Abstracts and Commentaries on Key Articles in the Literature

Reviewed by Wadie I. Najm, MD, MEd

Electroacupuncture reduces cocaine-induced seizures and mortality in mice.

Chen YH, Ivanic B, Chuang CM, Lu DY, Lin JG. *Evid-Based Complement Alternat Med.* 2013;2013:134610.

RESEARCHERS FROM CHINA MEDICAL UNIVERSITY, Taichung, Taiwan, and Children's University Hospital, Bratislava, Slovakia, conducted this animal study. The work was supported by grants from the National Science Council, Taipei, Taiwan.

In this study, electroacupuncture (EA) experiments were conducted to: (1) establish the applicability of EA to cocaine-induced seizure and mortality in a mouse model; (2) determine the frequency-dependent antiseizure activity of EA; and (3) correlate the efficacy of EA with the expression of Fos protein in the brain.

Male ICR mice were used for the study. Needles were applied into the murine equivalents of human acupoints GV 14 and GV 20. EA stimuli were delivered by an EA Trio 300 stimulator (Ito, Japan) at 1-mA intensities for 15 minutes at frequencies of 2, 50, or 100 Hz, with a pulse width of 150 μ s. EA was applied for 15 minutes to GV 14 and GV 20 acupoints prior to cocaine injection. In the control group, sham EA was performed by bilateral insertion of a pair of stainless steel acupuncture needles approximately 3–4 mm deep into the middle of each mouse's scapula, which is equivalent to the human *Tianzong* (SI 11) acupoint. Control animals were injected with saline.

Following injection of cocaine or saline, animals were placed in a plastic observation box, and seizure scores were assessed by the Itzhak scale, which categorizes five stages of seizures (Stage 1 = normal behavior to Stage 5 = full motor seizure), according to their severity over a 30-minute period.

The immunohistochemistry procedure used for this study was one that had been described by Inan et al.* Three brain sections, from –2.255 mm to –1.856 mm caudal to bregma, were randomly selected for immunohistochemistry procedures. Tissues were processed for c-Fos immunoreactivity.

In this study, cocaine at 75 mg/kg and at 125 mg/kg was injected intraperitoneally (i.p.) to induce seizures and death. Procaine (250 mg/kg and 400 mg/kg; i.p.) was used to induce seizures and death in mice, respectively.

Effects of EA on cocaine-induced seizures by a single dose of cocaine (75 mg/kg) in 6 groups of mice (a control group, three EA treatment groups, a sham EA group, and a needle-insertion group) were measured. EA, 50 Hz at the GV 14 and GV 20 acupoints, significantly reduced seizure scores induced by a single cocaine administration (75 mg/kg), whereas EA at 2 Hz and at 100 Hz had no such effect. In addition, cocaine-induced seizures were not significantly affected by either 15 minutes of needle insertion into GV 14 and GV 20 or by EA at SI 11.

Needle insertion into GV 14 and GV 20, as well as EA at 2 Hz and at 50 Hz applied to GV 14 and GV 20, significantly reduced the mortality rate induced by a larger single dose of cocaine (125 mg/kg).

In mice pretreated with EA (50 Hz) at acupoints GV 14 and GV 20, the incidence of seizures was not affected. In addition, EA at 2 Hz and 50 Hz, when applied to GV 14 and GV 20, failed to affect the mortality rate associated with procaine (400 mg/kg; i.p.) in mice.

To evaluate EA attenuation of cocaine-induced (75 mg/kg) c-Fos expression in the mouse brain, the mice were divided into 4 groups: (1) saline control, (2) EA alone, (3) cocaine, and (4) cocaine plus EA. c-Fos expression was examined in three brain areas, including the paraventricular thalamus, the amygdala area, and the caudoputamen. In the EA-alone group, c-Fos positive nuclei were found only in the paraventricular thalamus. No activity was found in the control group. In the cocaine group, c-Fos-positive nuclei were found in all three areas and these occurred at significantly higher levels than those seen in the saline control group. In the cocaine plus EA group, it appeared that pretreatment with EA at 50 Hz significantly reduced the number of c-Fos-positive cells induced by cocaine in the paraventricular thalamus, but not in the amygdala area and caudoputamen.

The dopamine D₃ receptor antagonist, SB-277011-A (30 mg/kg; administered subcutaneously), did not affect

cocaine-induced seizure severity, but it did prevent the effects of EA on cocaine-induced seizures.

In this study EA reduced seizures and mortality induced by a high dose of cocaine. Pretreatment with 50 Hz of EA significantly reduced the number of c-Fos-positive cells induced by cocaine in the paraventricular thalamus, but not in the amygdala or caudoputamen. As noted in prior published literature, acute cocaine administration increases c-Fos expression in many brain areas. Among these areas, the paraventricular thalamus and amygdala are structures associated with seizures, while the caudoputamen is associated with movement control. In this study, the results implicated involvement of the paraventricular thalamus in the effects of EA on cocaine-induced seizures.

*Inan S, Dun NJ, Cowan A. Nalfurafine prevents 5'-guanidinonaltrindole- and compound 48/80-induced spinal c-Fos expression and attenuates 5'-guanidinonaltrindole-elicited scratching behavior in mice. *Neuroscience*. 2009;163(1):23-33.

Effects of electroacupuncture on depression and the production of glial cell line-derived neurotrophic factor compared with fluoxetine: A randomized controlled pilot study.

Sun H, Zhao H, Ma C, Bao F, Zhang J, Wang DH, Zhang YX, He W. *J Altern Complement Med*. 2013;May 6:e-pub ahead of print.

THIS RANDOMIZED AND CONTROLLED STUDY, was conducted by researchers from the Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China; and Beijing Hospital of Traditional Chinese Medicine, Beijing, China. The study was sponsored by a grant from National Program for Biomedical Hightech, the Ministry of Science and Technology, People's Republic of China, and a grant from the National Program for Traditional Medicine, State Administration of Traditional Chinese Medicine, People's Republic of China.

The study was designed to compare the therapeutic effects of electroacupuncture (EA) and fluoxetine on patients with Depressive Disorder (DD) by assessing Hamilton Depression Rating Scale (HDRS) scores. Moreover to provide more objective scientific evidence of such effects, to glial cell line-derived neurotrophic factor (GDNF) in the sera of patients with DD was measured before and after treatment.

A total of 118 subjects with DD, ranging from age 18-70, were recruited from an outpatient acupuncture clinic in the Beijing Hospital of Traditional Chinese Medicine. The inclusion criteria included: (1) age between 18 and 70; (2) fulfillment of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*† criteria based on the Standard Clinical Interview for *DSM-IV*; and (3) a score of

≥ 20 on the 24-item HDRS for each symptom, as evaluated by a trained physician. Exclusion criteria were concomitant psychiatric illnesses, mental retardation, alcohol or drug abuse, severe somatic illnesses, positive medical history for cerebral diseases, and obesity. Patients who had histories of infection, known autoimmune diseases, or electroconvulsive therapy, or who used immunosuppressive agents or immune-stimulants within 6 months were excluded. In addition, pregnant or breastfeeding women were also excluded.

Following baseline evaluation and tests, subjects were randomly assigned to an EA treatment group, an EA control group, or a fluoxetine group, according to a random number table that had been prepared in advance.

Participants received acupuncture treatments, five times per week for 6 weeks. At the same time, participants in the fluoxetine group were treated with oral fluoxetine (20 mg/day) for 6 weeks. Symptoms were evaluated by a trained physician using the HDRS before treatment (0 weeks) and after 2, 4, and 6 weeks of treatment. Serum GDNF was measured before and after 6 weeks of treatment.

As noted there were 2 groups of subjects receiving acupuncture. Group 1, the treatment group, was comprised of 20 patients who underwent EA treatment for 6 weeks according to long-term clinical experience using acupoints DU 20 and ST 36 synchronously. Group 2, the EA control group, included 16 patients who underwent EA treatment, based on the acupoints frequently used for DD-associated symptoms in China, for 6 weeks, using the LR 3, SP 6, PC 6 and HT 7 acupoints.

All patients had HDRS scores of 20 or higher at enrollment. Treatment response was defined as a ≥ 50% reduction in HDRS score, and great improvement was defined as a final HDRS score ≤ 15.

A total of 75 patients were randomized into the study, and 25 patients were allocated to each treatment group. Sixteen subjects completed EA the control condition, while 20 in the treatment group completed EA treatment and 25 completed fluoxetine treatment.

There was no significant differences in the 3 groups' baseline HDRS scores. HDRS scores for the EA treatment group and the EA control group were lower at weeks 2 and 4; however, the differences became insignificant at the endpoint (week 6) of the trial ($p=0.161$). Both EA groups had a response rate of 75%, while the fluoxetine group had a response rate of 60%. There were significant differences among the three groups in the proportion of responders ($p<0.001$) for each group.

There was no significant difference in serum GDNF concentrations among the three groups before treatment. After 6 weeks of treatment, serum GDNF significantly increased in all groups compared with baseline ($p<0.05$). There were no significant differences in levels of GDNF among the three groups after the assigned treatment. GDNF level was inversely correlated with the HDRS scores in the EA treatment group ($p<0.05$) and the EA control group ($p<0.05$). However, there

was no significant correlation between GDNF level and HDRS score in the fluoxetine group.

In this study, EA had the same therapeutic effects as the conventional drug fluoxetine on patients with DD. The action of EA may be associated with alteration of GDNF concentration. Larger-scale studies are necessary to confirm these results.

[†]American Psychiatric Association (APA). Diagnostic and Statistical Manual of Mental Disorders, 4th edition. Arlington, VA: APA; 1994.

Effectiveness of abdominal acupuncture for patients with obesity-type polycystic ovary syndrome: A randomized controlled trial.

Zheng YH, Wang XH, Lai MH, Yao H, Liu H, Ma HX. *J Altern Complement Med.* 2013;May 15:e-pub ahead of print.

RESearchers from the first affiliated hospital of Guangzhou Medical College, Guangzhou, China, conducted this study. The Natural Science Foundation of China and the Natural Science Foundation of Guangdong Province supported the work.

This single-center, randomized clinical trial aimed to assess the effectiveness of abdominal acupuncture as a treatment for obesity-type polycystic ovary syndrome (PCOS). The effect of abdominal acupuncture therapy on obese women with PCOS, as well as a parallel comparison with metformin, was also studied. Female patients who met the inclusion criteria were randomly allocated in a 1:1 ratio to an abdominal acupuncture or a metformin group. Stratification by age and body mass index (BMI) ensured equal proportions of those variables across groups. Computer-generated randomization within each stratum was conducted by using permuted blocks of two; randomization was concealed until interventions were assigned.

Participants were recruited from an outpatient gynecology department, and the study took place at the First Affiliated Hospital of Guangzhou Medical College from January 2006 to May 2009. PCOS was defined according to modified Rotterdam criteria. Subjects were excluded if they were younger than 18 or older than 38, or had cardiovascular disease, diabetes mellitus, or an endocrinal or neoplastic cause of hyperandrogenemia.

Patients in the acupuncture group received acupuncture, twice per week for 6 months, by a registered acupuncturist. The acupuncture protocol was based on the researchers' clinical experience with treating women who have PCOS. Acupuncture points were located in abdominal muscles with innervations corresponding to the ovaries; Conception Vessel

CV 4, CV 6, CV 10, and CV 12; and Stomach meridian ST 21, ST 25, and ST 28 bilaterally. All needles were retained manually (to elicit De Qi) once they were inserted and they remained in place for 30 minutes during each treatment.

Patients in the metformin group received metformin hydrochloride tablets, 250 mg three times daily in the first week of the study; thereafter, the metformin dose was 500 mg, three times daily for the remaining 6 months.

All measurements were performed in the morning, after an overnight fast, at baseline and after 6 months. Outcome measures included anthropometric measures, and the homeostasis model assessment of insulin resistance (HOMA-IR) was used to quantify insulin resistance and β -cell function; transvaginal ultrasonography was performed to measure ovarian volume; menstrual frequency was calculated assessment of menstrual history starting 3 months before the study and for the duration of the study; and laboratory data, including total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides, luteotrophic hormone (LH), follicle-stimulating hormone (FSH), and free testosterone.

Among the 146 women screened at the outpatient clinic, 86 were enrolled and randomly assigned to the abdominal acupuncture group or the metformin group.

After 6 months, BMI, waist-to-hip ratio (WHR), Ferriman-Gallwey score, ovarian volume, LH, ratio of LH to FSH, testosterone, LDL-C, triglycerides, total cholesterol, fasting blood glucose, 2-hour blood glucose, fasting insulin, 2-hour postprandial insulin, and HOMA-IR were reduced significantly in the metformin and abdominal acupuncture groups ($p < 0.05$). Menstrual frequency and HDL-C levels increased significantly ($p < 0.05$) in both groups; FSH also increased in the 2 groups, but the changes were not significant. The abdominal acupuncture group had considerable advantages over the metformin group in terms of reduced BMI and WHR and increased menstrual frequency ($p < 0.05$).

Twenty-one patients in the metformin group had mild adverse effects that occurred in the first stages of metformin use (nausea or vomiting, mild diarrhea, and slight dizziness or weakness). No one in the metformin group withdrew from the study. No uncomfortable symptoms occurred in the abdominal acupuncture group.

The researchers concluded that abdominal acupuncture is effective for restoring the normal endocrine and metabolic functioning of patients with obesity-type PCOS. Compared with metformin, abdominal acupuncture improved menstrual frequency, BMI, and WHR.

Acupuncture for hypoxic ischemic encephalopathy in neonates.

Wong V, Cheuk DK, Chu V. *Cochrane Database Syst Rev.* 2013;1:CD007968.

THIS REVIEW WAS CONDUCTED by researchers from The University of Hong Kong, Queen Mary Hospital, Hong Kong SAR, China. Funding for this project was received from Hospital Authority, Hong Kong, Hong Kong, The University of Hong Kong, Hong Kong, and Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health, Department of Health and Human Services.

Peripartum asphyxia affects 3–5 neonates per 1000 live births, with moderate or severe hypoxic ischemic encephalopathy (HIE) in 0.5 to 1 per 1000 live births. In this review the researchers' objective was to determine the effect of acupuncture on mortality and morbidity in neonates with HIE and the safety of acupuncture in these patients.

The researchers explored the following hypotheses:

- (1) Acupuncture is effective for improving either short-term (seizures, death) or long-term (developmental delay, intellectual impairments, visual or auditory impairments) outcomes or both.
- (2) Acupuncture can improve speed of rehabilitation.
- (3) Acupuncture can reduce the extent of disability (as a result of HIE complications) in neonates with HIE.
- (4) Acupuncture can improve quality of life of neonates with HIE.
- (5) Acupuncture is safe.

Inclusion criteria were:

- (1) Newborn infants: term neonates with postnatal age of ≤ 28 days
- (2) Evidence of peripartum asphyxia with each enrolled infant satisfying at least one of the following criteria: (i) Apgar score of ≤ 5 at 10 minutes; (ii) mechanical ventilation or resuscitation at 10 minutes; and (iii) cord blood pH < 7.1 or arterial blood pH < 7.1 or base deficit of 12 or more within 60 minutes of birth.
- (3) Evidence of encephalopathy according to Sarnat staging: (i) stage 1 (mild) including hyperalertness, hyperreflexia, dilated pupils, tachycardia, and absence of seizures; (ii) stage 2 (moderate) including lethargy, hyperreflexia, miosis, bradycardia, seizures, and hypotonia with weak suck and Moro; and (iii) stage 3 (severe) including stupor, flaccidity, small-to-mid position pupils that react poorly to light, decreased stretch reflexes, hypothermia, and absent Moro.

Neonates with major congenital abnormalities or syndromes recognizable at birth were excluded.

Randomized controlled trials (RCTs) and quasirandomized trials were reviewed. All acupuncture studies (performed alone or in combination with other therapies) were included. Studies examining acupressure, laser acupuncture, and percutaneous neuromodulation were excluded. Control interventions were

no treatment, placebo acupuncture, sham acupuncture, or conventional medical treatment (which may be baseline treatment) for HIE. Frequency and duration of treatment were not restricted. The researchers excluded studies comparing different forms of acupuncture only (different manipulation methods or different acupoints), because these studies could not deduce the net effect of acupuncture.

Several electronic databases were searched including major Mainland Chinese academic literature databases. In addition, article references were reviewed and experts in the field were contacted. Two reviewers reviewed relevant articles independently and extracted data from included trials and assessed trial quality independently. When disagreements occurred, a third reviewer decided on the outcome.

The electronic searches yielded initially a total of 119 records. After removal of duplicates, and exclusion of articles based on information in the titles or abstracts, a total of 17 articles reporting 16 trials (one trial was reported in two articles) remained. After further review, the researchers excluded 16 records (reporting 15 trials). None of the trials fulfilled the inclusion criteria.

Among the excluded studies, 8 trials actually evaluated acupoint massage that did not involve needle acupuncture. One trial evaluated body massage and not needle acupuncture. One trial evaluated the effect of acupuncture combined with hyperbaric oxygen (HBO), limiting the ability to evaluate whether any treatment effect was the result of acupuncture or HBO. One trial did not assign treatment groups by randomization. Other trials did not involve neonates.

None of the identified articles satisfied the predefined inclusion criteria. The researchers concluded that, currently, there are no published RCTs trials evaluating the effectiveness of acupuncture for treatment of HIE in neonates. The safety of acupuncture for HIE in neonates is unknown, as there is no adequate evidence to assess the safety of acupuncture for HIE in neonates.

The researchers concluded that the rationale for acupuncture in neonates with HIE is unclear, and the evidence from RCTs is lacking. Therefore, the researchers did not recommend acupuncture for the treatment of HIE in neonates.

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