

# Novel Approaches to Study Design and Intervention for Residual Symptoms of MDD

David Mischoulon, MD, PhD

The management of residual depressive symptoms remains a complex and understudied topic in the field of depression research.<sup>1</sup> Residual insomnia in particular can be especially troublesome to patients when standard antidepressants fail to promote adequate sleep.<sup>2</sup> While there are various effective and safe hypnotic drugs, many individuals are reluctant to take them, in part because of concerns about dependence, daytime sedation, or both.<sup>3</sup> Nonpharmacologic techniques such as sleep hygiene, meditation, and others appear to be effective in some cases<sup>4</sup> but are often underutilized, perhaps in part because of patient reluctance and limited clinician familiarity with these interventions.<sup>5,6</sup> There is clearly a need for more effective and safe therapies for the management of insomnia in the context of depression.

Acupuncture is very popular in the United States and worldwide. Among its appeals are its safety and good tolerability as well as its being a nonpharmacologic treatment, which is associated with reduced stigmatization.<sup>7</sup> Yet the efficacy of acupuncture for psychiatric disorders, as well as for other conditions, remains unclear.<sup>8–11</sup> Most acupuncture research comes from China, but much of this work has yet to be translated to English,<sup>12</sup> and research on acupuncture in the United States remains scanty.

In this issue, Chung and colleagues<sup>13</sup> present a study investigating acupuncture for residual insomnia associated with major depression. The study was rigorously designed with many notable strengths, such as a large sample, multiple recruiting sites, strict eligibility requirements, varied outcome measures, and the use of 2 control interventions: minimal acupuncture, and sham acupuncture with nonpenetrating needles. While the findings suggested an advantage for verum acupuncture with regard to sleep-onset insomnia, most outcome measures did not support the intervention. Thus, the authors declared the study as negative, a trend common in many recent well-designed studies of acupuncture in mood disorders.<sup>14</sup> This work gives us an opportunity to discuss the challenges involved in acupuncture research and how we might try to overcome them.

The gold standard of clinical research is the double-blind, randomized clinical trial (RCT).<sup>15</sup> In antidepressant trials, blinding of patients and clinicians is done relatively easily, with a placebo pill that can be made to look like

(and sometimes taste like) the active medication. With acupuncture, however, double blinding is impossible, and even single blinding is not so easy.<sup>16</sup> Thus, even a rigorous, state-of-the-art investigation such as the one reported here may come up short.

## Approaches to Placebo Intervention

Historically, the preferred placebo intervention in acupuncture trials was minimal acupuncture, which involves needling at sites not considered relevant to the condition studied.<sup>12</sup> Unfortunately, even the needling of “irrelevant” sites has been shown to have clinical effects, resulting in high placebo response rates.<sup>17</sup> The effect of minimal acupuncture is understandable because (1) the ritualized nature of the treatment may in itself be enough to stimulate a response and (2) the complex interconnections between different points, meridians, and acupuncture systems in general suggest that many points can serve many functions, depending on when and how they are used and combined with other points.<sup>14,18</sup>

The second, more recently developed placebo intervention is the nonpenetrating Streitberger needle.<sup>19,20</sup> This needlelike device touches the surface of the skin but then retracts so as not to penetrate or even put pressure on the skin. These devices have been validated<sup>19–22</sup> but are expensive and cumbersome to use, requiring tape and rings to hold them in place. The high risk of unmasking necessitates recruitment of patients new to acupuncture, since individuals who have had previous acupuncture can more easily differentiate between verum and sham treatment compared to inexperienced patients. This makes recruitment more difficult and limits generalizability of the findings.

## Assessing Response

Because the practitioner who administered the verum and placebo treatments could not be blinded to the intervention, the authors assigned separate clinicians to deliver treatment and to assess clinical response. However, it is not known whether the administering clinician's knowledge of the intervention could be inadvertently communicated to the patient, thus influencing clinical response. In this particular study, the authors checked for adequacy of blinding, and found it mostly successful. Although more patients guessed acupuncture correctly, this did not lead to a significant advantage for acupuncture, suggesting that the patients may not have been so influenced by their belief. In a recent investigation<sup>23</sup> of patient beliefs about treatment received, we found that believing that one was receiving an active intervention seemed to correlate with clinical improvement more so than which intervention was actually received.

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**Corresponding author:** David Mischoulon, MD, PhD, 1 Bowdoin Sq, 6th Floor, Boston, MA 02114 (dmischoulon@partners.org).

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On the other hand, the “treatment-heavy” randomization may have contributed to a greater response to the placebo interventions. Subjects were told that minimal acupuncture was also associated with positive outcomes, thus presenting them with an 80% chance of receiving a potentially active treatment (only 20% received the nonpenetrating acupuncture). Papakostas et al<sup>24</sup> found that an increased chance of receiving an active treatment (eg, in a 3-arm study with 2 active treatments, versus a 2 arm study with 1 active treatment) resulted in a higher placebo response rate.

Another item of interest is whether *de qi* is needed for clinical effect. This term, which means, “the arrival of qi,” occurs upon penetration of the needle.<sup>25,26</sup> The patient feels a short-lived dull ache at the site of insertion. In traditional Chinese medicine, it is believed that this sensation indicates proper placement of the needle that has activated the *qi* in the acupuncture point. However, not all acupuncturists ascribe to the need for *de qi*; its importance varies from school to school and from practitioner to practitioner.<sup>27</sup>

The study had a relatively short treatment period of 3 weeks. Had the acupuncture proven more effective than the control interventions, its cost effectiveness could have been substantial, given that most antidepressant treatments require approximately 6–8 weeks to work. On the other hand, a shorter trial period risks a false-negative result, which may explain in part the modest findings. All treatment arms demonstrated at least some improvement in most outcome measures, which suggests that verum acupuncture may be effective, but that the other forms used here are also effective, either because of a placebo effect or because these interventions also have a real physiological effect, at least in the short term. A longer treatment period may have clarified this question. A related issue is that Chung and colleagues’ study<sup>13</sup> does not provide conclusions about long-term sustainability of acupuncture’s clinical effects, since patients were followed for only 5 weeks of posttreatment.

### Alternative Study Design for Improved Quality in Acupuncture Trials

What needs to be done next? One possible avenue for improving the quality of acupuncture trials is to search for another placebo intervention that is less likely to produce nonspecific effects. This may not prove easy, however.<sup>12</sup> Alternatively, we might explore novel study designs to maximize placebo-verum separation. Some years ago, our group proposed a new study design<sup>28</sup> that would compare acupuncture against an antidepressant and against placebo pill in a sample of patients with major depressive disorder. The design had 2 innovative features. First, we used the sequential parallel comparison design, which enriches the sample for placebo nonresponders.<sup>28</sup> Second, we introduced an element of patient deception. Patients were randomized to a “pill” arm in which they would receive a selective serotonin reuptake inhibitor or a placebo pill or to an “acupuncture” arm, in which they would receive true acupuncture but *would be told* they might receive either verum or minimal (nonspecific) acupuncture. Because acupuncture response

may be mediated by patient beliefs regarding its efficacy,<sup>29</sup> if study subjects believe they have a smaller chance to receive verum acupuncture, this could diminish placebo response and facilitate the use of an active antidepressant and pill placebo as comparators instead of placebo acupuncture. This design might circumvent the need for an acupuncture placebo, controlling cost and simplifying the protocol tremendously.

While patient deception always raises concerns about patient safety and autonomy,<sup>30</sup> our institutional review board approved the proposal on the grounds that since patients in the acupuncture arm would be getting a “better” intervention than what they were promised, the design was considered to fall within ethical boundaries. Unfortunately, we have not yet succeeded in obtaining the funding to carry out such a study. Given the real and serious limitations faced by acupuncture research, we need outside-the-box strategies for improving the quality of clinical trials. Novel designs such as the one proposed here may offer great rewards to enterprising investigators and to the field as a whole.

**Author affiliation:** Depression Clinical and Research Program, Massachusetts General Hospital, Harvard Medical School, Boston.

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