COMMENTARY ON THE COCHRANE REVIEW OF ACUPUNCTURE FOR DEPRESSION

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Background: There is interest from the community in the use of self-help and complementary therapies for depression. This review examined the currently available evidence supporting the use of acupuncture to treat depression.

Objectives: To examine the effectiveness and adverse effects of acupuncture in the treatment for depression.

Search Strategy: The following databases were searched: CCDAN-CTR, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (1966 to Dec 2008), EMBASE (1980 to Dec 2008), PSYCINFO (1874 to Dec 2008), the Database of Abstracts of Reviews of Effectiveness (DARE), CINAHL (1980 to Dec 2008), Wan Fang database (to Dec 2008). The following terms were used: depression, depressive disorder, dysthymic disorder and acupuncture.

Selection Criteria: Inclusion criteria included all published and unpublished randomized controlled trials comparing acupuncture with sham acupuncture, no treatment, pharmacological treatment, other structured psychotherapies (cognitive behavioral therapy, psychotherapy or counseling), or standard care. The following modes of treatment were included: acupuncture, electro acupuncture, or laser acupuncture. The participants included adult men and women with depression defined by clinical state description, or diagnosed by the Diagnostic and Statistical Manual (*DSM-IV*), Research Diagnostic Criteria (RDC), International Classification of Disease (ICD) or the Criteria for Classification and Diagnosis of Mental Diseases CCMD-3-R.

Data Collection and Analysis: Meta-analyses were performed using relative risk for dichotomous outcomes and standard mean differences for continuous outcomes, with 95% confidence intervals. Primary outcomes were reduction in the severity of depression, measured by self-rating scales, or by clinician rated scales and an improvement in depression defined as remission versus no remission.

Main Results: This review is an update and now contains data from 30 studies. Following recent searches, 23 new studies have been added and a further 11 trials were excluded (due to suboptimal doses of medication, no clinical outcomes, insufficient reporting). Thirty trials with 2,812 participants are included in the meta-analysis. There was a high risk of bias in the majority of trials. There was insufficient evidence of a consistent beneficial effect from acupuncture compared with a wait list control or sham acupuncture control. Two trials found acupuncture may have an additive benefit when combined with medication compared with medication alone. A subgroup of participants with depression as a comorbidity experienced a reduction in depression with manual acupuncture compared with SSRIs (RR 1.66, 95%CI 1.03, 2.68) (three trials, 94 participants). The majority of trials compared manual and electro acupuncture with medication and found no effect between groups.

Authors' Conclusions: We found insufficient evidence to recommend the use of acupuncture for people with depression. The results are limited by the high risk of bias in the majority of trials meeting inclusion criteria.

The Cochrane Complementary Medicine Field is the group within the Cochrane Collaboration focused on facilitating the conduct of Cochrane systematic reviews of CAM therapies. The CAM Field represents an international collaborative effort among researchers, clinicians, consumers, and CAM practitioners from nearly every continent. The Field's central office is located at the Center for Integrative Medicine, University of Maryland School of Medicine, 520 W. Lombard St, Baltimore, MD 21201. For more information, contact Eric Manheimer at: emanheimer@compmed.umm.edu. The Complementary Medicine Field is supported by Grant R24 AT001293 from the National Center for Complementary and Alternative Medicine (NCCAM). The contents of this article are solely the responsibility of the author and do not necessarily represent the official views of the NCCAM, or the National Institutes of Health.

COMMENTARY ON COCHRANE REVIEW

In the excellent Cochrane Review, Smith and colleagues provide the most comprehensive analysis of the evidence of acupuncture for depression to date, and in addition analyze the key factors that limit making evidence-based clinical recommendations. Despite the increased number of clinical trials conducted in this area, compared to the previously published Cochrane review,[1] evidence of the efficacy of acupuncture for depression remains insufficient, primarily, the authors conclude, because of the heterogeneity inherent in most of the existing trials. In addition, they point out, risk of bias and inadequate reporting continue to be a challenge in acupuncture studies.

A critical evaluation of the results and conclusions derived from this meta-analysis indicates the data is still insufficient not only to confirm but also to refute the potential clinical application of acupuncture for depression. Therefore, the question remains as to whether acupuncture may play a role in the management of this most prevalent condition, with a huge personal and socioeconomic cost to society.[2] A closer look at a couple of important areas highlighted by this review may help suggest strategies for moving forward.

THE PLACEBO EFFECT IN DEPRESSION

Depression is a complex, multifactorial, and recurrent condition, and although we

have made great advances in understanding the etiopathogenesis of this disorder, we have just barely begun to uncover the alterations in neural functioning that lead to depression.[2] Depression presents a number of key challenges to research in general, not only acupuncture. As noted by the authors of the review, the placebo response in Major Depression Disorder (MDD) is large regardless of the intervention.[3] Also noted by the reviewers are the meta-analysis findings of Kirsch and colleagues:[4] the difference in efficacy between antidepressants and placebo increased based on severity, but was relatively small even for severely depressed patients. These findings were supported by a different meta-analysis published in JAMA in 2010.[5]

Clearly, thousands if not millions of people believe to have benefited from antidepressant treatment, and physicians report significant clinical responses in their patients. Antidepressants are the most used type of prescription medication in adults (20-59);[6] from 1997 to 2004, the total expenditures for antidepressants more than doubled from $5.1 to $12.1 billion in the United States alone.[7] As can be imagined, the Kirsch and JAMA reports came as a shock and stirred a great deal of controversy in both academic journals[8] and the popular media and highlighted challenges in depression research: teasing apart the placebo effect, even in pharmacotherapy-based interventions is complex, especially in this patient population. Based on the evidence to date, it is inaccurate to assert that the effects of acupuncture in depression are indistinguishable from placebo effects;[9] more research is clearly needed.

ACUPUNCTURE VERSUS SHAM

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.[10-19] In this review of clinical trials, however, the authors found no significant differences between the effect of acupuncture and the sham controls used. Common wisdom would indicate that these findings suggest the mechanisms underlying the therapeutic effects of acupuncture are essentially placebo-related, and that any effects of either acupuncture or sham on depression are due to nonspecific factors. Furthermore, it could be argued that needle effects observed in basic science experiments are unrelated to therapeutic effects and may not be applicable to clinical research.[20] Nevertheless, a couple of small studies have found several physiological responses to be related to therapeutically relevant outcomes in humans,[21,22] indicating that more research is still needed.

Placebos by definition must be inert. It has been argued that many of the currently used acupuncture sham controls are not in fact inert,[23] and do not constitute a true placebo. Most acupuncture sham designs, especially the invasive needling shams used in these studies, assume that one or another needling parameter (ie, depth, placement, and stimulation) determines the clinical response to acupuncture. Little is known, however, about the role each of these needling components (ie, insertion depth, needle location, needle stimulation) may play on the therapeutic effect of acupuncture;[20] or whether this effect may vary as a result of the condition being treated. Not knowing the mechanisms by which these parameters may influence immediate and longer term physiological response to acupuncture, has handicapped our ability to design an effective sham.[20] It is possible that sham treatments used in these studies had some therapeutics effect and that significant differences between the groups would only be detected in much larger sample sizes or would only become evident in the long term, requiring a more substantial follow-up. Furthermore, acupuncture is a complex, interactive treatment intervention, and controlling for the specific effects of needling alone, may inadvertently ignore other nonneedling key components that are specific to acupuncture treatment, and which also need to be controlled (eg, palpation).[20]

TREATMENT INTERVENTIONS

Verum acupuncture treatment interventions tested in these studies rarely reflect the way in which acupuncture is used to manage patients with depression in clinical practice, and therefore, treatments may have been therapeutically inadequate. In China, for example, where cost, availability, and integration into routine care facilitates access to acupuncture as a monotherapy for treating depression, acupuncture is performed every day; it often combines both electro and manual stimulation, and uses scalp and body points concurrently. Very few sham-controlled studies reviewed in this meta-analysis report this kind of frequency or intensity of treatment. Protocols must be informed by clinical practice; dose response, and optimal treatments need to be assessed.

In addition, acupuncture is one modality within a complete system of care. It is often used as an adjunctive therapy and as part of a whole care package tailored to the individual and that often includes the internal administration of herbal medicine. Moreover, through education patients are encouraged to make important life-style changes (ie, nutritional support, stress management, diet, and exercise) and become committed to their care. It is also common, especially in the West for depression patients to be under the care of a qualified mental healthcare professional while receiving acupuncture. Acupuncture may play a very specific role in managing depression as part of a comprehensive treatment strategy; pragmatic trials and Whole Systems Research[24] are needed to answer this question. The Cochrane review was designed to assess the specific effects of acupuncture; therefore, none of the trials included evaluated acupuncture as part of a whole package of care. Despite the limitations presented by these types of studies–they cannot pinpoint which specific part(s) of the total package of treatment is responsible for the effects–they may help inform the development of future explanatory trials and basic science studies.

ACUPUNCTURE AUGMENTATION OF ANTIDEPRESSANTS

Despite the growing number of marketed antidepressants, between 19% and 34% of patients with MDD do not respond to

acute antidepressant treatment, 29% to 46% may fail to achieve and sustain a full remission,[25] and between 15% and 50% will have a recurrence of depression despite continuous antidepressant treatment.[26] Generally, clinicians tend to increase the dosage or augment with a second agent prior to considering switching agents altogether.[27-29] A higher dose of medication can increase the side-effect burden, and reduce patient adherence, while the use of multiple medications may increase risk of side effects or drug-drug interactions.

According to the Cochrane review, when used in conjunction with antidepressants, acupuncture may be promising in reducing both the symptoms and severity of depression. These findings are supported by the results of a recent small open design, nonrandomized pilot study (n = 30) of partial and nonresponders to antidepressants with MDD.[30] The overall response rates among completers (56%) and in the ITT sample (43%) were comparable to those seen with standard antidepressants,[31] which is particularly impressive, considering that this was a treatment-resistant sample.

Selective-serotonin reuptake inhibitors (SSRIs), the most commonly used type of antidepressant, are often described as having a delayed onset of effect in the treatment of depression.[32] Two recent studies (n = 59, n = 78) conducted by Zhang and colleagues[33] at the University of Hong Kong, indicate that a novel electroacupuncture stimulation modality could accelerate onset of antidepressant effect of SSRIs and augment their efficacy. For the relatively large proportion of individuals that does not respond well to antidepressants, acupuncture may offer an important augmentation option. More research is clearly needed in this area.

POSTSTROKE DEPRESSION

Depression in poststroke patients is quite common; the prevalence varies widely depending on the specific patients, the time elapsed since the stroke, and different diagnostic criteria used[34] with the location of lesion,[35] and accumulated damage due to previous strokes, playing a significant role.[36] As presented in the review, there is evidence that acupuncture may benefit poststroke patients with major depression and more research is clearly warranted.

MANAGING DEPRESSION IN VULNERABLE POPULATIONS

In the small number of studies that compared acupuncture to medication in the Cochrane review, there was no evidence that medication performed better than acupuncture; but rather acupuncture appeared to perform as well as medication–with the caveat that these studies did not indicate that the purpose of the research was to examine equivalence or noninferiority, or superiority. For vulnerable populations for whom the use of antidepressants may be questionable, such as the elderly, pregnant women, and children, prescribing antidepressants as the first line of treatment may not be justified by the risk to benefit ratio. What role may acupuncture play in managing depression symptoms in vulnerable patient populations? This question could be answered by short-term study designs that evaluate acupuncture alone or in combination with nonpharmacological strategies, followed as needed by antidepressants.

DEPRESSION DURING PREGNANCY

Major depressive disorder is unfortunately common during pregnancy; it has been reported to range between 10% and 20%.[37] Unfortunately, there are very few medically acceptable treatments for depression during pregnancy.[37] The use of antidepressants during pregnancy has been associated with higher risk of fetal problems and potentially presents significant health and developmental risks to the infant [38,39] Women who take SSRIs during pregnancy are more likely to deliver prematurely; their babies have lower five-minute Apgar scores, and are more likely to be admitted to the neonatal intensive care unit.[40] Recently drafted recommendations[41] suggest that nonpharmacological interventions such as Cognitive Behavioral Therapy, be made available to pregnant women as first-line treatments. Acupuncture may offer an additional option.

The results of a trial of acupuncture of 150 pregnant women who met *DSM-IV* criteria for MDD[42] indicates that acupuncture may be an effective and safe alternative to antidepressants for women during the perinatal period. The response rate was significantly greater for acupuncture (63.0%) than the combination of the two controls, acupuncture not specific for depression ("control acupuncture") and massage (44.3%; $P < .05$) and relative to the control acupuncture (37.5%; $P < .05$). There were no significant differences in symptom reduction or response rates between control acupuncture (37.5%) and massage (50.0%). There were no significant group differences in participants' or acupuncturists' expectations between acupuncture and the combined control conditions ($P > .36$). These results are consistent with a previous pilot study of 61 pregnant women conducted by the same team.[43] In both studies, acupuncture produced a response rate comparable to those observed in standard treatments for depression. Given the substantial risks associated with the use of antidepressants during pregnancy, acupuncture may provide a viable alternative to managing depression in the perinatal period.

REDEFINING THE ROLE OF ACUPUNCTURE IN DEPRESSION

The authors of the Cochrane review provided a comprehensive summary of the main issues that need to be addressed in future studies of acupuncture for depression. These include the following: improving the methodological design, adequately powering the studies, providing a sound rationale for treatment selection, consideration of the context of the research setting, and addition of other outcome measures besides clinical outcomes. Challenges for advancing acupuncture research in general and strategies for moving forward have been clearly articulated elsewhere.[20]

Given the complex role of placebo in depression as well as the challenges in establishing appropriate placebo controls in acupuncture, our inquiry of acupuncture's role in the treatment of depression needs to be expanded. Including additional questions (eg, mechanism) embedded in sham-controlled trials, and comparing

acupuncture to routine care while assessing a comparison to sham controls would be helpful. Preliminary research to establish dose response, optimal treatment interventions and appropriate controls is clearly needed. Further research is warranted in several areas: augmentation and acceleration of the effect of antidepressants; augmentation of nonpharmacological interventions (eg, Cognitive Behavioral Therapy); as a first-line treatment in vulnerable populations (eg, children, adolescents, elderly); prevention of postpartum depression; and reduction of medication side effects.

Acupuncture may play an important role in the treatment of depression and more research is clearly needed.

REFERENCES

1. Smith CA, Hay PP. Acupuncture for depression. *Cochrane Database Syst Rev*. 2005; 2:CD004046.
2. López-Muñoz F, Alamo C. Depression at the frontier of the new century. *Front Neurol Neurosci*. 2009;2:226-229.
3. Brunoni AR, Lopes M, Kaptchuk TJ, Fregni F. Placebo response of non-pharmacological and pharmacological trials in major depression: a systematic review and meta-analysis. *PLoS One*. 2009;4:e4824.
4. Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, Johnson BT. Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. *PLoS Med*. 2008;5:e45.
5. Fournier JC, DeRubeis RJ, Hollon SD, Dimidjian S, Amsterdam JD, Shelton RC, Fawcett J. Antidepressant drug effects and depression severity: a patient-level meta-analysis. *JAMA*. 2010;303:47-53.
6. Gu Q, Dillon CF, Burt VL. *Prescription Drug Use Continues to Increase: U.S. Prescription Drug Data for 2007-2008. NCHS Data Brief*, no 42. Hyattsville, MD: National Center for Health Statistics; 2010.
7. Stagnitti MN. *Trends in the Use and Expenditures for the Therapeutic Class Prescribed Psychotherapeutic Agents and All Subclasses, 1997 and 2004. Statistical Brief #163*. February 2007. Rockville, MD: Agency for Healthcare Research and Quality. Available at: http://www.meps.ahrq.gov/mepsweb/data_files/publications/st163/stat163.pdf.
8. Horder J, Matthews P, Waldmann R. Placebo, Prozac and PLoS: significant lessons for psychopharmacology. *J Psychopharmacol*. 2010 Jun 22.
9. Ernst E, Lee MS, Choi TY. Acupuncture for depression? A systematic review of systematic reviews. *Eval Health Prof*. 2010 Dec 7
10. Huang Q.-F. Exploration of the clinical regularity of acupuncture-moxibustion treatment for depression. *J Acupunct Tuina Sci*. 2009;7:57-60.
11. Han, JS. Electroacupuncture: an alternative to antidepressants for treating affective diseases? *Int J Neurosci*. 1986;29:79-92.
12. Dos Santos JG Jr, Kawano F, Nishida MM, Yamamura Y, Mello LE, Tabosa A. Antidepressive-like effects of electroacupuncture in rats. *Physiol Behav*. 2008;93:155-159.
13. Yoshimoto K, Fukuda F, Hori M, et al. Acupuncture stimulates the release of serotonin, but not dopamine, in the rat nucleus accumbens. *Tohoku J Exp Med*. 2006; 208: 321-326.
14. Zhuang LX, Xu SF, Chun-Zhi T. [Effects of different intervention methods on behavior changes in depression rats]. *Zhen Ci Yan Jiu*. 2007;32:93-97 [in Chinese].
15. Xu SF, Zhuang LX, Tang CZ, Yang J. [Effects of acupuncture and embedding thread on central monoamine neurotransmitters in the depression model rat]. *Zhongguo Zhen Jiu*. 2007;27:435-437 [in Chinese].
16. Lee B, Shim I, Lee HJ, Yang Y, Hahm DH. Effects of acupuncture on chronic corticosterone-induced depression-like behavior and expression of neuropeptide Y in the rats. *Neurosci Lett*. 2009;453:151-156.
17. Lu F, Zhu HM, Xie JJ, Zhou HH, Cen YL, Hu JY. [Effects of electroacupuncture on behavior, plasma COR and expressions of PKA and PKC in hippocampus of the depression model rat]. *Zhongguo Zhen Jiu*. 2008;28:214-218 [in Chinese].
18. Song C, Halbreich U, Han C, Leonard BE, Luo H. Imbalance between pro- and anti-inflammatory cytokines, and between Th1 and Th2 cytokines in depressed patients: the effect of electroacupuncture or fluoxetine treatment. *Pharmacopsychiatry*. 2009; 42:182-8. Epub 2009 Sep 1.
19. Hui KK, Marina O, Liu J, Rosen BR, Kwong KK. Acupuncture, the limbic system, and the anticorrelated networks of the brain. *Auton Neurosci*. 2010;157:81-90.
20. Langevin HM, Wayne PM, Macpherson H, et al. Paradoxes in acupuncture research: strategies for moving forward. *Evid Based Complement Alternat Med*. 2011:180805.
21. Zhou SH, Wu FD. [Therapeutic effect of acupuncture on female's climacteric depression and its effects on DA, NE and 5-HIAA contents]. *Zhongguo Zhen Jiu*. 2007;27:317-321 [in Chinese].
22. Pohl A, Nordin C. Clinical and biochemical observations during treatment of depression with electroacupuncture: a pilot study. *Hum Psychopharmacol*. 2002;17:345-348.
23. Linde K, Niemann K, Schneider A, Meissner K. How large are the nonspecific effects of acupuncture? A meta-analysis of randomized controlled trials. *BMC Med*. 2010;8:75.
24. Ritenbaugh C, Verhoef M, Fleishman S, Boon H, Leis A. Whole systems research: a discipline for studying complementary and alternative medicine. *Altern Ther Health Med*. 2003;9:32-36.
25. Fava M, Davidson KG. Definition and epidemiology of treatment-resistant depression. *Psychiatr Clin North Am*. 1996;19:179-200.
26. Fava M. New approaches to the treatment of refractory depression. *J Clin Psychiatry*. 2000;61(Suppl 1):26-32.
27. Rosenbaum JR. Managing selective serotonin reuptake inhibitor-drug interactions in clinical practice. *Clin Pharmacokinet*. 1995;29(Suppl 1):53-59.
28. Mischoulon D, Nierenberg AA, Kizilbash L, Rosenbaum JF, Fava M. Strategies for management of depression refractory to SSRI treatment: a survey of clinicians. *Can J Psychiatry* 2000;45:476-481.
29. Rush AJ, Fava M, Wisniewski SR, et al. Sequenced treatment alternatives to relieve depression (STAR*D): rationale and design. *Control Clin Trials*. 2004;25:119-142.
30. Yeung AS, Ameral VE, Chuzi SE, Fava M, Mischoulon D. A pilot study of acupuncture augmentation therapy in antidepressant partial and non-responders with major depressive disorder. *J Affect Disord*. 2010 Aug 5.
31. Yang H, Cusin C, Fava M. Is there a placebo problem in antidepressant trials? *Curr Top Med Chem*. 2005;5:1077-1086.
32. Taylor MJ, Freemantle N, Geddes JR, Bhagwagar Z. Early onset of selective serotonin reuptake inhibitor antidepressant action: systematic review and meta-analysis. *Arch Gen Psychiatry*. 2006;63:1217-1223.
33. Zhang, ZJ. Acupuncture therapy for Major Depressive Disorder: form empirical observation to evidence-based studies. *Hong Kong International Acupuncture Conference 2011*, pp.44-45.
34. Carota A, Berney A, Aybek S, et al. A prospective study of predictors of poststroke depression. *Neurology*. 2005;64:428-433.
35. Aström M, Adolfsson R, Asplund K. Major depression in stroke patients. A 3-year longitudinal study. *Stroke*. 1993;24:976-982.
36. Carson AJ, MacHale S, Allen K, et al. Depression after stroke and lesion location: a systematic review. *Lancet*. 2000;356:122-126.
37. Kuehn BM. No easy answers for physicians caring for pregnant women with depression. *JAMA*. 2009;302:2413-2414, 2420.
38. Pedersen LH, Henriksen TB, Vestergaard M, Olsen J, Bech BH. Selective serotonin reuptake inhibitors in pregnancy and congeni-

tal malformations: population based cohort study. *BMJ*. 2009;339:b3569.
39. Pedersen LH, Henriksen TB, Olsen J. Fetal exposure to antidepressants and normal milestone development at 6 and 19 months of age. *Pediatrics*. 2010;125:e600-e608.
40. Lund N, Pedersen LH, Henriksen TB. Selective serotonin reuptake inhibitor exposure in utero and pregnancy outcomes. *Arch Pediatr Adolesc Med*. 2009;163:949-954.
41. Yonkers KA, Wisner KL, Stewart DE, et al. The management of depression during pregnancy: a report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists. *Obstet Gynecol*. 2009;114:703-713.
42. Manber R, Schnyer RN, Lyell D, et al. Acupuncture for depression during pregnancy: a randomized controlled trial. *J Obstet Gynaecol*. 2010;115:511-520.
43. Manber R, Schnyer RN, Allen JJB, Rush J, Blasey C. Acupuncture: a promising treatment for depression during pregnancy. *J Affect Disord*. 2004;83:89-95.

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