

# Optimizing Treatment for Major Depressive Disorder in Adolescents: The Impact of Intradermal Acupuncture - A Randomized Controlled Trial Protocol

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**Background:** Major depressive disorder (MDD) exhibits a pronounced occurrence among adolescents, aligning closely with the lifetime prevalence rate of 16.6% observed in adults. It is difficult to treat and prone to recurrence. Acupuncture has shown potential in enhancing treatment effectiveness. Nonetheless, there is a lack of research on the use of intradermal acupuncture (IA) in treating adolescent MDD.

**Methods:** This study is a double-blind, randomized controlled trial. A cohort of 120 participants will be assigned randomly to three distinct groups, namely a Selective Serotonin Reuptake Inhibitors (SSRIs)-only group, a sham intradermal acupuncture combined with SSRIs (SIA) group, and an active intradermal acupuncture combined with SSRIs (AIA) group. Hamilton Depression Rating Scale will serve as the primary outcome, while Patient Health Questionnaire-9, Self-Rating Depression Scale, Pittsburgh Sleep Quality Index, and Short Form 36 Questionnaire will serve as secondary outcomes in assessing the amelioration of depressive symptoms in patients. These data will be analyzed using SPSS26.0 software.

**Results:** We will assess the efficacy and safety of IA for MDD using commonly employed clinical psychiatric scales.

**Conclusion:** The efficacy of IA in treating adolescent MDD may be demonstrated in this study, suggesting its potential for optimizing MDD treatment schemes.

**Trial Registration:** ClinicalTrials.gov Identifier: NCT 05832619 (April 27, 2023).

**Keywords:** major depressive disorder, intradermal acupuncture, selective serotonin reuptake inhibitors, adolescent, randomized controlled trial, protocol

## Introduction

Major depressive disorder (MDD) poses a significant public health challenge, often manifesting in individuals under the age of 18.<sup>1</sup> Adolescence is a crucial developmental stage marked by a significantly elevated incidence of MDD, which closely mirrors the adult lifetime prevalence rate of 16.6%.<sup>2,3</sup> The presentation of MDD in adolescents is comparable to that observed in adults. However, it has been observed that adolescents commonly exhibit fewer delusions as opposed to adults.<sup>4</sup> Adolescent MDD can have significant and lasting effects, such as a greater occurrence of depressive episodes leading to prolonged social and mental impairments, as opposed to MDD presenting in later adulthood, which should be taken into consideration.<sup>5</sup> Adolescents may exhibit a range of traits, including mood fluctuations, irritability, low

tolerance for frustration, temper tantrums, somatic discomfort, academic underperformance, and interpersonal difficulties, as an alternative to expressing depressive emotions overtly.<sup>6</sup> One of the most prevalent causes of death in this demographic is suicide.<sup>7</sup>

Current investigations in the domains of genetics, molecular biology, and neuroimaging are perpetually augmenting our understanding of the neurobiological foundations of MDD.<sup>8</sup> The release of numerous neurotransmitters and peptides is widely acknowledged to be induced by negative experiences.<sup>9</sup> One of the extensively acknowledged etiological mechanisms of MDD is the monoamine neurotransmitter hypothesis.<sup>10</sup> As per this hypothesis, the manifestation of MDD can be ascribed to the depletion of neurotransmitters like 5-hydroxytryptamine (5-HT), norepinephrine (NA), or dopamine (DA) within the Central Nervous System.<sup>11,12</sup> Previous studies have confirmed the correlation between the introduction of synthetically generated 5-HT in the cerebral region and a surge in cortisol concentrations. Subsequently, this surge in cortisol concentrations triggers the synthesis of hepatic tryptophan 2,3-dioxygenase, which in turn accelerates the breakdown of peripheral tryptophan. Additionally, this occurrence is linked to the activation of N-methyl-D-aspartate receptors.<sup>13–15</sup> Anhedonia, loss of motivation, energy, and attention, which are fundamental symptoms of MDD, have been associated with dysfunction in the DA system.<sup>16</sup> Changes in DA function are likely responsible for altered neural response to rewards and decision-making behavior in rewarded conditions.<sup>17</sup> In particular, cortico-striatal synapses, as the initial connections between cortical structures and the striatum in the basal ganglia processing stream, undergo Hebbian plasticity when exposed to rewards and punishments.<sup>18</sup> Specifically, it is proposed that the functioning of DA neurons in the mesolimbic pathway, which extends from the ventral tegmental area (VTA) to the nucleus accumbens in the ventral striatum (VS), plays a role in the development of MDD.<sup>19,20</sup> Moreover, the hypothesis has been supported by animal models, which have demonstrated that there is an elevation in the functioning of DA neurons located in the midbrain VTA. Furthermore, it has been observed that by suppressing this escalated activity, the behavioral symptoms associated with can be reversed.<sup>21</sup>

The complex mechanism underlying mental and neurological disorders is being clarified by neuroimaging studies, such as electroencephalography and resting-state functional magnetic resonance imaging (rs-fMRI).<sup>22–25</sup> These studies shed light on various aspects of MDD, such as the aberrations in emotion processing, reward pursuit, and emotion regulation.<sup>26</sup> By substantiating the involvement of these domains, neuroimaging studies provide valuable insights into the dysfunctional nature of MDD.<sup>27</sup> The amygdala–medial prefrontal cortex (mPFC) and hippocampus are neural regions that play a crucial role in the process of acquiring and consolidating emotional memories.<sup>28,29</sup> Additionally, reward valuation, cost/benefit analysis, decision-making and anhedonia are intricately interconnected with PFC.<sup>30</sup> VS and orbitofrontal cortex (OFC) play a contributory role in the experience of pleasure.<sup>31,32</sup> VTA, VS, and amygdala are closely associated with prediction, anticipation, and motivation.<sup>31,33</sup> In contrast to adults MDD, it has been demonstrated that a greater concentration of atypical brain regions in the limbic system and striatum (specifically, the caudate and lentiform nucleus) among adolescents MDD.<sup>34</sup>

Nowadays, interventions evaluated include psychotherapies, complementary and alternative medicines, exercise, second-generation antidepressants,<sup>35</sup> and family psychoeducation.<sup>36</sup> Among these treatments, selective serotonin reuptake inhibitor (SSRIs) is frequently utilized in the clinical management of adolescent MDD, despite the fact that approximately 50% of patients do not exhibit a satisfactory response to it.<sup>37,38</sup> Besides, some of the side effects of SSRIs take a prolonged period to manifest.<sup>39</sup> Therefore, optimal therapeutic strategies need to be established to address the this disabling ailment.

According to the American College of Physicians (ACP), acupuncture is a potential alternative medicine for the treatment of MDD.<sup>35</sup> Acupuncture has been frequently used as a complementary therapy for MDD in conjunction with antidepressant. Previously observed data suggests that acupuncture only or combination with traditional antidepressants significantly elevates therapeutic effects and mitigates adverse reactions of antidepressant.<sup>40,41</sup> In comparison to sham acupuncture treatment, acupuncture has been shown to enhance resting-state functional connectivity (rsFC) between the left amygdala and anterior cingulate cortex (ACC), as well as the right amygdala and left hippocampus. This increase in rsFC was found to be positively correlated with clinical improvement, suggesting that the therapeutic benefits of acupuncture are mediated by the limbic system, particularly the amygdala and ACC.<sup>42,43</sup> In parallel, research findings have revealed that acupuncture primarily achieves its therapeutic effects in MDD by enhancing rsFC between the inferior

VS and mPFC, ventral rostral putamen, as well as the amygdala. This indicates that acupuncture has the ability to modify the corticostriatal reward/motivation circuitry, thus leading to its therapeutic benefits.<sup>44</sup> Besides, prior research indicates that acupuncture can not only enhance the FC between the posterior central gyrus, PFC, and the bilateral ACC in individuals suffering from MDD but also decrease FC between the amygdala and OFC in patients with MDD.<sup>45,46</sup> Another study has demonstrated that acupuncture intervention significantly enhances FC between the hippocampus and ventral cephalic putamen in individuals with MDD during rs-fMRI.<sup>44</sup> Furthermore, there is evidence suggesting that acupuncture may impart a sustainable augmentation of the antidepressant properties of the prescribed medication. In instances where patients manifest susceptibility to the adverse effects of SSRIs, adjunctive acupuncture therapy might promote drug tolerance and potentially decrease the necessity to escalate medication dosage.<sup>47</sup>

Intradermal acupuncture (IA) is a method of acupuncture that involves the insertion and fixation of intradermal needles in acupoints on the skin for extended stimulation, which is effective in treating various diseases.<sup>48</sup> Compared to traditional acupuncture, this modality is less painful and steadily stimulates acupoints. The operation of IA is uncomplicated, and it has garnered a significant level of patient acceptance. Furthermore, Noda Y's group revealed that active IA (AIA) may induce alterations in vagal function to improve Beck's Depression Inventory scores in individuals with MDD.<sup>49</sup> However, the utilization of IA in the clinical setting to address adolescent MDD is relatively infrequent, and there exists a dearth of literature on the subject matter. Besides, previous clinical studies have been limited by possibility of bias, preventing them from providing an objective demonstration of the effectiveness of IA for individuals with MDD. What's more, the efficacy of combining SSRIs with IA is uncertain. Therefore, it is imperative to thoroughly investigate the safety and efficacy of IA treatment in individuals with MDD using a well-designed and comprehensive methodology.

## Methods

### Study Design

This is a double-blind, randomized controlled trial wherein eligible participants will be assigned randomly to three groups: SSRIs-only group, sham IA (SIA) combined with SSRIs group, and AIA combined with SSRIs group, all at a 1:1:1 allocation ratio. The study process is illustrated in [Figure 1](#), while the schedule of enrolment, treatments, and assessments can be seen in [Table 1](#). It is worth noting that the reporting of this protocol conforms with the SPIRIT reporting guidelines.<sup>50</sup>

### Setting

This study was approved by the Medical Ethics Committee of the Third Affiliated Hospital of Zhejiang Chinese Medical University (Ethical Number: ZSLL-KY-2022-001-01) and registered with the ClinicalTrials.gov Identifier: NCT 05832619.

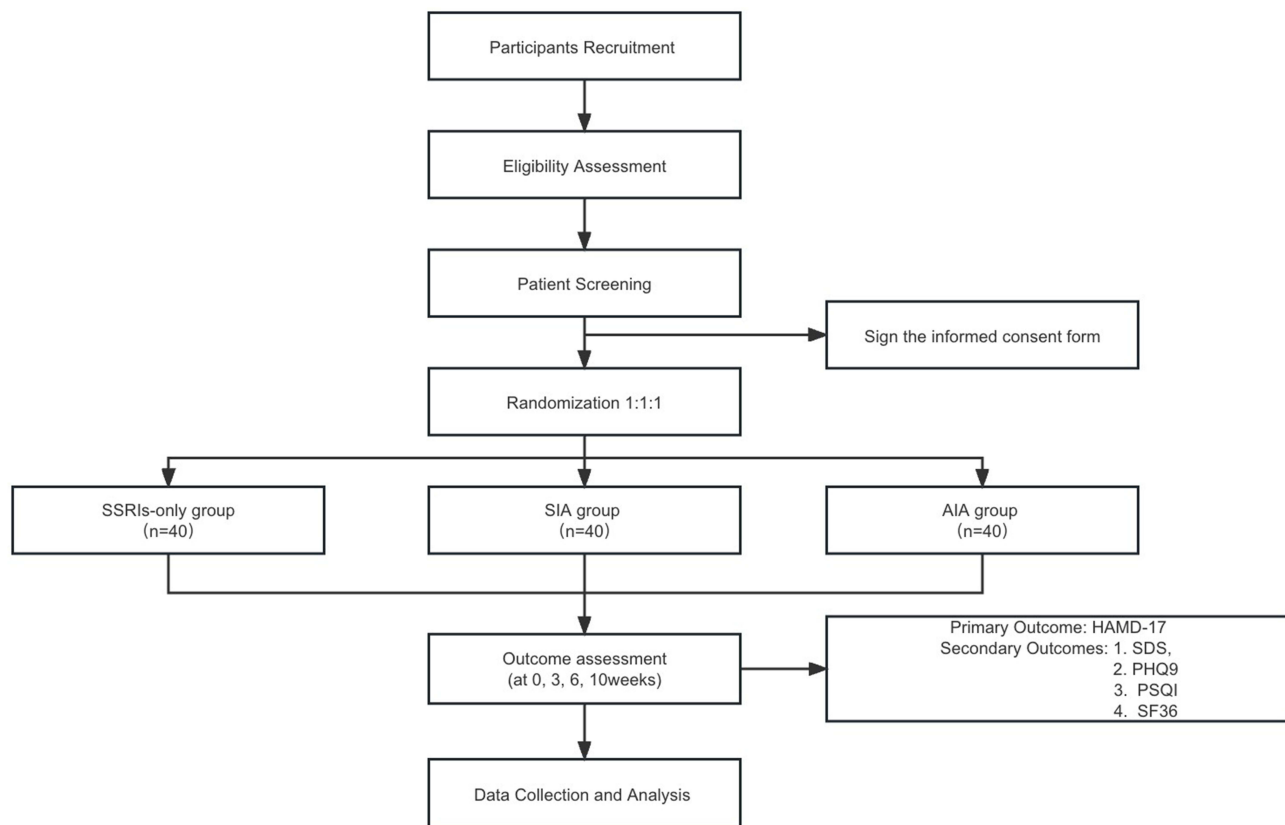
### Participant Recruitment

The recruitment of participants will involve enrollment from Third Affiliated Hospital of Zhejiang Chinese Medical University. Enrollment methods will primarily comprise the dissemination of advertisements on WeChat and posters in local communities and hospitals. Eligibility of prospective participants shall be subject to an assessment conducted by psychologists. Upon successful eligibility assessment, the participants and their guardians will be required to provide informed consent before proceeding with the baseline assessments.

### Eligibility Criteria

#### Inclusion Criteria

1. Patients meeting the diagnostic criteria for MDD as specified in the International Classification of Disease-10 (ICD-10); Hamilton Depression Rating Scale (HAM-D-17)  $\geq 7$ ;
2. Aged between 12 and 17 years (without gender restrictions);
3. Take SSRIs for a minimum of two weeks;
4. Written informed consent is obtained by the person and guardian.



**Figure 1** Flow chart of the study process.

### Exclusion Criteria

1. ICD-10 diagnoses: schizophrenia, bipolar disorder, manic episode or other psychotic disorders; alcohol and drug addiction;
2. Significant skin lesions, severe allergic diseases, tumors, and severe or unstable internal diseases involving the cardiovascular, digestive, endocrine, or hematological system;
3. Acute suicidal tendency (HAMD-17 suicide factor score above 3);
4. Allergy to adhesive tape and fear of IA;
5. Pregnancy and lactation;
6. Mental retardation and difficult to cooperate with doctors;
7. Participating in other clinical trials.

### Randomization and Allocation Concealment

The patients involved in this study will receive randomized sequences generated by the SPSS software (version 26.0) random number generator program. They will be distributed in a 1:1:1 ratio to three groups; namely, the waiting list group (comprising of patients receiving SSRIs treatment only), SIA with SSRIs group, and AIA with SSRIs group.

### Blinding

In order to guarantee the impartiality and credibility of the study, measures will be taken to ensure that the individuals involved in the research, including participants, outcome assessors, and statisticians, are unaware of the group assignment. Given the distinctive characteristics of acupuncture treatment, it is impractical to blind acupuncturists. However, they will be given explicit instructions to abstain from discussing treatment allocation with participants. Furthermore,

**Table 1** Schedule of Enrollment, Treatments, and Assessments

Study Period	Screening	Baseline Week 0	Treatment Period Week 3	Treatment Period Week 6	Follow-Up Period Week 10
Eligibility screening	×				
Demographic data	×				
Case data	×				
Inclusion criteria	×				
Exclusion criteria	×				
Informed consent	×				
Treatment			×	×	×
Outcome assessment					
HAMD-17		×	×	×	×
SDS		×	×	×	×
PHQ9		×	×	×	×
PSQI		×	×	×	×
SF36		×	×	×	×
SSRI		×	×	×	×

acupuncture sessions will be carried out in a designated space to prevent any form of interaction among participants, thereby ensuring the effective implementation of the blinding procedure.

## Intervention

All eligible participants will undergo a random assignment to one of three groups, namely the waiting list group, SIA group, or AIA group. Each group will receive therapy for 6 weeks and a follow-up period of 4 weeks. Patients assigned to the AIA group will undergo a course of 10 treatments with AIA, while their counterparts in the SIA group will receive an equal number of treatments with SIA. The treatment in the AIA group and the SIA group will be conducted by six licensed Traditional Chinese Medicine practitioners. These acupuncturists will receive standardized training to maintain the consistency of acupuncture point sites, needle retention time, and compression number. Assessment and medication prescription will be conducted by psychologists.

## Antidepressant Medication

All individuals deemed eligible for participation in the waiting list group will be exclusively administered with oral SSRIs once per day. These medications may include fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram and escitalopram. The research will be conducted exclusively using the initial recommended doses outlined in the guidelines.<sup>51</sup> These doses include 5 mg/d for fluoxetine and citalopram, 25 mg/d for fluvoxamine, and 50 mg/d for sertraline. Additionally, during a six-week period, dosage adjustments will be made by psychiatrists.

## Active Intradermal Acupuncture (AIA)

Patients in this specific cohort will receive a therapeutic regimen consisting of AIA and SSRIs for a total of ten treatments. The regulation of nuclei in the brain stem through the supraspinal neural shortcut is a potential mechanism by which AIA may exert its effects. When compared to treatment with SSRIs alone, AIA demonstrates added

therapeutic benefits in the management of patients suffering from MDD.<sup>52</sup> The acupoints that have been determined to be commonly utilized in the treatment of MDD have been identified by our research team through the process of data mining.<sup>53</sup> The most frequently used acupoints are Baihui (GV20), Taichong (LR3), Neiguan (PC6), Sanyinjiao (SP6), Yintang (GV29), and Shenmen (HT7). Due to the unique characteristics of IA, it is inconvenient to retain it on the patient's head and face for a long period of time. Therefore, we have selected LR3, PC6, SP6, and HT7 as the four acupoints for treatment. Given the anatomical characteristics of acupoints,  $\phi 0.20 \times 1.2$ mm AIA (Japanese Seirin) will be vertically inserted into the HT7 and PC6, with retention within the skin. Likewise,  $\phi 0.20 \times 1.5$ mm AIA will be inserted into LR3 and SP6. These needles will be kept in place for a period of 72 hours, after which they will be removed and rested for one day. The therapy will be administered at four-day intervals. Throughout the retention period, individuals will receive guidance on the frequency and duration of use; encouraging them to push the device 3–4 times daily for roughly 1 minute each session- dependent on the limit of the patient's tolerance-spacing treatments approximately 4 hours apart. The total number of administered treatments will amount to 10 throughout the 6-week duration. [Figure 2](#) provides AIA.

### Sham Intradermal Acupuncture (SIA)

The proposed treatment method involves the application of a device called SIA, which shares the same size, color, and material as the AIA. However, there is a notable variation in the SIA, as it features a slim silicone pad instead of a needle. The acupoints targeted by the SIA are identical to those targeted by the AIA. Each session with the SIA will last for 72 hours, after which it will be removed and allowed to rest for one day without any further stimulation. Ultimately, a total of ten SIA treatments will be administered over a period of six weeks. [Figure 3](#) provides SIA.

### The Position and Function of Acupoints

[Table 2](#) provides a comprehensive reference to the locations of acupoints in accordance with the 2021 People's Republic of China National Standard (GB/T 12346–2021) “Acupoints names and positioning”.

### Outcomes

#### Primary Outcome

The primary outcome will be evaluated prior to the initiation of the intervention, as well as at the 3-week, 6-week, and 10-week follow-up mark.



**Figure 2** Active intradermal acupuncture.



**Figure 3** Sham intradermal acupuncture.

### Hamilton Depression Rating Scale (HAMD-17)

HAMD-17 assessment tool serves as a means for individuals who suffer from MDD to measure the outcomes of the diagnostic evaluation.<sup>54</sup> This instrument categorizes MDD into four levels based on score ranges. A score between 0–7 signifies depressive symptoms, 8–16 reflects symptoms of possible MDD, 17–24 denotes significant MDD, and 25–52 reflects severe MDD. Furthermore, the scale comprises of seven impact factors which include anxiety/somatization, weight change, cognitive impairment, day-night change, blockage, sleep disturbance, and feelings of hopelessness.

### Secondary Outcome

Secondary outcomes shall be evaluated prior to implementation, during the 3rd and 6th weeks following the implementation, and at the culmination of the 10-week post-implementation follow-up.

### Patient Health Questionnaire-9 (PHQ-9)

The PHQ-9 is a self-assessment tool utilized for MDD diagnosis, developed by Spitzer et al in 1999 as part of the PRIME-MD.<sup>55</sup> Its primary objective is to detect and determine the severity of MDD symptoms present in patients over the previous two weeks through the assessment of the nine key symptoms. According to international guidelines, the PHQ-9 has been identified as the most dependable screening tool for effectively identifying MDD during screening

**Table 2** Locations of Acupuncture Acupoints

Acupoints	Location
Shenmen (HT7)	On the inner side of the wrist, at the distal transverse crease of the palmar side, lies the radial border of the flexor tendons of the wrist on the ulnar side of the forearm.
Taichong (LR3)	In the dorsal area, between the first and second metatarsals, there is a depression located in front of the plantar surface of the metatarsal bones where the pulse can be felt.
Neiguan (PC6)	On the anterior side of the forearm, 2 inches from the distal transverse crease on the palmar side, between the flexor carpi radialis and flexor pollicis longus tendons.
Sanyinjiao (SP6)	On the medial side of the calf, 3 inches above the medial malleolus, and posterior to the inner margin of the tibia.

processes. It is widely recognized and utilized for this purpose.<sup>56</sup> Each item on the scale is assessed on a gradation of 0 to 3, contributing to a cumulative score of 27 points. A score between 5 and 9 reflects mild MDD, while a score between 10 and 14 indicates moderate MDD. Moderately severe MDD is represented by a score ranging from 15 to 19, whereas a score of 20 or higher is indicative of severe MDD. Moreover, this scale is a straightforward and expeditious method of evaluation.

### Self-Rating Depression Scale (SDS)

With regard to SDS, the clinical diagnostic criteria is divided into pervasive affect, physiological equivalents or concomitants and psychological concomitants.<sup>57</sup> During testing, individuals are prompted to assess 20 distinct aspects and provide a rating based on a quantitative scale. The four available response options consist of “little time”, “a small portion of time”, “a considerable amount of time”, and “all of the time”. Subsequently, a raw score between the values of 20 to 80 is obtained and transformed into an index score by computing the sum of the raw scores divided by 80 and multiplying the quotient by 100.<sup>58</sup>

According to diagnostic criteria, a standard score below 50 is within the normal range. A score falling within the 50–60 range indicates mild MDD, while a score ranging from 61–70 denotes moderate MDD. Severe MDD may be indicated by a score of  $\geq 70$ . It should be noted that lower scores are indicative of a lesser degree of MDD, whereas higher scores suggest a higher degree of MDD.

### Pittsburgh Sleep Quality Index (PSQI)

The PSQI serves the purpose of evaluating an individual's sleep quality profile and disturbances in the preceding month through the administration of nineteen questions that are aggregated to generate seven distinct factors including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep medication, and daytime dysfunction. The cumulative superimposition of the scores of these factors produces the total score.<sup>59</sup> Scores in the range of 0–5 reflect good sleep quality, 6–10 indicate adequate sleep quality, 11–15 imply average sleep quality, while scores in the 16–21 range indicate very poor sleep quality.

### Short Form 36 Questionnaire (SF-36)

The SF-36 is a comprehensive scale that evaluates various aspects of health via eight distinct health concepts. These health concepts include assessing potential limitations pertaining to physical and social activities due to physical or emotional challenges, the impact of physical health problems on one's usual role activities, physical pain, general mental health, emotional challenges on one's usual role activities, vitality and energy levels, and overall perceptions of general health.<sup>60</sup>

## Data Collection and Management

This study will utilize case report form (CRF) to collect and organize data. Psychiatrists will complete the HAMD-17 assessment through communication with the patients, while the rest of the scales will be self-administered by the patients based on their actual condition. Follow-up visits will be conducted through telephone or WeChat. In addition, trained data management personnel will enter the data from the CRFs for statistical analysis.

## Quality Control

Before conducting formal trials, the research personnel will receive professional clinical training to ensure proficiency in administering IA therapy and educating patients on relevant information. Additionally, they will be required to sign a document outlining standard operating procedures and a confidentiality agreement.

## Statistical Analyses

The intention-to-treat (ITT) principle will guide the analysis' execution. Participants who deviate from the established protocol, specifically by not complying with the prescribed study medications or withdrawing from the study prematurely, are categorized as belonging to the treatment group to which they were initially assigned.<sup>61</sup> The statistical analysis



will be conducted using SPSS26.0. The descriptive statistics will be reported as  $\bar{x} \pm s$  for continuous data. In order to address biases that may deviate from the true value during the research process and to enhance the credibility and rationality of the research findings, it is imperative to conduct a normality test on the data. Pairwise comparisons will be analyzed using paired *t*-test for within-group comparisons and one-way ANOVA for between-group comparisons. If the data follows a normal distribution and satisfies the assumption of homogeneity of variances, a *t*-test will be employed for bias analysis. In the case of non-normal distribution or heterogeneity of variance, non-parametric tests like the Mann–Whitney *U*-test will be used. The *t*-test will calculate the degrees of freedom and determine whether there are significant differences in means among the samples. For repeated measures data, repeated measures ANOVA will be used. Furthermore, this study will assess the practical significance or importance of research findings with significant differences based on the magnitude of effect size. Statistical significance will be set at a *p*-value less than 0.05 for a two-tailed test.

## Discussion

The incidence of MDD among adolescents is notably high, accompanied by a distressing suicide rate. This disease poses formidable challenges in terms of treatment and management, as it is prone to relapse, exhibits numerous physical symptoms, and significantly disrupts the educational and familial lives of affected adolescents. The current situation regarding MDD is particularly grave. SSRIs established as the primary pharmacological intervention for MDD, are extensively utilized due to their demonstrated effectiveness. However, these medications are associated with considerable drawbacks, including a prolonged onset of action, pronounced toxic side effects, and notable withdrawal reactions. Furthermore, adolescent MDD frequently demonstrate negative attitudes and poor adherence to treatment, often resulting in irreparable consequences such as overdose, medication noncompliance, and disregard for medical advice. Traditional Chinese Medicine treatment, specifically acupuncture, offers a promising alternative due to its cost-effectiveness, safety, and enhanced patient compliance. Notably, acupuncture has displayed positive therapeutic outcomes in the treatment of adolescent MDD. Specifically, the efficacy of IA, a type of acupuncture, in augmenting the effectiveness of SSRIs has been substantiated. Nevertheless, the efficacy of IA as a treatment modality for adolescent MDD remains uncertain.

The purpose of this study is to examine the clinical effectiveness of IA in the treatment of adolescent MDD. The data extracted from RCTs exploring the effectiveness of acupuncture in the treatment of MDD was thoroughly analyzed by our research team. Considering the requirement for the application of IA to the skin surface for an extended duration, we made a deliberate decision to utilize the four acupoints that were most commonly utilized in MDD treatment for our interventions involving IA. These acupoints are PC6, HT7, SP6, and LR3. PC6 is the contact point in the pericardium meridian of the Pericardium Meridian and belongs to eight confluence points. Prior research has provided evidence that acupuncture administered at the PC6 point is efficacious in alleviating anhedonia that is associated with MDD. This is achieved by reversing the stress-induced reduction in latency in the open arms and significantly reducing Fos-like immunohistochemical activity in the paraventricular nucleus.<sup>62</sup> HT7 is a Yuan-source point and Shu-stream point of the Heart Meridian. The research findings conducted by Sabina Lim et al show that acupuncture at HT7 may play a significant role in antidepressant by increasing neuropeptide Y levels.<sup>63</sup> In addition, it has been established that SP6 marks the intersection of the three Yin meridians, and research has shown that acupuncture administered at this acupoint yields a distinct antidepressant effect in animal models of MDD. This effect is closely associated with the serotonergic system.<sup>64</sup> LR3, a Yuan-source point of the Liver Meridian, has been identified as effective in treating the depressed liver and is often selected for its ability to alleviate phlegm in order to stimulate mental activity. Previous study has illuminated acupuncture LR3's capacity to regulate levels of copper and zinc that are disrupted during depressive episodes, which represents a potential mechanism for effectively addressing MDD.<sup>65</sup> The implementation of acupuncture at PC6, HT7, LR3, and SP6 has been shown to effectively stimulate the heart and liver meridians while significantly improving both physical and mental symptoms of MDD.<sup>66</sup> Moreover, with regards to the evaluation of therapeutic effectiveness time, it is noteworthy that the therapeutic medications employed for the treatment of MDD may require a duration of up to six weeks to demonstrate their desired effects.<sup>67</sup> Additionally, it is important to acknowledge that previous RCTs assessing the efficacy of MDD

treatment have commonly utilized the sixth and tenth weeks post-treatment as designated evaluation time intervals.<sup>68</sup> Hence, this study will evaluate the efficacy at baseline, 3 weeks post-treatment, 6 weeks post-treatment, and 10 weeks post-treatment. Besides, in consideration of optimizing the therapeutic efficacy of acupuncture, this investigation opted for a retention time of three days, drawing upon the findings of prior research.<sup>69</sup> Regarding the randomization method, appropriate randomization techniques will be selected to reduce the bias that may arise during the process. Regarding acupuncture needle manipulation, the acupuncturist will provide education to the patients on the frequency, duration, interval, and intensity of daily needle manipulation. Regarding the inclusion and exclusion criteria for participants, individuals who have received AIA treatment will be excluded to ensure absolute blinding of the participants to the intervention measures.

Nevertheless, there are some limitations about this protocol remain to be solved. First of all, the secondary outcome indicators utilized in this study relied solely on self-rated questionnaires, which may lack objectivity. Secondly, the study is deficient in brief duration and lack of longitudinal follow-up. Thirdly, this study will only recruit patients from the Third Affiliated Hospital of Zhejiang Chinese Medicine University. As a result, the gathered cases are subject to regional constraints, thus lacking adequate representativeness. Additionally, the sample size utilized in this study is deemed insufficient. Finally, the implementation of a double-blind study is not fully utilized in this particular study. Due to the unique characteristics of acupuncture treatment, it is not feasible to blind acupuncturists. This study aims to actively address potential biases in the experiment. We intend to employ additional objective rating scales, such as the Montgomery-Asberg Depression Rating Scale (MADRS) in forthcoming investigations. These scales will undergo evaluation by psychologists in order to ensure the objective assessment of alterations in patients' conditions and the effects of antidepressant treatments. Furthermore, this research aims to prolong the duration of follow-up in order to effectively observe the long-term consequences of IA for MDD. Additionally, we will enhance the size of our study sample and broaden the scope of our research facility, with the purpose of thoroughly and impartially assessing the effectiveness of IA in treating MDD among adolescents.

Furthermore, our evaluation will focus on the effectiveness of utilizing SSRIs in conjunction with IA as a treatment for MDD in adolescents. The unique advantage of IA is that it can be held on the acupoints for long-term stable stimulation to improve emotions. IA presents a notable advantage of inducing less painful needle insertion, resulting in decreased apprehension and increased acceptance by adolescents. Given the chronic nature of MDD and the protracted duration of its treatment, IA has demonstrated the ability to provide a prolonged and continuous stimulation effect on the body surface. This technique offers a simple and convenient approach to treatment, allowing parents to treat their children at home after receiving proper training from acupuncturists. This alternative method circumvents the inconveniences faced by adolescents who would otherwise need to visit the hospital during their school studies. Moreover, the attachment of the needle to the skin ensures that daily activities and learning exercises remain unaffected. In contrast to traditional acupuncture, the patient has the ability to modify the intensity of IA stimulation, adjusting it according to their own tolerance level. This feature is crucial in mitigating patient apprehension towards the strong stimulation associated with acupuncture. Furthermore, IA possesses a unique characteristic of timeliness that sets it apart from other treatments. When a patient experiences feelings of depression and a loss of motivation, IA can be promptly applied to yield a timely therapeutic effect. The acupoints chosen for this study have been identified as the most commonly utilized in the treatment of MDD through thorough data analysis. These acupoints have demonstrated the ability to alleviate symptoms of MDD, mitigate the undesirable effects associated with SSRIs, such as nausea and vomiting, and enhance sleep quality. These findings hold significant potential for clinical application and advancement in the field. Enhancing MDD treatment programs and their efficacy can help adolescents with MDD who struggle with their social skills, quality of life, and academic performance. Specifically, this can improve harmonious interactions between family members, promote understanding, and foster positive relationships between teachers and students. It can also help to reduce anger and conflicts that result from peer communication issues. Additionally, it can improve somatic disorders, lessen physical pain, and ease other physical discomforts that adolescents experience, thereby lowering the rate of class dropouts. It can also encourage academic achievement and improve learning skills, strengthening a strong desire to learn. Finally, it can improve students' physical health and focus in class, further boosting their academic performance. Nowadays, there is an increasing emphasis on attaining maximum results with the least amount of suffering. Reducing the frequency of hospital visits and its effects on adolescents' daily life has thus emerged as a major issue. The use of online supervision by acupuncturists for IA, enabling patients to get treatment at home, is one potential

remedy. Additionally, online medical consultations provide a great degree of flexibility and convenience for follow-up sessions. IA is not confined solely to hospitals but can be applied across various specializations, departments, and communities. Furthermore, it has the potential to be promoted as a family-centered approach within the field of Traditional Chinese Medicine, thus facilitating further advancements in this domain. It is worth noting that this study represents an initial exploration into the clinical efficacy of IA for treating MDD in adolescents. As the field progresses, there will be a continued effort to standardize complementary therapies to ensure their effectiveness. Additionally, it is necessary to conduct more thorough and orderly research into the utilization of such therapies.

## Conclusion

The main objective of this research is to analyze and contrast the varying effectiveness of the AIA group, the SIA group, and the waiting list group in order to examine if IA can provide a therapeutic benefit for adolescents with MDD. The ultimate goal is to enhance the diagnostic and treatment approaches for MDD.

## Abbreviations

MDD, major depressive disorder; IA, intradermal acupuncture; SSRIs, Selective Serotonin Reuptake Inhibitors; RCT, randomized controlled trial; SIA, sham intradermal acupuncture; AIA, active intradermal acupuncture; HAMD-17, Hamilton Depression Rating Scale; PHQ-9, Patient Health Questionnaire-9; SDS, Self-Rating Depression Scale; PSQI, Pittsburgh Sleep Quality Index; SF-36, Short Form 36 Questionnaire; CRF, case report form.

## Ethics Approval and Consent to Participate

This study was approved by the Medical Ethics Committee of the Third Affiliated Hospital of Zhejiang Chinese Medical University (Ethical Number: ZSLL-KY-2022-001-01). This study will be carried out following relevant Chinese rules and the Declaration of Helsinki, and written informed consent will be obtained from all participants.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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