

In Review

# Acupuncture for Depression: A Review of Clinical Applications

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While increasing numbers of patients are seeking acupuncture treatment for depression in recent years, there is limited evidence of the antidepressant (AD) effectiveness of acupuncture. Given the unsatisfactory response rates of many Food and Drug Administration–approved ADs, research on acupuncture remains of potential value. Therefore, we sought to review the efficacy and safety of acupuncture treatment for depression in clinical applications. We conducted a PubMed search for publications through 2011. We assessed the adequacy of each report and abstracted information on reported effectiveness or efficacy of acupuncture as monotherapy for major depressive disorder (MDD) and as augmentation of ADs. We also examined adverse events associated with acupuncture, and evidence for acupuncture as a means of reducing side effects of ADs. Published data suggest that acupuncture, including manual-, electrical-, and laser-based, is a generally beneficial, well-tolerated, and safe monotherapy for depression. However, acupuncture augmentation in AD partial responders and nonresponders is not as well studied as monotherapy; and available studies have only investigated MDD, but not other depressive spectrum disorders. Manual acupuncture reduced side effects of ADs in MDD. We found no data on depressive recurrence rates after recovery with acupuncture treatment. Acupuncture is a potential effective monotherapy for depression, and a safe, well-tolerated augmentation in AD partial responders and nonresponders. However, the body of evidence based on well-designed studies is limited, and further investigation is called for.



Même si un nombre croissant de patients recherchent un traitement d'acupuncture pour la dépression ces dernières années, les données probantes sont limitées en ce qui concerne l'efficacité de l'acupuncture comme antidépresseur (AD). Étant donné les taux de réponse insatisfaisants de nombreux AD approuvés par la *Food and Drug Administration*, la recherche sur l'acupuncture demeure d'intérêt. Par conséquent, nous avons entrepris d'examiner l'efficacité et l'innocuité d'un traitement d'acupuncture pour la dépression dans des applications cliniques. Nous avons mené une recherche de publications jusqu'en 2011 dans PubMed. Nous avons évalué la justesse de chaque étude et extrait l'information sur l'efficacité ou l'efficacité rapportée de l'acupuncture comme monothérapie pour le trouble dépressif majeur (TDM) et comme appoint aux AD. Nous avons également examiné les effets indésirables associés à l'acupuncture, et les données probantes sur l'acupuncture comme moyen de réduire les effets secondaires des AD. Les données publiées suggèrent que l'acupuncture, qu'elle soit manuelle, électrique ou au laser, est une monothérapie généralement bénéfique, bien tolérée, et sécuritaire pour la dépression. Cependant, l'appoint de l'acupuncture chez les répondants et non-répondants partiels aux AD n'est pas aussi bien étudié que la monothérapie; et les études disponibles n'ont investigué que le TDM, mais aucun autre trouble du spectre dépressif. L'acupuncture manuelle réduisait les effets secondaires des AD dans le TDM. Nous n'avons trouvé aucune donnée sur les taux de récurrence de la dépression après le rétablissement suivant un traitement d'acupuncture. L'acupuncture est une monothérapie efficace potentielle pour la dépression, et un appoint sécuritaire et bien toléré pour les répondants et non-répondants partiels aux AD. Toutefois, l'ensemble des données probantes se basant sur des études bien conçues est limité, et il faut plus de recherche.

Depression is a serious psychiatric illness that involves symptoms such as depressed or sad mood, loss of interest or pleasure in activities, changes in weight, difficulty sleeping or oversleeping, energy loss, feelings of worthlessness, psychomotor changes, and thoughts of death or suicide. It constitutes a major public health problem, worldwide. The World Health Organization declared that the burden of depression is expected to be second only to heart disease by 2020.<sup>1</sup>

Depression includes MDD, MinD, antenatal depression, PPD, childhood depression, geriatric depression, organic depression, vascular depression, drug-induced depression, PSD, and depression comorbid with other diseases. MDD is common and can be disabling. Point prevalence rates of MDD are estimated at 5% to 13% for women and 2% to 8% for men,<sup>2,3</sup> with an estimated lifetime prevalence of 16.2% and a 12-month prevalence of 6.6%.<sup>4</sup> Over 80% of people who die by suicide are clinically depressed in the months prior to their deaths.<sup>5</sup>

Although pharmacological and psychotherapeutic interventions alleviate depression in 50% to 70% of treatment completers, 47% to 64% of all patients—completers and noncompleters, combined—fail to recover at all.<sup>6</sup> Nonresponse occurs in 19% to 34% of patients, 29% to 46% fail to achieve and sustain full remission,<sup>7</sup> and 15% to 50% will have recurrence of depression despite continuous AD treatment.<sup>8,9</sup> Recent findings from the Sequenced Treatment Alternatives to Relieve Depression (commonly referred to as STAR\*D) study suggested that remission and response rates from pharmacological and psychotherapeutic interventions are far from clinically satisfactory.<sup>10–12</sup>

## Abbreviations

5-HT	serotonin
AD	antidepressant
CAM	complementary and alternative medicine
DA	dopamine
DSM	Diagnostic and Statistical Manual of Mental Disorders
EA	electroacupuncture
HDRS	Hamilton Depression Rating Scale
HPA	hypothalamus—pituitary—adrenal
MDD	major depressive disorder
MinD	minor depression
NE	norepinephrine
PPD	postpartum depression
PSD	poststroke depression
RCT	randomized controlled trial
SNRI	serotonin and norepinephrine reuptake inhibitor
TCM	traditional Chinese medicine

## Clinical Implications

- Acupuncture is a popular and safe treatment for various illnesses, including psychiatric disorders such as depression.
- The published body of research currently has limited evidence for or against the use of acupuncture for treating depression and related mood disorders.
- Clinicians should be cautious when recommending acupuncture to patients with depression.

## Limitations

- Many published studies of acupuncture are not translated to English, and this may limit our understanding of the procedures and findings.
- Acupuncture research is particularly challenging to carry out, owing to a lack of adequate placebo interventions. This limits the quality of the available evidence.

A US-based survey revealed that 34% of psychiatric outpatients with MDD were using alternative therapies,<sup>13</sup> and 20% of mostly US-based depressed patients had used a CAM therapy, including acupuncture, for their depression<sup>14</sup>; in the United Kingdom, psychological distress, including depression, was found to be the second most common reason why people seek acupuncture.<sup>15</sup> Given the unsatisfactory response rates of AD treatment, and the growing interest in acupuncture and other CAM therapies, continued research in this area is of major importance.

## Concepts of Acupuncture and Depression in TCM

Acupuncture, a part of TCM, aims to restore and maintain health by stimulating specific points using various techniques. Diagnosis is aimed at differentiating underlying clinical and physiological imbalances and individually targeting treatment to restore adaptability and optimize function. The acupuncturist synthesizes and analyzes the symptoms and signs gathered from the history of the illness and from physical examination. For different syndromes in the same disease entity, different therapeutic methods are applied.<sup>16</sup>

In TCM, the proposed etiology of mental disorders is internal damage caused by the dysregulation of the 7 emotions, which are joy, anger, worry, contemplation (thinking), sorrow (grief), fear, and shock. When 1 of the 7 emotions is in excess, it may generate malfunction of related *zang-fu* (internal organs), resulting in mental disorder, as described in the book *Nèi Jīng*, 内经, commonly translated as, *The Inner Canon of Huangdi* or *Yellow Emperor's Inner Canon* (see Veith<sup>17</sup>). For example, excessive anger damages the liver, excessive joy damages the heart, excessive thinking damages the spleen, excessive grief damages the lung, and excessive fear damages the kidney.

## Proposed Physiologic Mechanisms of Acupuncture for Depression

Current physiological studies of acupuncture suggest that acupuncture mediates signals that control information exchange across a network of interconnected channels, to restore adaptability and maintain balance.<sup>18</sup> Acupoints can be thought of as interconnected nodes in this functional network.<sup>18</sup> Psychiatric symptoms of depression and anxiety are associated with key neurotransmitters, such as 5-HT, NE, and DA, as well as endorphin hormones.<sup>19–21</sup> Depression may also be associated with dysregulation of the HPA axis. Several animal and human experimental studies indicate that acupuncture needling has demonstrable physiological effects and that it may modify the neural functioning currently believed to be implicated in the pathophysiology of affective disorders.<sup>22</sup> Acupuncture is thought to influence neuroendocrine and immune systems, and it may treat depression by regulating levels of 5-HT, NE, DA, endorphins, or glucocorticoids<sup>23–26</sup> and by stimulating hypothalamic and hippocampal response.<sup>27–32</sup>

## Efficacy and Safety of Acupuncture for Depression

Three recent systematic reviews<sup>33–35</sup> indicate that there is insufficient evidence to determine acupuncture's efficacy in the treatment of depression, and emphasize the need for further study. Much of the published research on acupuncture has originated in China. We identified about 114 Chinese-language reports of acupuncture for depression, including 53 RCTs, 17 simple RCTs, 12 animal studies, 6 theoretical articles, and 30 review articles. While it is beyond the scope of our paper to examine all of these publications, some of them,<sup>36–38</sup> in addition to a few minor ones from Eastern Europe,<sup>39–42</sup> have been summarized by Schnyer et al,<sup>16</sup> but are difficult to fully evaluate, both because the diagnostic criteria used differ from those of the DSM-IV and because most of these studies have not been translated into English, except for the abstracts.

In 2008, a meta-analysis<sup>43</sup> examined the benefits of acupuncture for depression, and suggested that acupuncture could significantly reduce depressive severity. In 2010, another meta-analysis,<sup>44</sup> reviewing 207 related clinical studies, supported acupuncture as safe and effective for MDD and PSD. The efficacy of acupuncture monotherapy was comparable to ADs alone in improving clinical response and alleviating symptom severity of MDD, but the review also found that sham (control treatment) acupuncture had comparable effects on depression. There was limited evidence as to whether acupuncture combined with ADs could yield better outcomes than ADs alone in treating MDD. Acupuncture was superior to ADs and wait-list control subjects in improving both response and

symptom severity of PSD. Adverse events with acupuncture were significantly less common than with ADs. However, acupuncture's efficacy in other forms of depression remains to be determined.<sup>44</sup>

We will review clinical applications of acupuncture for depression, including as monotherapy and augmentation, and as for reducing AD side effects. We will also review adverse effects of acupuncture and discuss the limitations of current studies.

### *The Effectiveness of Acupuncture as Monotherapy for Depression*

Several clinical trials have been carried out with manual, electric, and laser acupuncture for different kinds of depression, including MDD, MinD, antenatal, PPD, menopause, geriatric, and PSD. We will review selected trials in this section.

*Manual Acupuncture as a Monotherapy for MDD.* Two well-designed clinical trials support acupuncture with manual stimulation as an effective monotherapy for depression. In a pilot study,<sup>45</sup> 38 women (aged 18 to 45 years) who met DSM-IV diagnostic criteria for current MDD were randomized to 1 of 3 treatments, delivered during 8 weeks (12 sessions): active acupuncture ( $n = 12$ ) to treat symptoms of depression; an active control acupuncture ( $n = 21$ ) to treat a TCM pattern configuration nonspecific to depression; and wait-list control subjects ( $n = 11$ ). Treatments were standardized, but individually tailored, and were provided in a double-blind fashion by separating assessors from treatment providers. A significant difference in symptom reduction between the groups was found on the HDRS,<sup>46</sup> with the active acupuncture resulting in greater symptom reduction during 8 weeks, compared with nonspecific acupuncture.

In a double-blind 8-week study of 151 men and women with MDD using the same design,<sup>47</sup> there was a significant decrease in depression severity by the 17-item HDRS across the entire sample, but the rate of change varied by group. Active and nonspecific acupuncture both were significantly more effective than the wait-list group, but neither acupuncture intervention was significantly better than the other.

*EA as a Monotherapy for MDD.* Several studies have investigated acupuncture with electrostimulation or EA in the treatment of MDD. Luo et al<sup>48–50</sup> compared EA with maprotiline in MDD in 3 separate studies ( $N = 317$ ) that found comparable decreases in HDRS scores and fewer side effects with EA. Another Chinese study<sup>49</sup> (summarized in Brewington et al<sup>51</sup>) also found comparable decreases in depressive symptoms in patients receiving EA and those receiving amitriptyline.

Yang et al<sup>52</sup> compared a combination of manual and EA with the tetracyclic AD mianserin in 29 patients and found a significant reduction in HDRS scores in both groups, but no difference between groups. In a study ( $N = 66$ ) comparing EA with the tetracyclic AD maprotiline in patients with anxiety somatization syndrome, Han et al<sup>53</sup> found that subjects receiving EA scored lower in self-report measures of depression and anxiety, and that the efficacy index was significantly higher for EA, compared with maprotiline. In a more recent study<sup>54</sup> of 60 patients, the same group found EA to be comparable to maprotiline, with fewer side effects.

*Laser Acupuncture as a Monotherapy for MDD.* A small, double-blind RCT<sup>55</sup> evaluated laser acupuncture for mild-to-moderate depression in a primary care setting. Thirty patients were randomized to either active or inactive laser treatment, and after 8 weeks there was a significant advantage for verum laser acupuncture, compared with sham laser acupuncture.

*Acupuncture as a Monotherapy for MinD.* Eich et al<sup>56</sup> conducted a double-blind study of 43 outpatients with MinD and 13 patients with generalized anxiety disorder and found greater improvement in the verum (active) acupuncture with manual stimulation, compared with the sham acupuncture.

*Acupuncture as a Monotherapy for Antenatal and PPD.* In a double-blind pilot study,<sup>57</sup> 61 pregnant women with MDD and an HDRS-17 score of 14 or more were randomly assigned to 1 of 3 treatments, delivered during 8 weeks: active acupuncture ( $n = 20$ ); an active control acupuncture ( $n = 21$ ); and, massage ( $n = 20$ ). Acupuncture treatments were standardized, but individually tailored. Responders to acute-phase treatment (50% or more reduction in HDRS-17 score from baseline) continued their original treatment until 10 weeks, postpartum. Response rates at the end of the acute phase were significantly higher for active acupuncture (69%) than for massage (32%). Response rate in the nonspecific acupuncture group was 47.4%, which is not significantly different from active acupuncture. Responders to all treatments combined had significantly lower depression scores at 10 weeks postpartum than nonresponders.<sup>57</sup>

This study<sup>57</sup> was replicated with 150 additional pregnant women with MDD.<sup>58</sup> Women who received acupuncture specifically for depression experienced a greater decrease in symptom severity, compared with the combined control subjects or control acupuncture alone. They also had a significantly greater response rate (63.0%) than the combined control subjects (44.3%) and control acupuncture alone (37.5%). Symptom reduction and response rates did not differ significantly between control subjects who received the control interventions (control acupuncture, 37.5%; massage, 50.0%). The study demonstrated symptom reduction and a response rate comparable to that

observed with standard depression treatments, suggesting acupuncture could be a viable option for depression during pregnancy.

*Acupuncture as a Monotherapy for Menopausal Depression.* A study of 60 patients<sup>59</sup> showed that abdominal acupuncture is an effective and safe method for menopausal depression. Acupuncture alleviated menopausal depressive symptoms, with lower relapse rates and fewer adverse reactions.

*Acupuncture as a Monotherapy for Geriatric Depression.* Some researchers<sup>60</sup> have investigated the effects of acupuncture on stress-related psychological symptoms and cellular immunity in young adults and elderly subjects. Subjects received 6 acupuncture sessions, with bilateral needling at acupoints LI4, SP6, and ST36. Psychological variables (depression, anxiety, and stress) were investigated using self-assessment inventories. Acupuncture significantly reduced depression, anxiety, and stress scores, and also significantly increased T-cell proliferation, especially in the elderly group. No changes in cellular sensitivity to dexamethasone were observed. The findings suggest that acupuncture may attenuate psychological distress and cellular immunosenescence.

*Acupuncture as a Monotherapy for PSD.* In a double-blind RCT study comparing acupuncture to fluoxetine in 43 patients with PSD,<sup>61</sup> the response rate was 73.9% for acupuncture, compared with 80.0% for fluoxetine. HDRS scores were reduced significantly in both groups. The incidence of adverse events was 13.0% and 15.0% in the acupuncture and fluoxetine group, respectively. This study<sup>61</sup> suggests that acupuncture for PSD has comparable efficacy to fluoxetine, without significant adverse reactions.

In another study from China involving TCM syndrome differentiation,<sup>62</sup> 300 PSD patients were randomized to acupuncture ( $n = 150$ ) or fluoxetine 20 mg/day ( $n = 150$ ). In acupuncture patients, acupoints Sishengcong (EX-HN 1), Baihui (GV 20), and Shenting (GV 24) were needled once daily in combination with other acupoints targeting different syndromes. After 2 months, the HDRS scores in both groups decreased significantly, and improvement with acupuncture was significantly greater than with fluoxetine. Remission (cure) rates in the medication and acupuncture groups were 23.3% and 10.7%, respectively; response rates (marked improvement) were 54.7% and 27.3%, respectively; partial response (improvement) rates were 11.3% and 38.0%, respectively; and nonresponse (ineffective) was 10.7% and 24.0%, respectively. Total efficacy rates were 89.3% for fluoxetine and 76.0% for acupuncture. The authors concluded, based on the chi-square test, that the therapeutic effect of acupuncture was significantly superior to that of medication; yet the results described in the abstract suggest that acupuncture was, at best, comparable to fluoxetine in efficacy for PSD.

### **Acupuncture Augmentation of ADs in Depression**

When people obtain limited benefit from an AD, clinicians usually increase the dose or augment with a second agent rather than switch medications.<sup>63</sup> Recent investigations of AD augmentation showed that the remission rates decreased with greater history of treatment failure,<sup>64</sup> suggesting a need for more effective augmentation strategies.

In view of the promising though preliminary evidence for neurobiological activity of acupuncture, an augmentation strategy combining acupuncture with ADs may provide additive or synergistic benefits. ADs are thought to act, in part, by increasing neurotransmitter availability in the neuronal synapse, hence increasing interaction with the postsynaptic cell and leading to various complex intracellular mechanisms that ultimately produce a clinical effect.<sup>21–29</sup> Opioid mechanisms have also been implicated.<sup>65</sup> In AD partial responders, acupuncture may theoretically augment the AD effect by increasing serotonergic and (or) noradrenergic activity in the synapse,<sup>23,25,66,67</sup> resulting in a combined SNRI-like mechanism of action. Alternatively, acupuncture's potential impact on endogenous endorphins<sup>26</sup> could complement the AD by dampening HPA axis activity and decreasing cortisol production.<sup>24,68</sup>

Yeung et al<sup>69</sup> carried out an open pilot study of acupuncture augmentation therapy in 30 AD partial responders and nonresponders with MDD, with the option of weekly or twice-weekly sessions of a fixed acupoint combination. Baseline ADs used by our sample included bupropion, citalopram, omega-3 fatty acids, and 5-methyltetrahydrofolate (brand name, Deplin); tricyclic ADs, SNRIs, and monoamine oxidase inhibitors were less represented. In the intent-to-treat sample, HDRS-17 scores decreased significantly from 18.5 (SD 3.8) to 11.2 (SD 5.3) in the weekly group, and from 18.5 (SD 3.3) to 11.8 (SD 4.8) in the twice-weekly group. Improvement did not differ significantly between treatment arms. Response rates were 47% for all, 50% for the weekly group, and 33% for the twice-weekly group. Our findings suggest that once- or twice-weekly acupuncture augmentation is safe, well tolerated, and effective in AD partial responders and nonresponders. A single-blind placebo-controlled study of 70 inpatients with MDD found that adding acupuncture to mianserin improved outcome slightly, but active acupuncture had no significant advantage, compared with nonspecific acupuncture.<sup>70</sup>

In a study of acupuncture augmentation in patients with bipolar depression and refractory depression ( $N = 26$ ), Dennehy et al<sup>71</sup> evaluated TCM acupuncture with manual stimulation against an active acupuncture control (nonspecific points) and against AD alone. Acupuncture augmentation showed equivalent, significant improvement, compared with nonspecific acupuncture in

the primary outcome measures, Inventory of Depressive Symptomatology and Global Assessment of Functioning.

In a randomized, double-blind, sham-controlled trial<sup>72</sup> of 80 patients with MDD, verum acupuncture plus low-dose fluoxetine (10 mg/day) produced significantly greater improvement in symptoms of anxiety and fewer side effects than sham acupuncture plus a higher dose of fluoxetine (20 to 30 mg/day), and results for depression were comparable overall. The overall rate of adverse events in the acupuncture group (8.75%) was significantly lower than in the high-dose fluoxetine group. This suggests that combining acupuncture with low-dose fluoxetine for depression with severe anxious symptoms is as effective as a standard dose of fluoxetine, and better tolerated.

There are no published controlled studies of acupuncture as an adjunct to the newer ADs, such as the selective serotonin reuptake inhibitors and SNRIs, though the open augmentation study by Yeung et al,<sup>69</sup> which included primarily bupropion and citalopram, supports the development of controlled studies.

### **Acupuncture for Reducing AD Side Effects**

ADs have many side effects,<sup>73</sup> and even the newest ADs may still cause weight gain, nausea, drowsiness, cognitive impairment, insomnia, and sexual dysfunction.<sup>74</sup> Many augmentation strategies focus on ameliorating side effects of the primary AD, especially when partial or complete AD response has been obtained.

Acupuncture has been used to manage various physical symptoms that can often present as side effects from ADs, including nausea,<sup>75</sup> weight gain,<sup>76</sup> and sexual dysfunction.<sup>77,78</sup> A Cochrane review of acupuncture for nausea and vomiting from postoperative sickness, chemotherapy, and pregnancy, showed superior effects of acupoint P6 over sham; pooled data of trials including different antiemetics showed that P6 stimulation was superior to antiemetic medication for nausea, and equivalent for vomiting.<sup>79</sup>

Preliminary studies on the antiobesity effects of acupuncture indicate that it may help facilitate weight loss by regulating appetite, intestinal motility, and metabolism, as well as emotional factors such as stress.<sup>66</sup> However, a critical review<sup>80</sup> found most trials to be descriptive, of short duration (12 weeks or less), and designed using nonstandard treatment protocols. A study of 800 patients receiving auricular acupuncture<sup>81</sup> found significant weight loss in 64.8% of participants after 3 months, and in 35.5% after 6 to 12 months.

Few studies have assessed the efficacy of acupuncture for sexual dysfunction, though the earliest Chinese medical texts mention this condition, and TCM has developed a framework for diagnosing and treating

sexual dysfunction.<sup>82</sup> A small prospective pilot study of 22 patients with psychogenic erectile dysfunction found that acupuncture achieved significantly better results in 68.4% of the participants as compared with 9% in the control group (acupuncture for headache).<sup>77</sup> To date, no studies have evaluated acupuncture's effect in AD-induced sexual dysfunction.

Possible mechanisms of action for the amelioration of medication-induced sexual dysfunction may involve serotonergic and noradrenergic pathways. Therefore, acupuncture augmentation could have a dually beneficial effect, by directly ameliorating depressive symptoms as well as controlling AD side effects. While currently there are no prospective studies examining acupuncture as a treatment for AD-induced side effects, the clinical trial<sup>72</sup> discussed in the previous section suggests that acupuncture in combination with low-dose fluoxetine was better tolerated than sham acupuncture with high-dose fluoxetine. Therefore, depressed patients with intolerable side effects from ADs may benefit from the combination of acupuncture and lower AD doses.

### ***Adverse Events Associated With Acupuncture for Depression***

There are few documented adverse effects of acupuncture.<sup>83</sup> In the previously discussed study with 30 subjects,<sup>69</sup> the most common side effects included soreness and (or) pain ( $n = 7$ ), bruising ( $n = 4$ ), and mild bleeding ( $n = 1$ ) at the needle site. Only one subject discontinued because of pain. In the previously discussed trial of 80 patients with MDD, the overall rate of adverse events owing to acupuncture was only 8.75%.<sup>72</sup> Given the well-established safety of acupuncture,<sup>84,85</sup> as evidenced by minimal side effects and no documented adverse interactions with ADs, it could, if effective, be readily incorporated when a preexisting AD regimen has been of partial benefit.

### ***Limitations of Studies to Date on Acupuncture for Depression***

While the published data suggest that acupuncture may be beneficial for depression, results should be interpreted with caution for numerous reasons as expanded on below:

*Limitations of Acupuncture Sham Controls.* Blinding acupuncturists is impossible,<sup>86</sup> needling nonacupuncture points can produce benefit,<sup>47</sup> and acupoints considered ineffective in one style or tradition may be effective in another.<sup>87,88</sup> Nonpenetrating acupuncture needlelike devices have been validated,<sup>89–92</sup> but the high risk of unmasking requires recruiting patients naive to acupuncture. These needles are also expensive and cumbersome, requiring tape and rings to hold them.

*Differential Effects on Depression With Different Acupuncture Treatment Protocols.* An example of different acupoint combinations and diverse types of acupuncture

stimulation would be manual acupuncture, compared with EA. Different point combinations may affect distinct depression pathways, and may account for differences in treatment response.<sup>86</sup> Studies of acupuncture for depression have used different types of needle stimulation (manual and electrical), making it difficult to generalize results. Most Chinese trials primarily used electrostimulation of scalp points, while US trials used manual stimulation of body points. No studies have compared the effectiveness of electrical and manual stimulation in depression, but neuroimaging studies indicate that different brain networks are involved in manual and EA.<sup>93</sup> Combined methods are commonly taught and used in clinical practice.

*Insufficient Systematic Training and Supervision of Treatment Providers.* Training of the acupuncturists in clinical trials is a fundamental step in assuring that all patients receive the same active or control interventions during the study.<sup>89,94</sup> Only a few studies<sup>45,47,57,58</sup> have implemented rigorous training, supervision, and reliability assessment.

*Methodological Limitations.*<sup>34</sup> These include poor description of the protocol, for example, including groups of points to choose from but no guidelines for their selection and implementation. Other reports do not describe the protocol or use fixed protocols for conditions such as depression.<sup>33</sup>

Online eTable 1 summarizes selected studies of acupuncture for depression that represent the wide range of investigations carried out since 1985.<sup>25,45,47,48,54–59,61,62,69–72,95–97</sup>

## **Conclusion**

Although the reviewed studies indicate that there is insufficient evidence on the AD effectiveness of acupuncture, they nonetheless suggest that acupuncture has the potential to be an effective, safe, and well-tolerated monotherapy for depression and a viable augmentation for AD partial responders and nonresponders. However, acupuncture augmentation of ADs was only investigated in MDD, and there is no report on whether acupuncture could be an effective augmentation of ADs for other kinds of depression. Manual acupuncture may also help to reduce side effects of ADs. There are no reports on acupuncture for preventing recurrence after recovery from a depressive episode—a key problem in the treatment of depression, given the high recurrence rates. Further investigation into all of these aspects of acupuncture and depression is needed.

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