [53, 54] but also exhibited an amoeboid morphology to invade lesions in protecting the host against harmful microorganisms [55]. Not surprisingly, long-term activation of microglia also led to immune pathology, mainly with the overwhelming production of various neurotoxins, including inflammatory cytokines, nitric oxide, and others [56], ultimately aggravating neuronal damage [57]. The receptor of translocator protein which were labeled with radioligands, was highly expressed in activated microglia [58]. In a positron emission tomography (PET) study, this radioligand in PFC, ACC, and insula was significantly increasing [59], suggesting that the proportion of activated microglia was elevated in these brain regions. As such, it's gradually recognized that activated microglia are the core of the pathophysiology of depression.

Behavioral symptoms caused by infection or inflammation are mainly evoked by inflammatory cytokines in peripheral tissues, which directly acted on the CNS *via* leaky regions of the blood-brain barrier (BBB) [60, 61] (Fig. **1D**). In recent decades, a significant focus has always been placed on the monoamine depletion hypothesis, which indicated that the imbalance of serotonergic and noradrenergic neurotransmission plays a key role in the pathogenesis of mood disorders [62]. The interaction between inflammation and brain-immune could induce the imbalance of serotonergic and noradrenergic neurotransmission, which was involved in the occurrence and development of depressive disorder [63]. Activated microglia produced a variety of proinflammatory cytokines in response to inflammation and stress, resulting in the neurodegeneration and depressive behaviors through two different pathways: (1) evoking the imbalance of serotonergic and noradrenergic neurotransmission through the hypothalamic-pituitary-adrenal axis (HPA); (2) decreasing the level of 5-HT *via* increasing the activity of the enzyme indoleamine-2,3-deoxygenase (IDO) (Fig. **1C**). Additionally, the persistent inflammatory response was also associated with the unresponsiveness of antidepressant treatment [64]. The imbalance of immune response in the peripheral or central system was considered as another cause in the development of depression. Therefore, targeting inflammation may be a promising therapeutic avenue.

Acupuncture significantly improved sucrose preference and locomotor activities of depressive rats and decreased pro-inflammatory cytokine serum levels [65]. The stimulation of the vagal nerve (VNS) is a long-term adjunctive treatment for severe depressive disorder, which was approved by the US Food and Drug Administration in 2005 [66]. Acupuncture, as a non-invasive method of VNS, may be a potential therapeutic regimen to treat the inflammatory response in depression [67, 68]. The α7nAChR, which is activated by acetylcholine released from the cholinergic nerve endings, is the crucial target for attenuation of proinflammatory cytokines released from macrophages [69]. Acupuncture could activate the α7nAChR to reduce the production of inflammatory cytokines *via* the vagal nerve [70]. It was naturally postulated that acupuncture is a promising non-pharmacology treatment for depression through the exciting vagal nerve to suppress the inflammatory responses in the peripheral and central systems.

Growing evidence implicated the importance of gut microbiota permeability in accelerating the production of proinflammatory cytokines in depressive patients (Fig. **1E**). Compared with healthy controls, gut macrobiotic compositions were significantly different in major depressive disorder [71]. Meanwhile, depressive patients had a marked increase of IgM and IgA in serum compared with healthy individuals, which suggested invasive enterobacteria had more opportunities to induce the inflammatory response in the peripheral and central systems *via* increasing gastrointestinal permeability [72]. Similarly, rats that received fecal microbiota from patients with depression exhibited depression-like behavior and decreased hippocampal neurotransmitters, increased pro-inflammatory cytokines in serum and damaged of the

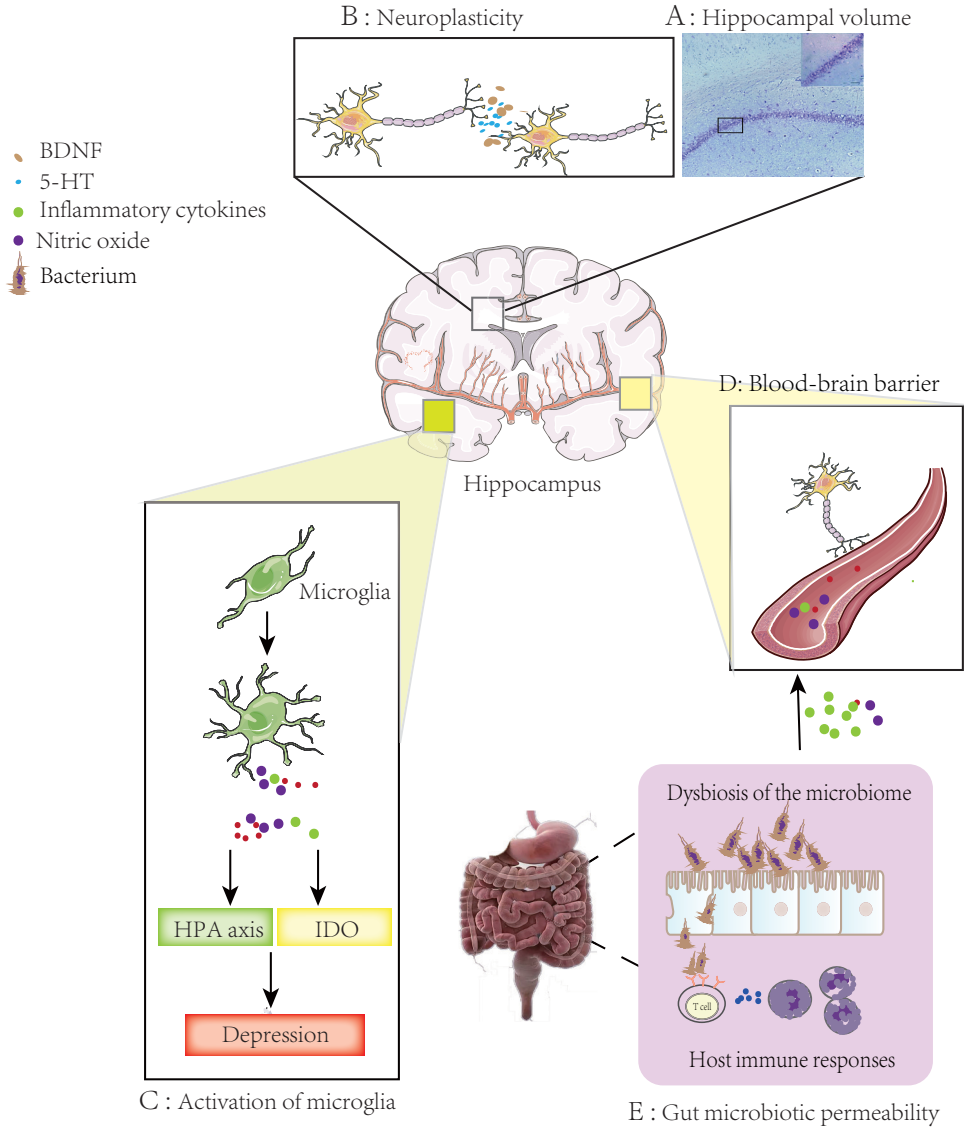

Fig. (1). Hypothesis of neuroplasticity and immune involvement in the pathophysiology of major depressive disorder. The reduction in hippocampal volume was related to the duration of depression (**A**). The synaptic contacts and processions between neurons were decreased in major depressive disorder, which can be reversed by upregulating the expression of 5-HT and BDNF (**B**). Activated microglia produce inflammatory cytokines and nitric oxide that can contribute to depression through hyper-activation of the HPA axis and IDO (**C**). Gut microbiotic permeability accelerated the production of inflammatory cytokines in peripheral tissues (**D**), which act directly on the CNS *via* leaky regions of the brain-brain barrier (**E**). 5-HT, serotonin; BDNF, Brain-derived neurotrophic factor; HPA, the hypothalamic-pituitary-adrenal axis; IDO, the enzyme indoleamine-2,3-deoxygenase. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

intestinal epithelial cells [73]. Meanwhile, acupuncture could adjust the count and proportion of the intestinal microbiota to recover its stability and ameliorate the intestinal barrier function by promoting the interaction between intestinal microbiota and brain-gut axis and then suppressing the production of pro-inflammatory cytokines [74, 75]. The vagal nerve connects the brain and gastrointestinal tract, indicating that it not only modulates the depression-associated brain regions or circuits (*e.g.*, amygdala, PFC) but also suppresses the systemic and central inflammation *via* different neuropathways (*e.g.*, splenic nerve) [76]. Therefore, we proposed an assumption that acupuncture may act on the following two pathways to suppress the inflammation and ameliorate depression: (1) inhibition of the release of inflammatory cytokines by activating the vagal nerve; (2) regulation of the brain-gut axis through intestinal microbiota.

Besides, endorphin has been found to suppress the function of macrophages, natural killer cells, and T cells in order to control inflammatory and neuropathic pain [77]. Acupuncture has been demonstrated to relieve pain and enhance the healing process by releasing corticosteroids and enhancing endogenous opioids in central and peripheral nervous systems, such as dynorphin, endorphin, encephalin [78]. There is a plausible assumption that acupuncture could increase endorphin expression, which suppressed the inflammation

via μ-opioid receptors, in turn, ameliorated depression [79], especially in post-stroke depression (PSD) and pain-related depression (PRD), which were associated with inflammation. Endorphins have been linked to cases of mental illness, including autism, depression, and depersonalization disorder, as well as to activities such as laughter and vigorous aerobic exercise [80], indicating that the release of endorphins could directly ameliorate depressive disorder, rather than through inflammation. Levels of microglial activation in primary depression have been shown to be low both at post-mortem and on PET imaging [81], which demonstrated that inflammation was more likely to be reactive than causative. The increasing of endorphins release in individuals may be another acceptable explanation for the beneficial effects of acupuncture in primary depression.

4.3. Summary

In this review, we found out that the primary cause of depression is brain inflammation and BBB disruption, which caused a neuronal loss in brain regions (especially in hippocampus), reduced monoaminergic levels, and impaired brain network connectivity. Studies with animal models of depression and patients have shown that acupuncture can increase brain regions and network neuroplasticity and decrease brain inflammation, in turn, have the potential to alleviate the depressive disorder.

5. CLINICAL EVIDENCE FOR ACUPUNCTURE ON DEPRESSION

From a clinical perspective, the depressive disorder can be divided into different subtypes, such as primary depression and secondary depression. An 8-week controlled clinical study with 60 patients to compare the effects of electroacupuncture and SSRIs in depressive patients found that electroacupuncture showed greater improvement in global clinical impression, anxiety/somatization, and feelings of despair than SSRIs [82]. Besides, an RCT compared SSRIs alone versus SSRIs together with manual acupuncture or electroacupuncture in 477 moderate to severely depressed patients [83], identifying that compared with SSRIs alone, both manual acupuncture and electroacupuncture were significantly better on 17-item Hamilton Depression Rating Scale (HDRS) response rate, HDRS-17 early-onset rate, Self-Rating Depression Scale (SDS), Clinical Global Impression (CGI) and Rating Scale foe Side Effects (SERS), indicating that acupuncture have therapeutic effects in addition to SSRIs alone in patients with moderate to severe depression, and was well tolerated. Similarly, several high-quality RCTs also found that acupuncture may be not only a safe adjunctive treatment with antidepressants but also more effective in improving depressive symptoms [84, 85]. Although growing evidence indicated that acupoint stimulation was a very promising treatment for primary depressive disorder, there was still insufficient evidence to determine the efficacy of acupuncture due to lacking well-designed studies.

A significant focus of acupuncture has been placed on secondary depression, which has a similar pathophysiological mechanism to primary depression. Indeed, the depressive disorder has been associated with a significant reduction in life expectancy, partly due to suicide, and the rest resulting from a significant increase in the likelihood of major illness, including cardiovascular disease, stroke, cancer, and other conditions. Meanwhile, physical diseases also contributed to the development of depression. Therefore, multi-target therapy may be a promising avenue for the treatment of secondary depression. Among secondary depressive disorders, PSD, PRD, and postpartum depression (PPD) are the most common diseases in acupuncture. Based on current procurable evidence, the significant effects of acupuncture in ameliorating depression were manifested in patients compared with both usual care and waiting-list.

5.1. Post-stroke Depression

PSD is the most common neuropsychiatric consequence of stroke, afflicting around 33% of stroke survivors [86]. Depressive disorder is a high-risk factor for stroke, which seriously affects patients' attitude towards disease treatment, reduces the quality of life, increases the chance of recurrence of neurovascular events, poor functional recovery, and high morbidity and mortality [87]. A meta-analysis in 2019, which involved 15 prospective cohort studies with a total of 250,294 participants followed from 1 to 15 years, showed that PSD is a highly prevalent risk factor for a marked increase in mortality among stroke patients [88]. Meanwhile, somatic disability may further promote the development of depressive behaviors. While actively and effectively controlling the primary disease, efforts should also be put into improving patients' psychological and social function. Therefore, the use of antidepressant pharmacotherapy in the early stage of stroke could not only reduce the prevalence of depression [89-91] but also give patients a positive attitude toward treatment and then promote long-term functional recovery after stroke [92, 93]. Clinical evidence showed that acupuncture could improve PSD-related symptoms.

A system review involving 31 trials with 2,257 participants in the subacute or chronic stages of stroke found that acupuncture had therapeutic effects on the improvement of depression and dependency, global neurological deficiency, and some specific neurological impairments [94]. For PSD, a meta-analysis including 7 trials with 514 participants found that acupuncture had a significantly higher treatment effect than controls in symptoms of PSD, with low study heterogeneity. Besides, subgroup analysis further showed that acupuncture alone was superior to medication in improving depression-associated symptoms, but was no statistically significant difference between acupuncture combined with medicine groups [95]. Likely, an overview of systematic reviews with meta-analyses on acupuncture in PSD research, including four systematic reviews and ten systemic reviews with good methodological quality, revealed that compared with an antidepressant, acupuncture significantly reduced the score of HDRS after two weeks of treatment and acupuncture usage was not associated with increased risk of adverse events [96]. This review suggested that acupuncture is safe and improves cognitive function and depressive disorder without obvious serious adverse events for PSD. Therefore, the promising efficacy and safety of acupuncture on PSD patients have been confirmed by several systemic reviews and meta-analyses.

A population-based cohort study recruited 8,487 stroke patients, of whom 1,036 patients received more than five post-stroke acupuncture stimulations, 1,053 patients received 1-5 times, and 6,398 did not receive acupuncture. This study showed that acupuncture might lower the risk of PSD by 52.5% and 28.2% in frequent and infrequent acupuncture users, respectively [97]. These results provided powerful evidence to support the viewpoint that post-stroke acupuncture significantly decreased the risk of depressive disorder. In a study, 58 participants with ischemic PSD received acupuncture and placebo starch tablets treatment or fluoxetine tablets add body acupuncture treatment during a 12-week intervention period, found that both acupuncture and fluoxetine could reduce the depressive scores, but the former had no obvious adverse reaction and side effects [98], indicating that the effects of acupuncture were comparable to first-line treatments in PSD patients

5.2. Summary

Psychological stress associated with a physical disability may lead to the occurrence of PSD, and depression could worsen stroke behaviors. Therefore, PSD is of high clinical importance. Despite the familiar occurrence of PSD with impressive medical expenses and poor quality of life, the current treatment options are limited. A meta-analysis in 2019, which identified a total of 63 eligible trials recruiting 9,168 participants, found that no reliable evidence supported the view that routinely using SSRIs could markedly improve the physical recovery after stroke [99]. In contrast, most studies supported that the effects of acupuncture were comparable or even exceeded the pharmacological treatment in PSD, indicating that acupuncture may be more suitable for treating PSD without serious complications. The robust effects of acupuncture on PSD, at least in part, could be explained by multiple therapeutic targets for stroke patients. In addition to the antidepressant mechanisms mentioned above, acupuncture treatment also improved stroke rehabilitation and global or specific neurological deficits, whose improvements have been found to be greatly helpful in reducing depressive symptoms in stroke patients [94, 100]. Therefore, acupuncture was comparable or superior to antidepressants in improving both response and symptom severity of PSD with low adverse, which can be considered as an alternative option in PSD patients.

5.3. Pain-related Depression

Depression and pain are the most common debilitating diseases that have a powerful impact on society as a whole [101]. Nearly 80% of patients with chronic pain have depression at the same time [102], which markedly reduced the quality of life and led to the occurrence of high mortality [103]. RCTs reported that compared with patients without pain, these patients with pain were more likely to report depression [104, 105].

However, the majority of patients with depression and pain comorbidities did not respond to pharmacological treatments for pain or depression, all of which significantly made this co-morbidity disorder to reduce the quality of life and then impose a heavy burden on society [106]. Multitarget of depression and pain may be an attractive target for therapeutics. Acupuncture, as a unique treatment of traditional Chinese medicine, played a therapeutic role through multiple targets, such as both treating pain and improving depression. Therefore, acupuncture has been reported as a potential alternative treatment for patients with depression and pain comorbidities.

A systematic review that recruited 7 available RCTs with 535 patients in 2020 found that compared with medicine therapy, acupuncture significantly decreased the scores of pain and depressive symptoms assessing by Visual Analogue Scale (VAS) and HDRS, separately, and lower side effects in PRD patients. This review supported the view that acupuncture can be used in patients with poorer responses to conventional medical therapy or suffering from serious side effects [107]. Similarly, another systemic review and meta-analysis with 8 studies (636 participants) in 2021 showed that single acupuncture treatment and drug treatment had the same effects in improving the HDRS score and alleviating the VAS score, but acupuncture was safer. In addition, acupuncture combined with drugs was more beneficial in HDRS score and VAS score [108]. These systematic reviews supported the view that acupuncture is an effective and safe treatment for PRD, and acupuncture combined with drug therapy is more effective than single-drug therapy.

A clinical study recruited 270 patients with episodic or chronic tension-type headaches who were randomly divided into the waiting-list group, acupuncture group, and minimal acupuncture group (superficial needling at non-acupuncture points) with 12 sessions over eight weeks. This clinical study found that compared with the waiting-list group, acupuncture fared significantly better for the pain and depression assessment by the Allgemeine Depressionsskala scale (ADS) after 8-week treatment. However, the efficacy of acupuncture and the minimal acupuncture group was no significant different [109]. However, He *et al.* found that compared with sham acupuncture, acupuncture also reduced pain intensity of pain and depressive behaviors in 24 patients with chronic neck and shoulder pain [110]. In this study, patients were randomly assigned to an acupuncture group or sham acupuncture group (sham points) for 10 times during three to four weeks. After treatment, acupuncture improved the pain and depression compared with sham acupuncture, which was again significantly different at 6 months and 3 years follow-ups. A secondary analysis of an RCT with 755 patients also found that acupuncture was most marked in the reduction of depression and pain compared with counseling or usual care [111].

5.4. Summary

Depression is explained as an emotional state, which is different from physical pain. However, a multitude of clinical studies has shown that depressive disorder and pain have a high degree of comorbidity, which will increase the health burden and affect the quality of life. Acupuncture has been increasingly accepted as an integrative or complementary treatment for pain with little risk of serious adverse [112]. Concomitant with the rising use of acupuncture in pain, the comorbidities of depression and pain are drawing public attention. In most cases, acupuncture was effective for both depression and pain. Despite the interest, most studies fo-

cused on pain, and very little work has addressed depression and its causal relationship to pain in the treatment of acupuncture. Current studies indicated that compared with medical treatment, acupuncture has therapeutic effects in reducing pain and relieving symptoms of depression in patients with PRD.

5.5. Postpartum Depression

PPD, one of the most common mental disorders associated with childbirth, usually occurs between the first day and four months after giving birth [113]. It clinically presented as low energy, extreme sadness, irritability, and suicidal tendencies [114]. When pregnant women suffered from depressive disorder, there were tangible but subtle negative effects on newborns, including increasing the incidence of violence during adolescence or adulthood [115]. Pharmacological treatments are the standard therapy for major depressive disorder. However, the majority of postpartum women are unwilling to take medicine, mainly or partly due to its serious adverse effects and addictiveness [116]. The tolerability and safety of treatment play a key role in compliance. In the majority of studies, acupoint stimulation was easily tolerated, and the undesirable side effects were rare. Acupuncture was acceptable to pregnant women who were not utilizing conventional approaches, as well as an adjunct for those using standard depression therapeutics. Therefore, it may be more suitable to receive the treatment of acupuncture for depression in postpartum women.

A meta-analysis involving 12 RCTs recruited 877 PPD patients, of whom 443 patients received acupuncture treatment, and 444 patients were in the control group. This study found that compared with the control group, the patients who received acupoint stimulation had more significantly improved depressive symptoms, assessed by the HDRS [117]. A systematic review and meta-analysis involving 8 prospective trials with 517 participants also found that acupuncture decreased the score of depression but no beneficial effects in clinical response and estradiol [114]. By contrast, another systematic review and meta-analysis including 9 trials with 653 women demonstrated that compared with the control group, acupuncture could obviously improve the overall effective rate and increase oestradiol levels, but there was no difference in depression [118].

An RCT involved 57 PPD patients found that compared with muscle relaxation or usual care, there was a significantly lower depression score after acupuncture treatment without adverse event [119]. Similarly, another trial with 150 PPD who were randomized to receive either acupuncture specific for depression or one of two active controls: control acupuncture or massage, also found that compared with the control group, acupuncture got a greater rate of decrease in symptom severity and response [120]. Some small but reliable studies also demonstrated the therapeutic effect of acupuncture in PRD patients. A study of prospective case series enrolled 15 PPD patients to receive acupuncture therapy with 20 min for one session and eight times for 4 weeks. Compared with six patients who did not finish this treatment, nine patients who completed treatment had more obvious improvement of pain and depression [121]. However, a double-blind RCT involving 20 PPD women who received electroacupuncture or non-invasive sham acupuncture two sessions weekly for four weeks found that electroacupuncture and sham acupuncture both reduced the score of HDRS, Edinburgh Postnatal Depression Scale, Hospital Anxiety and Depression Scale and Clinical Global Impression and was no significant difference between two groups [122].

5.6. Summary

Compared with pharmacological treatment, acupuncture may be reasonable to consider for women during pregnancy or postpartum due to fewer adverse effects. Pregnant women suffering from depression are willing to try acupuncture, despite having little prior knowledge of it, indicating that there is an increasing demand for acupuncture in the PPD field. In recent years, four systemic reviews evaluated the efficacy and safety of acupuncture for PPD [114, 117, 118, 123], and they all indicated that acupuncture was effective for PPD patients. While there is a risk of bias associated with acupuncture, general consensus suggests that the benefits of acupuncture outweigh the drawbacks.

6. ACUPUNCTURE *VS.* PHARMACOLOGICAL TREATMENTS

6.1. Acupuncture may be more Effective or Suitable in Some Depression

Antidepressant pharmacological treatment is the current standard of treatment for depression [124]. A host of high-quality RCTs supported the view that pharmacological treatment was superior to non-pharmacological treatments in major depressive disorder [125, 126]. However, the severity of baseline symptoms determines whether the medication was effective or not. Several meta-analyses of RCTs have compared pharmacotherapy with placebo to explore whether baseline symptom severity affected the efficacy of antidepressant pharmacological treatment. These studies found that the higher the severity of baseline symptoms, the better the efficacy of pharmacological treatment [127, 128]. Kirsch *et al.* extrapolated from their findings that the minimum baseline of HDRS score had to be greater than 23 for a clinical difference between pharmacological treatment and placebo. For baseline with a lower HDRS score, the clinical difference was able to negligible. Importantly, according to the American Psychiatric Association Taskforce for the Handbook of Psychiatric Measures, a score of more than 23 indicated a very serious depressive disorder [129]. In fact, a recent survey of depressed treatment-seeking outpatients found that 71% of the 503 patients assessed had HDRS score less than 22 [130], indicating that the magnitude of benefit of pharmacological treatment may be minimal or nonexistent in patients with mild or moderate depressive symptoms [129, 131].

Acupuncture, as a promising non-pharmacological treatment, has the protentional to treat mild or moderate major depressive disorder by regulating neuroplasticity and inflammation, and the therapeutic effects were comparative or might even exceed antidepressant pharmacological treatment. A multicenter, randomized, positive-controlled clinical trial enrolled 242 perimenopause women with the mild-moderate depressive symptom, who were randomly assigned

to received 36 sessions of electroacupuncture or escitalopram treatment. This study found that there was no difference between the two groups in depressive scores, menopause-specific quality of life, and serum sexual hormones [132], indicating that electroacupuncture was effective and safe in relieving depression symptoms and improving the quality of life. Similarly, a small RCT with 30 patients with mild to moderate depression who were randomized to receive active or inactive (sham) laser acupuncture found that compared with sham acupuncture, the decreasing of the depressive score was higher in laser acupuncture, indicating that acupuncture may be worth further investigation as a treatment for mild to moderate depression in primary care [133]. Therefore, acupuncture may be potentially effective monotherapy for mild to moderate depression.

There are improvements of depressive symptoms by medication in some special patients, including PPD and geriatric depression, and these improvements have also been seen in non-pharmacological treatment, including acupuncture [115]. Those patients may prefer non-pharmacological options because antidepressant pharmacological treatment also comes with considerable risks for harm, such as higher systolic and diastolic blood pressure, addictiveness. A prospective study with 15 patients diagnosed with mild PPD to explore the effects of acupuncture found that acupuncture alone could decrease the depressive scores and alleviate symptoms of mild PPD, with no side effects [121]. In conclusion, these findings indicated that compared with pharmacological treatments, acupoint stimulation is at least as effective as or possibly more suitable, with a very rare occurrence of side effects for mild to moderate depressive disorder or special depressive patients.

6.2. Acupuncture may be an Adjunct Treatment in Severe Depression

Severe depression, the most disabling form of depression, was commonly treated by second-generation antidepressants, such as SSRIs, which were recommended as the first-step therapy by most evidence-based guidelines [113]. In antidepressant pharmacological treatment, approximately 60% of patients respond well to medication. However, about 30% do not respond well. Besides, up to 63% of patients on second-generation antidepressants experienced adverse events [114]. The tolerability and safety of treatment play a key role in compliance; therefore, a large proportion of severe depressive patients were forced to abandon antidepressant pharmacological treatment in midway due to the undesirable side effects and end up with relapse and dysfunction [115].

In addition, accumulating evidence have demonstrated that acupuncture combined with antidepressant medication was more effective than antidepressants alone, and was safe, well-tolerated, and had an early onset of action [7]. A systematic review and meta-analysis involving 1,046 subjects in 13 RCTs shown that acupuncture in combination with SSRIs had a stronger antidepressant effect and an early onset of action and was safer and well-tolerated than SSRIs alone during the first six weeks of treatment [9]. Immune deregulation was associated with the unresponsiveness of antidepressant pharmacological treatment. Meanwhile, a growing body of evidence from RCTs found that compared with placebo, using anti-inflammatory medicine alone also significantly improved the depression [114], and acupuncture, as a non-invasive method of VNS, maybe a potential therapeutic regimen to treat the inflammatory response in depression [63, 64]. Meanwhile, acupuncture combined with SSRIs could significantly reduce HDRS-17 score in the first week compared with SSRIs alone, suggesting that the addition of acupuncture may shorten the onset time of SSRIs [12]. In addition to needing a long time to onset of action, typical monoamine reuptake inhibitor antidepressants required a longer time to effectively reverse the abnormal structure of depressive disorder [19]. Electroacupuncture showed therapeutic effects on neurogenesis by upregulating the proliferation of hippocampus progenitor cells [116]. These findings indicated that combination or augmentation strategies of antidepressants with acupuncture are more effective and have an early onset of action in severe depression

Acupuncture combined with antidepressant pharmacological treatment may have the potential to reduce the side effects of medical treatment, but it remains controversial due to limited research. Although acupuncture has been used to manage various physical symptoms that may present as side effects from antidepressants, including nausea [117], insomnia [9], weight gain, and sexual dysfunction [118], few studies have directly demonstrated that acupuncture could improve the side effects of antidepressants. Here, we found only a randomized, double-blind, double-dummy, sham-controlled trial to identify. In this study, 80 depressive patients were divided into acupuncture group (acupuncture, 10 mg/day fluoxetine plus 10-20 mg/day placebo) and sham acupuncture group (sham acupuncture and 20-30 mg/day fluoxetine). This research found no significant difference between the two groups in therapeutic response rates and depressive score, whereas the patients in the acupuncture group showed better improvement than the sham acupuncture group in side-effects of antidepressants [85]. Therefore, further studies using large- and high-quality samples are needed to confirm it.

CONCLUSION

Mechanistically, acupuncture has the potential to alleviate depressive disorders by increasing hippocampal and network neuroplasticity and decreasing brain inflammation. In addition, overall clinical studies indicated that acupuncture could relieve primary depression, particularly milder cases, and was helpful in the management of PSD, PRD and PPD both as an isolated and adjunct treatment. In summary, substantial evidence from animal and human researches supported the beneficial effect of acupuncture in depression. However, the effect of acupuncture remains to be assessed in large and well-designed clinical trials.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

This work was supported by funds from the National Key R&D Program of China (2019YFC1712100).

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Penner-Goeke, S.; Binder, E.B. Epigenetics and depression . *Dialogues Clin. Neurosci.,* **2019**, *21*(4), 397-405. http://dx.doi.org/10.31887/DCNS.2019.21.4/ebinder PMID: 31949407

[2] Battle, D.E. Diagnostic and statistical manual of mental disorders (DSM). *CoDAS,* **2013**, *25*(2), 191-192. PMID: 24413388

[3] Ménard, C.; Hodes, G.E.; Russo, S.J. Pathogenesis of depression: Insights from human and rodent studies. *Neuroscience,* **2016**, *321*, 138-162. http://dx.doi.org/10.1016/j.neuroscience.2015.05.053 PMID: 26037806

[4] Zhang, Y.; Chen, Y.; Ma, L. Depression and cardiovascular disease in elderly: Current understanding. *J. Clin. Neurosci.,* **2018**, *47*, 1-5. http://dx.doi.org/10.1016/j.jocn.2017.09.022 PMID: 29066229

[5] Bener, A.; Dafeeah, E.E.; Abou-Saleh, M.T.; Bhugra, D.; Ventriglio, A. Co-morbidity between major depression and schizophrenia: Prevalence and clinical characteristics. *Psychiatr. Danub.,* **2020**, *32*(1), 78-83. http://dx.doi.org/10.24869/psyd.2020.78 PMID: 32303036

[6] Rush, A.J.; Trivedi, M.H.; Wisniewski, S.R.; Nierenberg, A.A.; Stewart, J.W.; Warden, D.; Niederehe, G.; Thase, M.E.; Lavori, P.W.; Lebowitz, B.D.; McGrath, P.J.; Rosenbaum, J.F.; Sackeim, H.A.; Kupfer, D.J.; Luther, J.; Fava, M. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report. *Am. J. Psychiatry,* **2006**, *163*(11), 1905-1917. http://dx.doi.org/10.1176/ajp.2006.163.11.1905 PMID: 17074942

[7] Wang, Z.; Wang, X.; Liu, J.; Chen, J.; Liu, X.; Nie, G.; Jorgenson, K.; Sohn, K.C.; Huang, R.; Liu, M.; Liu, B.; Kong, J. Acupuncture treatment modulates the corticostriatal reward circuitry in major depressive disorder. *J. Psychiatr. Res.,* **2017**, *84*, 18-26. http://dx.doi.org/10.1016/j.jpsychires.2016.09.014 PMID: 27693978

[8] Smith, C.A.; Armour, M.; Lee, M.S.; Wang, L.Q.; Hay, P.J. Acupuncture for depression. *Cochrane Database Syst. Rev.,* **2018**, *3*(3), CD004046. PMID: 29502347

[9] Chan, Y.Y.; Lo, W.Y.; Yang, S.N.; Chen, Y.H.; Lin, J.G. The benefit of combined acupuncture and antidepressant medication for depression: A systematic review and meta-analysis. *J. Affect. Disord.,* **2015**, *176*, 106-117. http://dx.doi.org/10.1016/j.jad.2015.01.048 PMID: 25704563

[10] Wei, H.N.; Jiang, L.P.; Xiong, B.; Zhou, S.; Yu, L.; Huang, Y.M.; Liu, D.G.; Ling, W.; Song, X.N.; Zhang, X.X.; Zhao, H.L. Characteristic patterns of normal meridian acupoint temperature. *J. Chin. Med. Assoc.,* **2017**, *80*(7), 419-426. http://dx.doi.org/10.1016/j.jcma.2016.12.007 PMID: 28476445

[11] Li, Z.; Hu, Y.Y.; Zheng, C.Y.; Su, Q.Z.; An, C.; Luo, X.D.; Liu, M.C. Rules of meridians and acupoints selection in treatment of Parkinson's disease based on data mining techniques. *Chin. J. Integr. Med.,* **2020**, *26*(8), 624-628. http://dx.doi.org/10.1007/s11655-017-2428-6 PMID: 29335862

[12] Zeng, L.F.; Cao, Y.; Wang, L.; Dai, Y.K.; Hu, L.; Wang, Q.; Zhu, L.T.; Bao, W.H.; Zou, Y.P.; Chen, Y.B.; Xu, W.H.; Liang, W.X.; Wang, N.S. Role of medicinal plants for liver-Qi regulation adjuvant therapy in post-stroke depression: A systematic review of literature. *Phytother. Res.,* **2017**, *31*(1), 40-52. http://dx.doi.org/10.1002/ptr.5740 PMID: 27762458

[13] Wen, X.; Wu, Q.; Liu, J.; Xu, Z.; Fan, L.; Chen, X.; He, Q.; Ma, R.; Wu, Y.; Jiang, S.; Xu, S.; Fu, W. Randomized single-blind multicenter trial comparing the effects of standard and augmented acupuncture protocols on sleep quality and depressive symptoms in patients with depression. *Psychol. Health Med.,* **2018**, *23*(4), 375-390. http://dx.doi.org/10.1080/13548506.2017.1363399 PMID: 28899206

[14] Gong, Q.; He, Y. Depression, neuroimaging and connectomics: A selective overview. *Biol. Psychiatry,* **2015**, *77*(3), 223-235. http://dx.doi.org/10.1016/j.biopsych.2014.08.009 PMID: 25444171

[15] Berton, O.; McClung, C.A.; Dileone, R.J.; Krishnan, V.; Renthal, W.; Russo, S.J.; Graham, D.; Tsankova, N.M.; Bolanos, C.A.; Rios, M.; Monteggia, L.M.; Self, D.W.; Nestler, E.J. Essential role of BDNF in the mesolimbic dopamine pathway in social defeat stress. *Science,* **2006**, *311*(5762), 864-868. http://dx.doi.org/10.1126/science.1120972 PMID: 16469931

[16] Hao, Y.; Ge, H.; Sun, M.; Gao, Y. Selecting an appropriate animal model of depression. *Int. J. Mol. Sci.,* **2019**, *20*(19), 4827. http://dx.doi.org/10.3390/ijms20194827 PMID: 31569393

[17] Willner, P. The validity of animal models of depression. *Psychopharmacology (Berl.),* **1984**, *83*(1), 1-16. http://dx.doi.org/10.1007/BF00427414 PMID: 6429692

[18] Henn, F.A.; Vollmayr, B. Stress models of depression: forming genetically vulnerable strains. *Neurosci. Biobehav. Rev.,* **2005**, *29*(4-5), 799-804. http://dx.doi.org/10.1016/j.neubiorev.2005.03.019 PMID: 15925700

[19] Kandola, A.; Ashdown-Franks, G.; Hendrikse, J.; Sabiston, C.M.; Stubbs, B. Physical activity and depression: Towards understanding the antidepressant mechanisms of physical activity. *Neurosci. Biobehav. Rev.,* **2019**, *107*, 525-539. http://dx.doi.org/10.1016/j.neubiorev.2019.09.040 PMID: 31586447

[20] Maes, M.; Carvalho, A.F. The compensatory immune-regulatory reflex system (CIRS) in depression and bipolar disorder. *Mol. Neurobiol.,* **2018**, *55*(12), 8885-8903. http://dx.doi.org/10.1007/s12035-018-1016-x PMID: 29611101

[21] Yrondi, A.; Sporer, M.; Péran, P.; Schmitt, L.; Arbus, C.; Sauvaget, A. Electroconvulsive therapy, depression, the immune system and inflammation: A systematic review. *Brain Stimul.,* **2018**, *11*(1), 29-51. http://dx.doi.org/10.1016/j.brs.2017.10.013 PMID: 29111078

[22] Duman, R.S. Neurobiology of stress, depression, and rapid acting antidepressants: Remodeling synaptic connections. *Depress. Anxiety,* **2014**, *31*(4), 291-296. http://dx.doi.org/10.1002/da.22227 PMID: 24616149

[23] Liu, W.; Ge, T.; Leng, Y.; Pan, Z.; Fan, J.; Yang, W.; Cui, R. The role of neural plasticity in depression: From hippocampus to prefrontal cortex. *Neural Plast.,* **2017**, *2017*, 6871089. http://dx.doi.org/10.1155/2017/6871089 PMID: 28246558

[24] Samara, Z.; Evers, E. A.T.; Peeters, F.; Uylings, H.B.M.; Rajkowska, G.; Ramaekers, J.G.; Stiers, P. Orbital and medial prefrontal cortex functional connectivity of major depression vulnerability and disease. *Biol.Psychiat-Cogn. N.,* **2018**, *3*(4), 348-357.

[25] Ge, R.; Downar, J.; Blumberger, D.M.; Daskalakis, Z.J.; Vila-Rodriguez, F. Functional connectivity of the anterior cingulate cortex predicts treatment outcome for rTMS in treatment-resistant depression at 3-month follow-up. *Brain Stimul.,* **2020**, *13*(1), 206-214. http://dx.doi.org/10.1016/j.brs.2019.10.012 PMID: 31668646

[26] Ferri, J.; Eisendrath, S.J.; Fryer, S.L.; Gillung, E.; Roach, B.J.; Mathalon, D.H. Blunted amygdala activity is associated with depression severity in treatment-resistant depression. *Cogn. Affect. Behav. Neurosci.,* **2017**, *17*(6), 1221-1231. http://dx.doi.org/10.3758/s13415-017-0544-6 PMID: 29063521

[27] Bagot, R.C.; Parise, E.M.; Peña, C.J.; Zhang, H.X.; Maze, I.; Chaudhury, D.; Persaud, B.; Cachope, R.; Bolaños-Guzmán, C.A.; Cheer, J.F.; Deisseroth, K.; Han, M.H.; Nestler, E.J. Ventral hippocampal afferents to the nucleus accumbens regulate susceptibility to depression. *Nat. Commun.,* **2015**, *6*, 7062. http://dx.doi.org/10.1038/ncomms8062 PMID: 25952660

[28] Müller, V.I.; Cieslik, E.C.; Serbanescu, I.; Laird, A.R.; Fox, P.T.; Eickhoff, S.B. Altered brain activity in unipolar depression revisited: Meta-analyses of neuroimaging studies. *JAMA Psychiatry,* **2017**, *74*(1), 47-55. http://dx.doi.org/10.1001/jamapsychiatry.2016.2783 PMID: 27829086

[29] Zhang, F.F.; Peng, W.; Sweeney, J.A.; Jia, Z.Y.; Gong, Q.Y. Brain structure alterations in depression: Psychoradiological evidence. *CNS Neurosci. Ther.,* **2018**, *24*(11), 994-1003. http://dx.doi.org/10.1111/cns.12835 PMID: 29508560

[30] Padmanabhan, J.L.; Cooke, D.; Joutsa, J.; Siddiqi, S.H.; Ferguson, M.; Darby, R.R.; Soussand, L.; Horn, A.; Kim, N.Y.; Voss, J.L.; Naidech, A.M.; Brodtmann, A.; Egorova, N.; Gozzi, S.; Phan, T.G.; Corbetta, M.; Grafman, J.; Fox, M.D. A human depression circuit derived from focal brain lesions. *Biol. Tsychiat.,* **2019**, *86*(10), 749-758. http://dx.doi.org/10.1016/j.biopsych.2019.07.023

[31] Enneking, V.; Leehr, E.J.; Dannlowski, U.; Redlich, R. Brain structural effects of treatments for depression and biomarkers of response: A systematic review of neuroimaging studies. *Psychol. Med.,* **2020**, *50*(2), 187-209. http://dx.doi.org/10.1017/S0033291719003660 PMID: 31858931

[32] Sheline, Y.I.; Gado, M.H.; Kraemer, H.C. Untreated depression and hippocampal volume loss. *Am. J. Psychiatry,* **2003**, *160*(8), 1516-1518. http://dx.doi.org/10.1176/appi.ajp.160.8.1516 PMID: 12900317

[33] MacQueen, G.; Frodl, T. The hippocampus in major depression: Evidence for the convergence of the bench and bedside in psychiatric research? *Mol. Psychiatry,* **2011**, *16*(3), 252-264. http://dx.doi.org/10.1038/mp.2010.80 PMID: 20661246

[34] Price, J.L.; Drevets, W.C. Neurocircuitry of mood disorders. *Neuropsychopharmacology,* **2010**, *35*(1), 192-216. http://dx.doi.org/10.1038/npp.2009.104 PMID: 19693001

[35] Zhou, H.X.; Chen, X.; Shen, Y.Q.; Li, L.; Chen, N.X.; Zhu, Z.C.; Castellanos, F.X.; Yan, C.G. Rumination and the default mode network: Meta-analysis of brain imaging studies and implications for depression. *Neuroimage,* **2020**, *206*, 116287. http://dx.doi.org/10.1016/j.neuroimage.2019.116287 PMID: 31655111

[36] Liu, X.; Zhong, S.; Yan, L.; Zhao, H.; Wang, Y.; Hu, Y.; Jia, Y. Correlations among mRNA expression levels of ATP7A, serum ceruloplasmin levels, and neuronal metabolism in unmedicated major depressive disorder. *Int. J. Neuropsychopharmacol.,* **2020**, *23*(10), 642-652. http://dx.doi.org/10.1093/ijnp/pyaa038 PMID: 32427278

[37] Lui, S.; Wu, Q.; Qiu, L.; Yang, X.; Kuang, W.; Chan, R.C.; Huang, X.; Kemp, G.J.; Mechelli, A.; Gong, Q. Resting-state functional connectivity in treatment-resistant depression. *Am. J. Psychiatry,* **2011**, *168*(6), 642-648. http://dx.doi.org/10.1176/appi.ajp.2010.10101419 PMID: 21362744

[38] Li, X.; Zhao, J.; Li, Z.; Zhang, L.; Huo, Z. Applications of Acupuncture Therapy in Modulating the Plasticity of Neurodegenerative Disease and Depression: Do microRNA and neurotrophin BDNF shed light on the underlying mechanism? *Neural Plast.,* **2020**, *2020*, 8850653. http://dx.doi.org/10.1155/2020/8850653 PMID: 33029119

[39] Xiao, L.Y.; Wang, X.R.; Yang, Y.; Yang, J.W.; Cao, Y.; Ma, S.M.; Li, T.R.; Liu, C.Z. Applications of acupuncture therapy in modulating plasticity of central nervous system. *Neuromodulation,* **2018**, *21*(8), 762-776. http://dx.doi.org/10.1111/ner.12724 PMID: 29111577

[40] Kang, H.J.; Voleti, B.; Hajszan, T.; Rajkowska, G.; Stockmeier, C.A.; Licznerski, P.; Lepack, A.; Majik, M.S.; Jeong, L.S.; Banasr, M.; Son, H.; Duman, R.S. Decreased expression of synapse-related genes and loss of synapses in major depressive disorder. *Nat. Med.,* **2012**, *18*(9), 1413-1417. http://dx.doi.org/10.1038/nm.2886 PMID: 22885997

[41] Duric, V.; Banasr, M.; Stockmeier, C.A.; Simen, A.A.; Newton, S.S.; Overholser, J.C.; Jurjus, G.J.; Dieter, L.; Duman, R.S. Altered expression of synapse and glutamate related genes in post-mortem hippocampus of depressed subjects. *Int. J. Neuropsychopharmacol.,* **2013**, *16*(1), 69-82. http://dx.doi.org/10.1017/S1461145712000016 PMID: 22339950

[42] Stockmeier, C.A.; Mahajan, G.J.; Konick, L.C.; Overholser, J.C.; Jurjus, G.J.; Meltzer, H.Y.; Uylings, H.B.; Friedman, L.; Rajkowska, G. Cellular changes in the postmortem hippocampus in major depression. *Biol. Psychiatry,* **2004**, *56*(9), 640-650. http://dx.doi.org/10.1016/j.biopsych.2004.08.022 PMID: 15522247

[43] Wang, X.; Wang, Z.; Liu, J.; Chen, J.; Liu, X.; Nie, G.; Byun, J.S.; Liang, Y.; Park, J.; Huang, R.; Liu, M.; Liu, B.; Kong, J. Repeated acupuncture treatments modulate amygdala resting state functional connectivity of depressive patients. *Neuroimage Clin.,* **2016**, *12*, 746-752. http://dx.doi.org/10.1016/j.nicl.2016.07.011 PMID: 27812501

[44] Lesch, K.P.; Waider, J. Serotonin in the modulation of neural plasticity and networks: Implications for neurodevelopmental disorders. *Neuron,* **2012**, *76*(1), 175-191. http://dx.doi.org/10.1016/j.neuron.2012.09.013 PMID: 23040814

[45] Han, X.; Wu, H.; Yin, P.; Chen, Z.; Cao, X.; Duan, Y.; Xu, J.; Lao, L.; Xu, S. Electroacupuncture restores hippocampal synaptic plasticity *via* modulation of 5-HT receptors in a rat model of depression. *Brain Res. Bull.,* **2018**, *139*, 256-262. http://dx.doi.org/10.1016/j.brainresbull.2018.03.004 PMID: 29524471

[46] Chen, L.; Yao, Z.; Qu, S.; Zhang, J.; Zhang, J.; Zhang, Z.; Huang, Y.; Zhong, Z. Electroacupuncture improves synaptic plasticity by regulating the 5-HT1A receptor in hippocampus of rats with chronic unpredictable mild stress. *J. Int. Med. Res.,* **2020**, *48*(5), 300060520918419. http://dx.doi.org/10.1177/0300060520918419 PMID: 32363965

[47] Duan, D.; Tu, Y.; Yang, X.; Liu, P. Electroacupuncture restores 5-HT system deficit in chronic mild stress-induced depressed rats. *Evid. Based Complement. Alternat. Med.,* **2016**, *2016*, 7950635. http://dx.doi.org/10.1155/2016/7950635 PMID: 27994633

[48] Luo, T.; Tian, H.; Song, H.; Zhao, J.; Liya, A.; Fang, Y.; Mou, J.; Li, Z.; Chaoketu, S. Possible involvement of tissue plasminogen activator/brain-derived neurotrophic factor pathway in antidepressant effects of electroacupuncture in chronic unpredictable mild stress-induced depression in rats. *Front. Psychiatry,* **2020**, *11*, 63. http://dx.doi.org/10.3389/fpsyt.2020.00063 PMID: 32153441

[49] Lin, D.; Wu, Q.; Lin, X.; Borlongan, C.V.; He, Z.X.; Tan, J.; Cao, C.; Zhou, S.F. Brain-derived neurotrophic factor signaling pathway: Modulation by acupuncture in telomerase knockout mice. *Altern. Ther. Health Med.,* **2015**, *21*(6), 36-46. PMID: 26567448

[50] Jiang, H.; Zhang, X.; Lu, J.; Meng, H.; Sun, Y.; Yang, X.; Zhao, B.; Bao, T. Antidepressant-like effects of acupuncture-insights from DNA methylation and histone modifications of brain-derived neurotrophic factor. *Front. Psychiatry,* **2018**, *9*, 102. http://dx.doi.org/10.3389/fpsyt.2018.00102 PMID: 29636708

[51] Park, H.; Yoo, D.; Kwon, S.; Yoo, T.W.; Park, H.J.; Hahm, D.H.; Lee, H.; Kim, S.T. Acupuncture stimulation at HT7 alleviates depression-induced behavioral changes *via* regulation of the serotonin system in the prefrontal cortex of maternally-separated rat pups. *J. Physiol. Sci.,* **2012**, *62*(4), 351-357. http://dx.doi.org/10.1007/s12576-012-0211-1 PMID: 22627707

[52] Czeh, M.; Gressens, P.; Kaindl, A.M. The yin and yang of microglia. *Dev. Neurosci.,* **2011**, *33*(3-4), 199-209. http://dx.doi.org/10.1159/000328989 PMID: 21757877

[53] Rawdin, B.J.; Mellon, S.H.; Dhabhar, F.S.; Epel, E.S.; Puterman, E.; Su, Y.; Burke, H.M.; Reus, V.I.; Rosser, R.; Hamilton, S.P.; Nelson, J.C.; Wolkowitz, O.M. Dysregulated relationship of inflammation and oxidative stress in major depression. *Brain Behav. Immun.,* **2013**, *31*, 143-152. http://dx.doi.org/10.1016/j.bbi.2012.11.011 PMID: 23201587

[54] Zunszain, P.A.; Anacker, C.; Cattaneo, A.; Carvalho, L.A.; Pariante, C.M. Glucocorticoids, cytokines and brain abnormalities in depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2011**, *35*(3), 722-729. http://dx.doi.org/10.1016/j.pnpbp.2010.04.011 PMID: 20406665

[55] Raivich, G. Like cops on the beat: The active role of resting microglia. *Trends Neurosci.,* **2005**, *28*(11), 571-573. http://dx.doi.org/10.1016/j.tins.2005.09.001 PMID: 16165228

[56] Venneti, S.; Lopresti, B.J.; Wiley, C.A. Molecular imaging of microglia/macrophages in the brain. *Glia,* **2013**, *61*(1), 10-23. http://dx.doi.org/10.1002/glia.22357 PMID: 22615180

[57] Venneti, S.; Lopresti, B.J.; Wiley, C.A. The peripheral benzodiazepine receptor (Translocator protein 18kDa) in microglia: From pathology to imaging. *Prog. Neurobiol.,* **2006**, *80*(6), 308-322. http://dx.doi.org/10.1016/j.pneurobio.2006.10.002 PMID: 17156911

[58] Doorduin, J.; de Vries, E.F.; Dierckx, R.A.; Klein, H.C. PET imaging of the peripheral benzodiazepine receptor: Monitoring disease progression and therapy response in neurodegenerative disorders. *Curr. Pharm. Des.,* **2008**, *14*(31), 3297-3315. http://dx.doi.org/10.2174/138161208786549443 PMID: 19075709

[59] Steiner, J.; Bielau, H.; Brisch, R.; Danos, P.; Ullrich, O.; Mawrin, C.; Bernstein, H.G.; Bogerts, B. Immunological aspects in the neurobiology of suicide: Elevated microglial density in schizophrenia and depression is associated with suicide. *J. Psychiatr. Res.,* **2008**, *42*(2), 151-157. http://dx.doi.org/10.1016/j.jpsychires.2006.10.013 PMID: 17174336

[60] Dantzer, R.; O'Connor, J.C.; Freund, G.G.; Johnson, R.W.; Kelley, K.W. From inflammation to sickness and depression: When the immune system subjugates the brain. *Nat. Rev. Neurosci.,* **2008**, *9*(1), 46-56. http://dx.doi.org/10.1038/nrn2297 PMID: 18073775

[61] Frick, L.R.; Williams, K.; Pittenger, C. Microglial dysregulation in psychiatric disease. *Clin. Dev. Immunol.,* **2013**, *2013*, 608654. http://dx.doi.org/10.1155/2013/608654 PMID: 23690824

[62] Massart, R.; Mongeau, R.; Lanfumey, L. Beyond the monoaminergic hypothesis: Neuroplasticity and epigenetic changes in a transgenic mouse model of depression. *Philos. Trans. R. Soc. Lond. B Biol. Sci.,* **2012**, *367*(1601), 2485-2494. http://dx.doi.org/10.1098/rstb.2012.0212 PMID: 22826347

[63] Song, C.; Wang, H. Cytokines mediated inflammation and decreased neurogenesis in animal models of depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2011**, *35*(3), 760-768. http://dx.doi.org/10.1016/j.pnpbp.2010.06.020 PMID: 20600462

[64] Carvalho, L.A.; Torre, J.P.; Papadopoulos, A.S.; Poon, L.; Juruena, M.F.; Markopoulou, K.; Cleare, A.J.; Pariante, C.M. Lack of clinical therapeutic benefit of antidepressants is associated overall activation of the inflammatory system. *J. Affect. Disord.,* **2013**, *148*(1), 136-140. http://dx.doi.org/10.1016/j.jad.2012.10.036 PMID: 23200297

[65] Cai, W.; Ma, W.; Wang, G.T.; Li, Y.J.; Shen, W.D. Antidepressant, anti-inflammatory, and antioxidant effects of electroacupuncture through sonic hedgehog-signaling pathway in a rat model of post-stroke depression. *Neuropsychiatr. Dis. Treat.,* **2019**, *15*, 1403-1411. http://dx.doi.org/10.2147/NDT.S205033 PMID: 31190842

[66] Conway, C.R.; Kumar, A.; Xiong, W.; Bunker, M.; Aaronson, S.T.; Rush, A.J. Chronic vagus nerve stimulation significantly improves quality of life in treatment-resistant major depression. *Prog. Neuro-Psychoph.,* **2018**, *35*(3), 760-768. http://dx.doi.org/10.4088/JCP.18m12178

[67] Dou, Y.; Luo, J.; Yu, J.; Xia, Y.; Dai, Y. Cholinergic system is involved in the therapeutic effect of madecassoside on collagen-induced arthritis in rats. *Int. Immunopharmacol.,* **2019**, *75*, 105813. http://dx.doi.org/10.1016/j.intimp.2019.105813 PMID: 31404889

[68] Browning, K.N.; Verheijden, S.; Boeckxstaens, G.E. The vagus nerve in appetite regulation, mood, and intestinal inflammation. *Gastroenterology,* **2017**, *152*(4), 730-744. http://dx.doi.org/10.1053/j.gastro.2016.10.046 PMID: 27988382

[69] Stakenborg, N.; Gomez-Pinilla, P.J.; Boeckxstaens, G.E. Postoperative ileus: Pathophysiology, current therapeutic approaches. *Handb. Exp. Pharmacol.,* **2017**, *239*, 39-57. http://dx.doi.org/10.1007/164_2016_108 PMID: 27999957

[70] Yang, N.N.; Yang, J.W.; Ye, Y.; Huang, J.; Wang, L.; Wang, Y.; Su, X.T.; Lin, Y.; Yu, F.T.; Ma, S.M.; Qi, L.Y.; Lin, L.L.; Wang, L.Q.; Shi, G.X.; Li, H.P.; Liu, C.Z. Electroacupuncture ameliorates intestinal inflammation by activating α7nAChR-mediated JAK2/STAT3 signaling pathway in postoperative ileus. *Theranostics,* **2021**, *11*(9), 4078-4089. http://dx.doi.org/10.7150/thno.52574 PMID: 33754049

[71] Zheng, P.; Zeng, B.; Zhou, C.; Liu, M.; Fang, Z.; Xu, X.; Zeng, L.; Chen, J.; Fan, S.; Du, X.; Zhang, X.; Yang, D.; Yang, Y.; Meng, H.; Li, W.; Melgiri, N.D.; Licinio, J.; Wei, H.; Xie, P. Gut microbiome remodeling induces depressive-like behaviors through a pathway mediated by the host's metabolism. *Mol. Psychiatry,* **2016**, *21*(6), 786-796. http://dx.doi.org/10.1038/mp.2016.44 PMID: 27067014

[72] Slyepchenko, A.; Maes, M.; Jacka, F.N.; Köhler, C.A.; Barichello, T.; McIntyre, R.S.; Berk, M.; Grande, I.; Foster, J.A.; Vieta, E.; Carvalho, A.F. Gut microbiota, bacterial translocation, and interactions with diet: Pathophysiological links between major depressive disorder and non-communicable medical comorbidities. *Psychother. Psychosom.,* **2017**, *86*(1), 31-46. http://dx.doi.org/10.1159/000448957 PMID: 27884012

[73] Liu, S.; Guo, R.; Liu, F.; Yuan, Q.; Yu, Y.; Ren, F. Gut microbiota regulates depression-like behavior in rats through the neuroendocrine-immune-mitochondrial pathway. *Neuropsychiatr. Dis. Treat.,* **2020**, *16*, 859-869. http://dx.doi.org/10.2147/NDT.S243551 PMID: 32280227

[74] Jang, J.H.; Yeom, M.J.; Ahn, S.; Oh, J.Y.; Ji, S.; Kim, T.H.; Park, H.J. Acupuncture inhibits neuroinflammation and gut microbial dysbiosis in a mouse model of Parkinson's disease. *Brain Behav. Immun.,* **2020**, *89*, 641-655. http://dx.doi.org/10.1016/j.bbi.2020.08.015 PMID: 32827699

[75] Wang, L.; An, J.; Song, S.; Mei, M.; Li, W.; Ding, F.; Liu, S. Electroacupuncture preserves intestinal barrier integrity through modulating the gut microbiota in DSS-induced chronic colitis. *Life Sci.,* **2020**, *261*, 118473. http://dx.doi.org/10.1016/j.lfs.2020.118473 PMID: 32971101

[76] Han, W.; Tellez, L.A.; Perkins, M.H.; Perez, I.O.; Qu, T.; Ferreira, J.; Ferreira, T.L.; Quinn, D.; Liu, Z.W.; Gao, X.B.; Kaelberer, M.M.; Bohórquez, D.V.; Shammah-Lagnado, S.J.; de Lartigue, G.; de Araujo, I.E. A neural circuit for gut-induced reward. *Cell,* **2018**, *175*(3), 665-678.e23. http://dx.doi.org/10.1016/j.cell.2018.08.049 PMID: 30245012

[77] Plein, L.M.; Rittner, H.L. Opioids and the immune system - Friend or foe. *Br. J. Pharmacol.,* **2018**, *175*(14), 2717-2725. http://dx.doi.org/10.1111/bph.13750 PMID: 28213891

[78] Patil, S.; Sen, S.; Bral, M.; Reddy, S.; Bradley, K.K.; Cornett, E.M.; Fox, C.J.; Kaye, A.D. The role of acupuncture in pain management. *Curr. Pain Headache Rep.,* **2016**, *20*(4), 22. http://dx.doi.org/10.1007/s11916-016-0552-1 PMID: 26896946

[79] Su, T.F.; Zhang, L.H.; Peng, M.; Wu, C.H.; Pan, W.; Tian, B.; Shi, J.; Pan, H.L.; Li, M. Cannabinoid CB2 receptors contribute to upregulation of β-endorphin in inflamed skin tissues by electroacupuncture. *Mol. Pain,* **2011**, *7*, 98. http://dx.doi.org/10.1186/1744-8069-7-98 PMID: 22177137

[80] Balchin, R.; Linde, J.; Blackhurst, D.; Rauch, H.L.; Schönbächler, G. Sweating away depression? The impact of intensive exercise on depression. *J. Affect. Disord.,* **2016**, *200*, 218-221. http://dx.doi.org/10.1016/j.jad.2016.04.030 PMID: 27137088

[81] Jia, X.; Gao, Z.; Hu, H. Microglia in depression: Current perspectives. *Sci. China Life Sci.,* **2021**, *64*(6), 911-925. http://dx.doi.org/10.1007/s11427-020-1815-6 PMID: 33068286

[82] Yang, X.; Gong, W.; Ma, X.; Wang, S.; Wang, X.; Guo, T.; Guo, Z.; Sun, Y.; Li, J.; Zhao, B.; Tu, Y. Factor analysis of electroacupuncture and selective serotonin reuptake inhibitors for major depressive disorder: An 8-week controlled clinical trial. *Acupunct. Med.,* **2020**, *38*(1), 45-52. http://dx.doi.org/10.1136/acupmed-2017-011412 PMID: 31544488

[83] Zhao, B.; Li, Z.; Wang, Y.; Ma, X.; Wang, X.; Wang, X.; Liu, J.; Huang, Y.; Zhang, J.; Li, L.; Hu, X.; Jiang, J.; Qu, S.; Chai, Q.; Song, M.; Yang, X.; Bao, T.; Fei, Y. Manual or electroacupuncture as an add-on therapy to SSRIs for depression: A randomized controlled trial. *J. Psychiatr. Res.,* **2019**, *114*, 24-33. http://dx.doi.org/10.1016/j.jpsychires.2019.04.005 PMID: 31015098

[84] Li, W.; Sun, M.; Yin, X.; Lao, L.; Kuang, Z.; Xu, S. The effect of acupuncture on depression and its correlation with metabolic alterations: A randomized controlled trial. *Medicine (Baltimore),* **2020**, *99*(43), e22752. http://dx.doi.org/10.1097/MD.0000000000022752 PMID: 33120777

[85] Zhang, W.J.; Yang, X.B.; Zhong, B.L. Combination of acupuncture and fluoxetine for depression: A randomized, double-blind, sham-controlled trial. *J. Altern. Complement. Med.,* **2009**, *15*(8), 837-844. http://dx.doi.org/10.1089/acm.2008.0607 PMID: 19678773

[86] Robinson, R.G.; Jorge, R.E. Post-stroke depression: A review. *Am. J. Psychiatry,* **2016**, *173*(3), 221-231. http://dx.doi.org/10.1176/appi.ajp.2015.15030363 PMID: 26684921

[87] Loubinoux, I.; Kronenberg, G.; Endres, M.; Schumann-Bard, P.; Freret, T.; Filipkowski, R.K.; Kaczmarek, L.; Popa-Wagner, A. Post-stroke depression: Mechanisms, translation and therapy. *J. Cell. Mol. Med.,* **2012**, *16*(9), 1961-1969. http://dx.doi.org/10.1111/j.1582-4934.2012.01555.x PMID: 22348642

[88] Cai, W.; Mueller, C.; Li, Y.J.; Shen, W.D.; Stewart, R. Post stroke depression and risk of stroke recurrence and mortality: A systematic review and meta-analysis. *Ageing Res. Rev.,* **2019**, *50*, 102-109. http://dx.doi.org/10.1016/j.arr.2019.01.013 PMID: 30711712

[89] Rasmussen, A.; Lunde, M.; Poulsen, D.L.; Sørensen, K.; Qvitzau, S.; Bech, P. A double-blind, placebo-controlled study of sertraline in the prevention of depression in stroke patients. *Psychosomatics,* **2003**, *44*(3), 216-221. http://dx.doi.org/10.1176/appi.psy.44.3.216 PMID: 12724503

[90] Niedermaier, N.; Bohrer, E.; Schulte, K.; Schlattmann, P.; Heuser, I. Prevention and treatment of poststroke depression with mirtazapine in patients with acute stroke. *J. Clin. Psychiatry,* **2004**, *65*(12), 1619-1623. http://dx.doi.org/10.4088/JCP.v65n1206 PMID: 15641866

[91] Robinson, R.G.; Jorge, R.E.; Long, J. Prevention of poststroke mortality using problem-solving therapy or escitalopram. *Am. J. Geriatr. Psychiatry,* **2017**, *25*(5), 512-519. http://dx.doi.org/10.1016/j.jagp.2016.10.001 PMID: 28029510

[92] Narushima, K.; Paradiso, S.; Moser, D.J.; Jorge, R.; Robinson, R.G. Effect of antidepressant therapy on executive function after stroke. *Br. J. Psychiatry,* **2007**, *190*, 260-265. http://dx.doi.org/10.1192/bjp.bp.106.025064 PMID: 17329748

[93] Acler, M.; Robol, E.; Fiaschi, A.; Manganotti, P. A double blind placebo RCT to investigate the effects of serotonergic modulation on brain excitability and motor recovery in stroke patients. *J. Neurol.,* **2009**, *256*(7), 1152-1158. http://dx.doi.org/10.1007/s00415-009-5093-7 PMID: 19306038

[94] Yang, A.; Wu, H.M.; Tang, J.L.; Xu, L.; Yang, M.; Liu, G.J. Acupuncture for stroke rehabilitation. *Cochrane Database Syst. Rev.,* **2016**, *2016*(8), CD004131. PMID: 27562656

[95] Zhang, X.Y.; Li, Y.X.; Liu, D.L.; Zhang, B.Y.; Chen, D.M. The effectiveness of acupuncture therapy in patients with post-stroke depression: An updated meta-analysis of randomized controlled trials. *Medicine (Baltimore),* **2019**, *98*(22), e15894. http://dx.doi.org/10.1097/MD.0000000000015894 PMID: 31145349

[96] Hung, C.Y.; Wu, X.Y.; Chung, V.C.; Tang, E.C.; Wu, J.C.; Lau, A.Y. Overview of systematic reviews with meta-analyses on acupuncture in post-stroke cognitive impairment and depression management. *Integr. Med. Res.,* **2019**, *8*(3), 145-159. http://dx.doi.org/10.1016/j.imr.2019.05.001 PMID: 31304087

[97] Tseng, S.P.; Hsu, Y.C.; Chiu, C.J.; Wu, S.T. A population-based cohort study on the ability of acupuncture to reduce post-stroke depression. *Medicines (Basel),* **2017**, *4*(1), 16. http://dx.doi.org/10.3390/medicines4010016 PMID: 28930231

[98] Li, M.; Zhang, B.; Meng, Z.; Sha, T.; Han, Y.; Zhao, H.; Zhang, C. Effect of Tiaoshen Kaiqiao acupuncture in the treatment of ischemic post-stroke depression: A randomized controlled trial. *J. Tradit. Chin. Med.,* **2017**, *37*(2), 171-178. http://dx.doi.org/10.1016/S0254-6272(17)30041-9 PMID: 29960288

[99] Legg, L.A.; Tilney, R.; Hsieh, C.F.; Wu, S.; Lundström, E.; Rudberg, A.S.; Kutlubaev, M.A.; Dennis, M.; Soleimani, B.; Barugh, A.; Hackett, M.L.; Hankey, G.J.; Mead, G.E. Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery. *Cochrane Database Syst. Rev.,* **2019**, *2019*(11), CD009286. http://dx.doi.org/10.1002/14651858.CD009286.pub3 PMID: 31769878

[100] Paolucci, S. Epidemiology and treatment of post-stroke depression. *Neuropsychiatr. Dis. Treat.,* **2008**, *4*(1), 145-154. http://dx.doi.org/10.2147/NDT.S2017 PMID: 18728805

[101] Huang, W.J.; Chen, W.W.; Zhang, X. Endocannabinoid system: Role in depression, reward and pain control (Review). *Mol. Med. Rep.,* **2016**, *14*(4), 2899-2903. http://dx.doi.org/10.3892/mmr.2016.5585 PMID: 27484193

[102] Poole, H.; White, S.; Blake, C.; Murphy, P.; Bramwell, R. Depression in chronic pain patients: Prevalence and measurement. *Pain Pract.,* **2009**, *9*(3), 173-180. http://dx.doi.org/10.1111/j.1533-2500.2009.00274.x PMID: 19298363

[103] Hassett, A.L.; Aquino, J.K.; Ilgen, M.A. The risk of suicide mortality in chronic pain patients. *Curr. Pain Headache Rep.,* **2014**, *18*(8), 436. http://dx.doi.org/10.1007/s11916-014-0436-1 PMID: 24952608

[104] Kalaydjian, A.; Merikangas, K. Physical and mental comorbidity of headache in a nationally representative sample of US adults. *Psychosom. Med.,* **2008**, *70*(7), 773-780. http://dx.doi.org/10.1097/PSY.0b013e31817f9e80 PMID: 18725426

[105] Green, C.R.; Hart-Johnson, T.; Loeffler, D.R. Cancer-related chronic pain: Examining quality of life in diverse cancer survivors. *Cancer,* **2011**, *117*(9), 1994-2003. http://dx.doi.org/10.1002/cncr.25761 PMID: 21509777

[106] Gameroff, M.J.; Olfson, M. Major depressive disorder, somatic pain, and health care costs in an urban primary care practice. *J. Clin. Psychiatry,* **2006**, *67*(8), 1232-1239. http://dx.doi.org/10.4088/JCP.v67n0809 PMID: 16965201

[107] Yan, B.; Zhu, S.; Wang, Y.; Da, G.; Tian, G. Effect of acupuncture on chronic pain with depression: A systematic review. *Evid. Based Complement. Alternat. Med.,* **2020**, *2020*, 7479459. http://dx.doi.org/10.1155/2020/7479459 PMID: 32714417

[108] You, J.; Li, H.; Xie, D.; Chen, R.; Chen, M. Acupuncture for chronic pain-related depression: A systematic review and meta-analysis. *Pain Res. Manag.,* **2021**, *2021*, 6617075. http://dx.doi.org/10.1155/2021/6617075 PMID: 33680223

[109] Melchart, D.; Streng, A.; Hoppe, A.; Brinkhaus, B.; Witt, C.; Wagenpfeil, S.; Pfaffenrath, V.; Hammes, M.; Hummelsberger, J.; Irnich, D.; Weidenhammer, W.; Willich, S.N.; Linde, K. Acupuncture in patients with tension-type headache: Randomised controlled trial. *BMJ,* **2005**, *331*(7513), 376-382. http://dx.doi.org/10.1136/bmj.38512.405440.8F PMID: 16055451

[110] He, D.; Høstmark, A.T.; Veiersted, K.B.; Medbø, J.I. Effect of intensive acupuncture on pain-related social and psychological variables for women with chronic neck and shoulder pain--an RCT with six month and three year follow up. *Acupunct. Med.,* **2005**, *23*(2), 52-61. http://dx.doi.org/10.1136/aim.23.2.52 PMID: 16025785

[111] Hopton, A.; Macpherson, H.; Keding, A.; Morley, S. Acupuncture, counselling or usual care for depression and comorbid pain: Secondary analysis of a randomised controlled trial. *BMJ Open,* **2014**, *4*(5), e004964. http://dx.doi.org/10.1136/bmjopen-2014-004964 PMID: 24793257

[112] Kelly, R.B.; Willis, J. Acupuncture for pain. *Am. Fam. Physician,* **2019**, *100*(2), 89-96. PMID: 31305037

[113] Lee, D.; Yip, A.; Chiu, H.; Leung, T.; Chung, T. A psychiatric epidemiological study of postpartum chinese women. *Am. J. Psychiatry,* **2001**, *158*(2), 220-226. http://dx.doi.org/10.1176/appi.ajp.158.2.220 PMID: 11156804

[114] Li, W.; Yin, P.; Lao, L.; Xu, S. Effectiveness of acupuncture used for the management of postpartum depression: A systematic review and meta-analysis. *BioMed. Res. Int.,* **2019**, *2019*, 6597503. http://dx.doi.org/10.1155/2019/6597503 PMID: 31016194

[115] O'Hara, M.W.; McCabe, J.E. Postpartum depression: Current status and future directions. *Annu. Rev. Clin. Psychol.,* **2013**, *9*, 379-407. http://dx.doi.org/10.1146/annurev-clinpsy-050212-185612 PMID: 23394227

[116] Cameron, E.E.; Hunter, D.; Sedov, I.D.; Tomfohr-Madsen, L.M. What do dads want? Treatment preferences for paternal postpartum depression. *J. Affect. Disord.,* **2017**, *215*, 62-70. http://dx.doi.org/10.1016/j.jad.2017.03.031 PMID: 28319693

[117] Tong, P.; Dong, L.P.; Yang, Y.; Shi, Y.H.; Sun, T.; Bo, P. Traditional Chinese acupuncture and postpartum depression: A systematic review and meta-analysis. *J. Chin. Med. Assoc.,* **2019**, *82*(9), 719-726. http://dx.doi.org/10.1097/JCMA.0000000000000140 PMID: 31259837

[118] Li, S.; Zhong, W.; Peng, W.; Jiang, G. Effectiveness of acupuncture in postpartum depression: A systematic review and meta-analysis. *Acupunct. Med.,* **2018**, *36*(5), 295-301. http://dx.doi.org/10.1136/acupmed-2017-011530 PMID: 29907576

[119] Ormsby, S.M.; Smith, C.A.; Dahlen, H.G.; Hay, P.J. The feasibility of acupuncture as an adjunct intervention for antenatal depression: A pragmatic randomised controlled trial. *J. Affect. Disord.,* **2020**, *275*, 82-93. http://dx.doi.org/10.1016/j.jad.2020.05.089 PMID: 32658830

[120] Manber, R.; Schnyer, R.N.; Lyell, D.; Chambers, A.S.; Caughey, A.B.; Druzin, M.; Carlyle, E.; Celio, C.; Gress, J.L.; Huang, M.I.; Kalista, T.; Martin-Okada, R.; Allen, J.J.B. Acupuncture for depression during pregnancy: A randomized controlled trial. *Obstet. Gynecol.,* **2010**, *115*(3), 511-520. http://dx.doi.org/10.1097/AOG.0b013e3181cc0816 PMID: 20177281

[121] Tian, C.B. Acupuncture at BL67 for mild postpartum depression: A prospective case series. *Acupunct. Med.,* **2018**, *36*(5), 339-342. http://dx.doi.org/10.1136/acupmed-2017-011473 PMID: 29540339

[122] Chung, K.F.; Yeung, W.F.; Zhang, Z.J.; Yung, K.P.; Man, S.C.; Lee, C.P.; Lam, S.K.; Leung, T.W.; Leung, K.Y.; Ziea, E.T.; Taam, W.V. Randomized non-invasive sham-controlled pilot trial of electroacupuncture for postpartum depression. *J. Affect. Disord.,* **2012**, *142*(1-3), 115-121. http://dx.doi.org/10.1016/j.jad.2012.04.008 PMID: 22840621

[123] van Ravesteyn, L.M.; Lambregtse-van den Berg, M.P.; Hoogendijk, W.J.; Kamperman, A.M. Interventions to treat mental disorders during pregnancy: A systematic review and multiple treatment meta-analysis. *PLoS One,* **2017**, *12*(3), e0173397. http://dx.doi.org/10.1371/journal.pone.0173397 PMID: 28358808

[124] Pandarakalam, J.P. Challenges of treatment-resistant depression. *Psychiatr. Danub.,* **2018**, *30*(3), 273-284. http://dx.doi.org/10.24869/psyd.2018.273 PMID: 30267518

[125] Lapidus, K.A.; Levitch, C.F.; Perez, A.M.; Brallier, J.W.; Parides, M.K.; Soleimani, L.; Feder, A.; Iosifescu, D.V.; Charney, D.S.; Murrough, J.W. A randomized controlled trial of intranasal ketamine in major depressive disorder. *Biol. Psychiatry,* **2014**, *76*(12), 970-976. http://dx.doi.org/10.1016/j.biopsych.2014.03.026 PMID: 24821196

[126] Suppes, T.; Silva, R.; Cucchiaro, J.; Mao, Y.; Targum, S.; Streicher, C.; Pikalov, A.; Loebel, A. Lurasidone for the treatment of major depressive disorder with mixed features: A randomized, double-blind, placebo-controlled study. *Am. J. Psychiatry,* **2016**, *173*(4), 400-407. http://dx.doi.org/10.1176/appi.ajp.2015.15060770 PMID: 26552942

[127] Kirsch, I.; Deacon, B.J.; Huedo-Medina, T.B.; Scoboria, A.; Moore, T.J.; Johnson, B.T. Initial severity and antidepressant benefits: A meta-analysis of data submitted to the Food and Drug Administration. *PLoS Med.,* **2008**, *5*(2), e45. http://dx.doi.org/10.1371/journal.pmed.0050045 PMID: 18303940

[128] Khan, A.; Leventhal, R.M.; Khan, S.R.; Brown, W.A. Severity of depression and response to antidepressants and placebo: An analysis of the Food and Drug Administration database. *J. Clin. Psychopharmacol.,* **2002**, *22*(1), 40-45. http://dx.doi.org/10.1097/00004714-200202000-00007 PMID: 11799341

[129] Fournier, J.C.; DeRubeis, R.J.; Hollon, S.D.; Dimidjian, S.; Amsterdam, J.D.; Shelton, R.C.; Fawcett, J. Antidepressant drug effects and depression severity: A patient-level meta-analysis. *JAMA,* **2010**, *303*(1), 47-53. http://dx.doi.org/10.1001/jama.2009.1943 PMID: 20051569

[130] Zimmerman, M.; Posternak, M.A.; Chelminski, I. Symptom severity and exclusion from antidepressant efficacy trials. *J. Clin. Psychopharmacol.,* **2002**, *22*(6), 610-614. http://dx.doi.org/10.1097/00004714-200212000-00011 PMID: 12454561

[131] Zimmerman, M.; Clark, H.L.; Multach, M.D.; Walsh, E.; Rosenstein, L.K.; Gazarian, D. Symptom severity and the generalizability of antidepressant efficacy trials: Changes During the past 20 years. *J. Clin. Psychopharmacol.,* **2016**, *36*(2), 153-156. http://dx.doi.org/10.1097/JCP.0000000000000466 PMID: 26848791

[132] Li, S.; Li, Z.F.; Wu, Q.; Guo, X.C.; Xu, Z.H.; Li, X.B.; Chen, R.; Zhou, D.Y.; Wang, C.; Duan, Q.; Sun, J.; Luo, D.; Li, M.Y.; Wang, J.L.; Xie, H.; Xuan, L.H.; Su, S.Y.; Huang, D.M.; Liu, Z.S.; Fu, W.B.A. A multicenter, randomized, controlled trial of electroacupuncture for perimenopause women with mild-moderate depression. *BioMed Res. Int.,* **2018**, *2018*, 5351210. http://dx.doi.org/10.1155/2018/5351210 PMID: 30003102

[133] Quah-Smith, J.I.; Tang, W.M.; Russell, J. Laser acupuncture for mild to moderate depression in a primary care setting--A randomised controlled trial. *Acupunct. Med.,* **2005**, *23*(3), 103-111. http://dx.doi.org/10.1136/aim.23.3.103 PMID: 16259308