RELIAS
Formerly AHC Media

Integrative Medicine

Vol. 21, Issue 7, July 2018
AHCMedia.com

Evidence-based summaries and critical reviews on the latest developments in integrative therapies [ALERT]

INCONTINENCE

ABSTRACT &COMMENTARY

Is Electroacupuncture the Answer to Stress Urinary Incontinence?

By Jeffrey H. Baker, MD, DABMA, DABIHM

Assistant Professor, Department of Family and Community Medicine, Penn State College of Medicine, State College

Dr. Baker reports no financial relationships relevant to this field of study.

SYNOPSIS: Following six weeks of every other day treatment, women treated with electroacupuncture in the sacral region reported less urinary incontinence than women receiving sham acupuncture in the same region.

SOURCE: Liu Z, Liu Y, Xu H, et al. Effect of electroacupuncture on urinary leakage among women with stress urinary incontinence: A randomized clinical trial. *JAMA* 2017;317:2493-2501.

Liu et al studied the effects of acupuncture on stress urinary incontinence, recognizing that there are few adequate therapies for this prevalent condition and the overall psychological effects of this problem can be far reaching in a woman's life.[1,2] In a randomized, clinical trial at 12 hospital sites, the authors enrolled 504 women and assigned them in a 1:1 ratio (in blocks of six women at each trial site) to real or sham acupuncture. The women were not compensated for their participation. Participants were 40 to 75 years of age. They were recruited through posters and newspaper advertisements and reported involuntary leakage on effort, exertion, sneezing, or coughing that ceased as the stress ended. Inclusion in the participation group required an incontinence pad weight gain of > 1 g in a one-hour pad test. The participants were told to void two hours prior to testing; on arrival, they wore a pre-weighed pad, drank 500 mL of water in 15 minutes, and then performed strenuous activity (going up and down stairs, walking, running, bending over to pick up coins, coughing, etc.).[3] The weight of the wet pad was then compared to the weight of the dry pad.

Financial Disclosure: *Integrative Medicine Alert*'s Executive Editor David Kiefer, MD; Peer Reviewer Suhani Bora, MD; AHC Media Executive Editor Leslie Coplin; Editor Jonathan Springston; and Editorial Group Manager Terrey L. Hatcher report no financial relationships relevant to this field of study.

[INSIDE]

sTMS for Migraine Prevention
page 78

Emotional Freedom Technique and Post-traumatic Stress Disorder
page 80

Integrative Medicine [ALERT]

Integrative Medicine Alert (ISSN 1096-942X) is published 12 times annually by AHC Media, a Relias Learning company, 111 Corning Road, Suite 250, Cary, NC 27518-9238.

Periodicals Postage Paid at Cary, NC, and additional mailing offices.

GST Registration Number: R128870672.
POSTMASTER: Send address changes to Integrative Medicine Alert, Relias Learning, 111 Corning Road, Suite 250, Cary, NC 27518-9238.

SUBSCRIBER INFORMATION
(800) 688-2421
Customer.Service@AHCMedia.com
AHCMedia.com

Questions & Comments:
Please contact Executive Editor Leslie Coplin, at lcoplin@relias.com

Subscription Prices
United States
Print: 1 year with free *AMA PRA Category 1 Credits™*: $319
Add $19.99 for shipping & handling.
Online only: 1 year (Single user) with ***free*** *AMA PRA Category 1 Credits™*: $269

Multiple Copies: Discounts are available for group subscriptions, multiple copies, site-licenses, or electronic distribution. For pricing information, please contact our Group Account Managers at Groups@AHCMedia.com or (866) 213-0844.

Back issues: $42. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Canada: Add 7% GST and $30 shipping.
Elsewhere: Add $30 shipping.

ACCREDITATION
Relias Learning is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Relias Learning designates this enduring material for a maximum of *3 AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

The American Osteopathic Association has approved this continuing education activity for up to 2 AOA Category 2-B credits.

This CME activity is intended for physicians and researchers interested in integrative medicine. It is in effect for 36 months from the date of the publication.

Summary Point

- When compared to sham acupuncture, electroacupuncture in the lumbosacral region improved urinary incontinence difficulties after six weeks.

The researchers excluded those who had urge, overflow, or mixed incontinence; vaginal prolapse greater than degree two; intercurrent urinary tract infection; pregnant; significant cardiac, hepatic, central nervous system, or psychiatric disease; limited mobility; metal allergy, or needle phobia.[4]

Preparations were made to mimic real acupuncture in the sham group. Sham acupuncture was accomplished through "pragmatic placebo needles" placed at sham points, 20 mm from the real acupoint, and lateral to the line consistent with the bladder meridian. Liu et al developed the use of pragmatic placebo needles and found them to be useful in previous research.[5] Pragmatic placebo needles are blunt acupuncture needles, shielded on the working end from the patient's sight with a 5 mm polyethylene foam collar that allows the needle to stand straight without skin penetration by adhesive on the collar.[5] No skin penetration, electrical stimulation, or needle manipulation was used for the sham group, but the same equipment setup, including electrical stimulation equipment and set, was used. At weeks 3 and 6, participants at two sites were asked to guess whether they were receiving sham or real acupuncture. The results of the two groups in the patient blinding analysis at the two intervals were similar as described below.

All participants received their blinded treatment three times a week for six weeks. The electroacupuncture was performed at two points bilaterally along the bladder meridian, BL-33 and BL-35, found in the sacral area. (*See Figure 1.*) As a component of ideal acupuncture therapy, de qi (soreness, heaviness, numbness at the site of insertion) was obtained. The needle handles of each side (BL-33 and BL-35) were stimulated at a continuous wave of 50 Hz and a current intensity of 1-5 mA. Electroacupuncture treatments lasted 30 minutes.

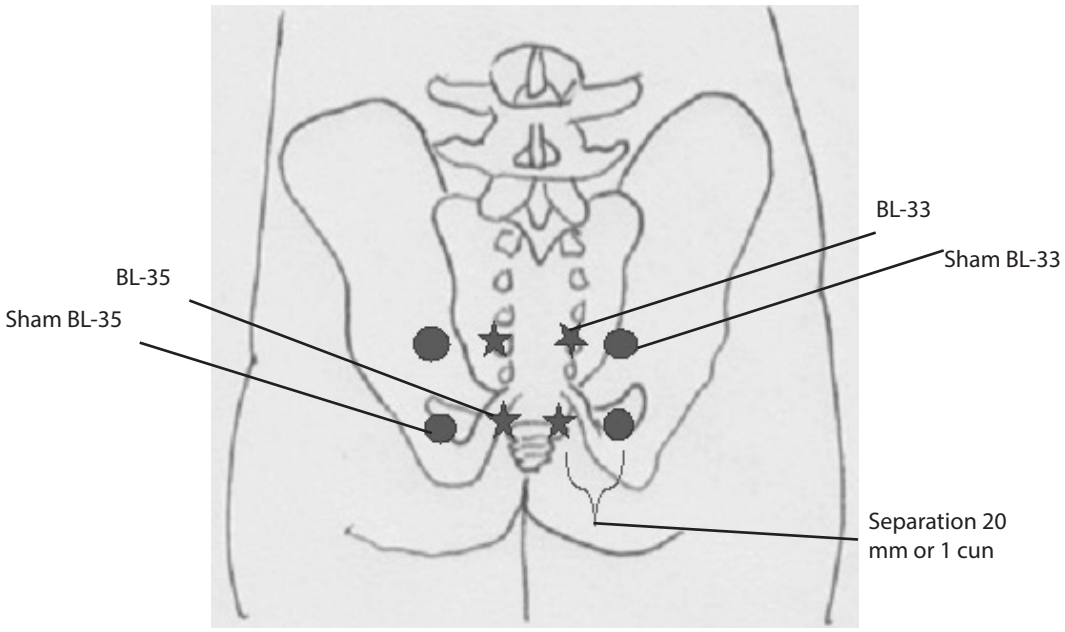
The sham acupuncture participants were treated with a placebo needle placed 20 mm (1 cun, a functional measurement of distance used in acupuncture) lateral to the locations of real BL-33 and BL-35 points. (*See Figure 1.*) All procedures for the two groups were identical, but no skin penetration, electricity output, or needle manipulation were used on the sham group. All participants of the trial were treated separately to prevent communication.

The primary outcome to be measured was change in urine leakage measured by the one-hour pad test at six weeks' intervention. Three groups were preplanned for sub-analysis: mild leakage of 1.1-9.9 g urine in one hour, moderate leakage of 10-49.9 g in one hour, and severe leakage of ≥ 50 g in one hour.[6] Although there is controversy surrounding the reproducibility of the test,[7] the one-hour pad test was performed at baseline, two weeks, and six weeks as a measurement of incontinence. It was chosen for measurement, as it was the only incontinence test with a standardized protocol.[8]

A number of secondary outcomes were measured, including change in urine leakage from baseline at two weeks; 72-hour urinary incontinence episodes measured by bladder diary at various points in the study (weeks 1-6, weeks 15-18, and weeks 27-30); the number of incontinence pads used reported in the 72-hour diaries; participant-reported severity of their stress urinary incontinence (mild, moderate, or severe); and the participants' self-evaluation of therapeutic help (no help, little help, medium help, and great help) at weeks 1-6, 7-18, and 19-30.

Adverse events were documented throughout the trial. Hematoma and fatigue occurred in 1.6% of the electroacupuncture group and 2% of the sham group.

Figure 1: Real and Sham Acupuncture Point Placement



The primary outcome was analyzed according to intention-to-treat principles. A sample size of 144 participants per group was estimated to provide 90% power to detect between-group differences of 1 g of urine measured in the one-hour pad test, but the groups were enlarged to 250 participants to compensate for a potential 20% loss to follow-up. The results of the six-week trial showed that despite the time commitment needed to undergo 18 acupuncture treatments, a reduction in incontinence and an improvement in quality of life could be obtained by this modality. (*See Table 1 and Table 2.*)

As to the primary outcome, the mean urine leakage in the electroacupuncture group, measured by the one-hour pad test, was 18.4 g (95% confidence interval [CI], 15.5-21.4 g) at baseline and 8.2 g (95% CI, 6.3-10.0 g) at week 6, while the sham group measured a mean of 19.1 g (95% CI, 15.6-22.7 g) at baseline and 16.8 g (95% CI, 13.5-20.1 g) at week 6. The electroacupuncture group had a greater reduction in the amount of urine leakage at week 6 (mean, -9.9 g) than the sham group (-2.6 g), with a difference of 7.4 g (95% CI, 4.8-10.0 g; $P < 0.001$). Similar results were observed at week 2. At week 6, greater success was found in decreasing urine incontinence by at least 50% in the electroacupuncture group (64.6%) compared with the sham group (21.7%).

At weeks 6, 18, and 30, the electroacupuncture group self-reported scores of symptom severity and evaluation of the effects of their treatment as more improved than the sham group. No difference was found between the two groups in the number of pads per week used to help control the episodes of incontinence. At week 3 of treatment, 31 of 41 (75.6%) participants receiving acupuncture guessed that they were receiving acupuncture, while 29 of 42 (69.0%) sham procedure participants thought they were receiving acupuncture as well. At week 6, 32 of 42 (78%) participants in the electroacupuncture group and 25 of 39 (64.1%) participants in the sham group believed they were receiving acupuncture.

The authors acknowledged that the study involved many limitations, including the use of fixed block randomization, allowing prediction of treatment bias at centers, and the assessment of blinding of participants at only two centers. They did not reassess the amount of urine leakage at the 24-week follow-up, and they did not pre-define a "meaningful difference" in the use of the one-hour pad test.

The authors presented valid arguments for the comparability of their technique to other methods of stress urinary incontinence treatment. They compared their acupuncture results to cited articles in the field showing that they provided similar results to pelvic floor strengthening and duloxetine prescription for decreases in 72-hour incontinence episodes and the proportion of participants with at least a 50% reduction in mean 72-hour incontinence episodes. Satisfaction rates for acupuncture treatment and pelvic floor muscle training were noted to be similar.

Table 1: Primary and Secondary Outcomes				
Primary Outcome				
Variable	**Electroacupuncture**	**Sham**	**Difference**	***P* Value**
Mean urine leakage at 6 weeks (95% CI)	8.2 g (6.3 to 10.0)	16.8 g (13.5 to 20.1)	NA	NA
Change in leakage at 6 weeks (95% CI)	-9.9 g (-12.5 to -7.3)	-2.6 g (-5.2 to 0.0)	7.4 g (4.8 to 10.0)	< 0.001
Secondary Outcome				
Variable	**Electroacupuncture**	**Sham**	**Difference**	***P* Value**
Change in mean number of 72-hour incontinence episodes per week (95% CI)				
Weeks 1 to 6	-2.9 (-3.6 to -2.2)	-2.0 (-2.7 to -1.2)	1.0 (0.2 to 1.7)	0.01
Week 2	-5.8 (-8.3 to -3.2)	-2.0 (-4.6 to -0.5)	3.7 (1.5 to 6.0)	< 0.001
Weeks 27 to 30	-5.0 (-5.8 to -4.3)	-3.0 (3.7 to -2.2)	2.1 (1.3 to 2.8)	< 0.001
Reduction > 50% urine leakage from baseline at week 6	159/246 (64.6)	52/240 (21.7)	-43.0 (-50.9 to 35.0)	< 0.001
Reduction > 50% mean 72-hour incontinence episodes from baseline				
Weeks 1 to 6	91/239 (38.1)	56/243 (23.1)	-15.0 (-23.2 to -6.9)	< 0.001
Weeks 27 to 30	160/237 (67.5)	99/236 (42.0)	-25.6 (-34.2 to -16.9)	< 0.001
Weekly mean use of urinary pads				
Weeks 1 to 6	3.0 (1.7-6.0)	3.7 (1.7-7.0)	NA	0.12
Weeks 27 to 30	3.0 (1.0-6.0)	3.8 (2.0-7.0)	NA	0.02

■ COMMENTARY

Options for treating stress incontinence in women are varied, yet often are not very effective. Behaviors have been modified, drugs consumed, and surgeries endured, without arriving at a distinct set of treatments that are reliable to use universally.[9] Through a series of studies, Liu et al attempted to show that acupuncture may be considered among the therapies showing promise as an option to help women with this common and inconvenient disorder.

Previous attempts at reviewing non-acupuncture forms of electrostimulation as treatment for stress urinary incontinence produced little in the way of conclusions, citing low quality of evidence in the literature.[10] Most recently, the Cochrane review group found that too little adequate research exists to make conclusions regarding acupuncture treatment for stress urinary incontinence.[11] Liu et al took measures to ensure that their data would be acceptable (group size, effect size, and power) as an acupuncture trial (data on guessing whether a participant received real acupuncture and the use of a sham group). Previously, they demonstrated that the use of a pragmatic placebo needle, placed in acupuncture points without skin penetration and shielded visually from Chinese participants, could be perceived to be real. The Chinese are very aware of acupuncture treatments and how they should feel and appear, thus making the pragmatic placebo needle a very good tool in blinding patients from real acupuncture.[5]

In the same *JAMA* issue, Wang criticized the study by taking issue with his perception that traditional

Table 2: Participant Self-evaluation

Week 6				Week 30		
Severity of SUI	**Electroacupuncture**	**Sham acupuncture**	***P* value**	**Electroacupuncture**	**Sham acupuncture**	***P* value**
None	5.3%	2.4%		21.1%	24%	
Mild	56.1%	49.2%	0.03	60.7%	58.6%	< 0.001
Medium	35.8%	41.5%		16.1%	27.6%	
Severe	2.8%	6.9%		2.1%	3.8%	
Self-evaluation of therapy						
No help	0.8%	30.5%		6.2%	34.3%	
Little help	13.8%	39.0%	< 0.001	18.5%	37.2%	< 0.001
Medium help	48.8%	19.1%		39.1%	16.7%	
Great help	37.0%	11.4%		36.2%	11.7%	

Chinese medicine (TCM) diagnostic criteria were not used for the ultimate acupuncture treatment, as historically, acupuncture treatment is based on a TCM diagnosis. He noted that the quality of acupuncturists was not ensured and that the number of incontinence pads remained relatively constant throughout the trial.[12] Liu et al responded in kind, noting that their previous study was the basis of this trial and that the uniqueness of their point selection (stimulating the third sacral nerve inferior gluteal nerves) was congruent with TCM theory that all acupuncturists were required to attend training prior to their involvement in the trial.[13]

The use of acupoints is not unique to TCM therapy or eastern medicine practices. Urologists treat overactive bladder successfully with electrical stimulation. The technique involves repeated "stimulation of the tibial nerve."[14,15] The two stimulation points used in this procedure by urologists are similar to the electroacupuncture of points of kidney-6 (KI-6) and kidney-7 (KI-7) found near the medial ankle area.

This study is not an end, but an important beginning. Liu et al successfully tested a different approach to help women with urinary stress incontinence. By adhering to the current rigors of research review standards, they have opened the door to uncovering further treatment options and directions for stress urinary incontinence. They also have shown that acupuncture research can be accomplished in a complete and acceptable fashion. Women can now use further alternatives to the current palate of treatment options in this common disorder. ■

REFERENCES

1. Kobashi K, Albo ME, Dmochowski RR, et al. Surgical treatment of female stress urinary incontinence (SUI): AUA/SUFU Guideline. 2017. Available at: http://www.auanet.org/guidelines/stress-urinary-incontinence-(sui)-new-(aua/sufu-guideline-2017). Accessed May 31, 2018.
2. Sinclair AJ, Ramsay IN. The psychosocial impact of urinary incontinence in women. *The Obstetrician & Gynaecologist* 2011;13:143-148. Available at: https://pdfs.semanticscholar.org/53fb/01aa4b392fe9a24cd43a2050059e5500149d.pdf. Accessed May 31, 2018.
3. Abrams P, Blaivas JG, Stanton SL, Andersen JT. The standardisation of terminology of lower urinary tract function. The International Continence Society Committee on Standardisation of Terminology. *Scand J Urol Nephrol Suppl* 1988;114:5-19.
4. Liu Z, Xu H, Chen Y, et al. The efficacy and safety of electroacupuncture for women with pure stress urinary incontinence: Study protocol for a multicenter randomized controlled trial. *Trials* 2013;14:315. doi: 10.1186/1745-6215-14-315.
5. Liu B, Xu H, Ma R, et al. Effect of blinding with a new pragmatic placebo needle: A randomized controlled crossover study. *Medicine* (Baltimore) 2014;93:e200.
6. Smither AR, Guralnick ML, Davis NB, See WA. Quantifying the natural history of post-radical prostatectomy incontinence using objective pad test data. *BMC Urol* 2007;7:2.
7. Simons AM, Yoong WC, Buckland S, Moore KH. Inadequate repeatability of the one-hour pad test: The need for a new incontinence outcome measure. *BJOG* 2001;108:315-319.
8. Lose G, Rosenkilde P, Gammelgaard J, Schroeder T. Pad-weighing test performed with standardized bladder volume. *Urology* 1988;32: 78-80.
9. Lukacz ES, Santiago-Lastra Y, Albo ME, Brubaker L. Urinary incontinence in women: A review. *JAMA* 2017;318:1592-1604.
10. Stewart F, Berghmans B, Bø K, Glazener CMA. Electrical stimulation with non-implanted devices for stress urinary incontinence in women. *Cochrane Database Syst Rev* 2017;12:CD012390.
11. Wang Y, Zhishun L, Peng W, et al. Acupuncture for stress urinary incontinence in adults. *Cochrane Database Syst Rev* 2013;7:CD009408.
12. Wang M. Acupuncture for stress urinary incontinence. *JAMA* 2017; 318:1500.
13. Liu Z, Liu Y, Liu B. Acupuncture for stress urinary incontinence-reply. *JAMA* 2017;318:1500.

14. Staskin DR, Peters KM, MacDiarmid S, et al. Percutaneous tibial nerve stimulation: A clinically and cost effective addition to the overactive bladder algorithm of care. *Curr Urol Rep* 2012;13:327-334.
15. Sherif H, Abdelwahab O. Posterior tibial nerve stimulation as treatment for the overactive bladder. *Arab J Urol* 2013;11:131-135.

ABSTRACT & COMMENTARY

sTMS for Migraine Prevention

By Ellen Feldman, MD

Altru Health System, Grand Forks, ND

Dr. Feldman reports no financial relationships relevant to this field of study.

SYNOPSIS: This observational study adds evidence for daily use of single-pulse, transcranial stimulation (sTMS) for the prevention of migraines.

SOURCE: Starling AJ, Tepper SJ, Marmura MJ, et al. A multicenter, prospective, single arm, open label, observational study of sTMS for migraine prevention (ESPOUSE Study). *Cephalagia* 2018;38:1038-1048.

Described in 2006 as a "forgotten epidemic," historically, migraine has been both underdiagnosed and underestimated as a major contributor to public health problems.[1] With improved recognition and newer techniques for gathering and analyzing data, the 2016 Global Burden of Disease study bestowed on migraine the dubious distinction of being ranked as the number one cause of disability worldwide in persons between the ages of 15 and 49 years.[2]

Despite this heightened recognition, treatment and prevention lag behind. Tolerability and efficacy issues interfere with adherence to medication regimen. Current estimates are that over a period of one year, 80% of patients with chronic migraine fail to comply with preventive medication as prescribed or directed. Many patients have reported a desire for nonpharmacologic, noninvasive, and effective treatments to address this problem.[3]

Single-pulse transcranial magnetic stimulation (sTMS) offers patients with migraine an alternative to traditional psychopharmacological intervention. Starling et al instructed patients to apply electrical current or pulse outside the scalp on the occiput. The devices used were small, portable, and simple enough to be used safely within a home setting and without a provider's direct supervision.

The idea is that electromagnetic induction allows current to be carried into cortical areas. Animal models have demonstrated that sTMS changes the electrical environment of neurons. Among other effects, sTMS modulates some nociceptive neurons and inhibits cortical spreading depression thought to be key in development of aura in migraines.[4] The initial 2017 FDA approval for this device was for the acute treatment of migraines with aura.[5] Starling et al conducted this study to provide evidence to extend and broaden the FDA approval to include migraine prevention with or without aura.

Summary Points

- This was a prospective, non-randomized, observational study initially involving 263 patients recruited from headache clinics.
- After completing a one-month headache diary, all eligible subjects were given a portable sTMS device and instructed to apply four pulses to occiput twice daily for prevention and three consecutive pulses for breakthrough headaches.
- There was no sham or placebo arm; instead, the authors used a statistically derived placebo calculation based on several previous studies to evaluate results.
- When compared with baseline, there was a mean reduction in number of headache days of 2.75 during the month-long study period, which was significantly lower than the statistically derived placebo response ($P < 0.001$).

Potential participants ages 18 to 65 years were recruited from headache clinics and spent the initial month of the study completing a baseline headache diary. Of 263 subjects, 217 met eligibility criteria to participate in the study and were given sTMS devices. Notably, while a minimum number of four headache

Table 1: Selected Results			
	Subjects	**Calculated placebo or "performance goal"**	***P* value**
Mean number of headache days	-2.45 (9.06 days at baseline)	-0.63	$P < 0.0001$
Percentage of subjects with at least 50% reduction in headache days	46%	20%	$P < 0.0001$

days/month was required for inclusion in this study, the presence or absence of aura was not a factor. There was some attrition and further exclusions from this group, eventually leaving 117 subjects. The majority of the exclusions were due to participants not meeting more nuanced criteria for number of headache days.

The 117 remaining subjects completed a three-month headache diary while using the sTMS device as instructed — four pulses to occiput twice daily for prevention and three pulses consecutively when necessary, with the ability to repeat the three pulses up to three times. Acute medication was permitted to be used if a headache remained 30 minutes after the first of the three acute pulses, and preventive medications were permitted to be continued.

The primary outcome measured was a reduction in the number of headaches compared to the statistically derived placebo response or "performance goal." The percentage of participants with a > 50% reduction in headache days also was measured. The performance goal was calculated based on three other migraine studies (two with topiramate and one with a device) conducted with a similar population to that used by Starling et al. Results are shown in Table 1 and indicate both a significant reduction in mean number of headache days and that 46% of subjects recorded at least a 50% reduction in headache days. In addition, subjects showed a mean reduction in the Headache Impact (HIT-6) questionnaire of 3.10 ($P < 0.0001$) and a reduction in acute medication use measured in days of -2.93 ($P < 0.0001$).

Adverse effects were evaluated closely. Of the 62 side effects reported, 16 were believed to be unrelated to the device, 30 were deemed possibly related to the device, and 12 were deemed definitely related to the treatment. None of the side effects, which included lightheadedness, tingling, scalp discomfort, and difficulty tolerating noise from the device, were thought to be serious. Nine participants dropped out of the study because of side effects.

■ COMMENTARY

The results of the Starling et al study, along with observational data from a U.K. study and results from a previous randomized, controlled study, led to an extension of the initial 2014 FDA approval for sTMS in the treatment of migraine with aura to prevention and acute treatment of migraine with and without aura. Currently, FDA approval for sTMS in migraines is limited to a specific device — the SpringTMS made by eNeura Therapeutics.[5] Starling et al also used this device in their study.

Clearly, a simple, easy-to-administer, and effective preventive intervention for migraine is needed to combat the significant disability stemming from repetitive migraines. Migraine prevalence peaks during childbearing years; disability in this demographic is particularly worrisome because of the effect on family life and employment. A robust preventive treatment could have important "trickle-down" effects and significant public health implications.[2]

Conventional prophylactic migraine treatment includes medications such as anticonvulsants (topiramate and Depakote) or beta-blockers, which have varying efficacy and significant side effects. Studies show about a 50% discontinuation of preventive medication within 60 days and up to 85% noncompliance with preventive treatment by the end of 12 months.[3] Although data from the Starling study regarding compliance are encouraging, it is notable that the data collection ended at week 12. It is hoped that investigataors will plan longer-term studies to determine if the pattern of noncompliance with preventive medications is reversed with the sTMS device.

Integrative methods of addressing migraine prevention include dietary modification, acupuncture, sleep hygiene, hydration, and some supplements. The efficacy of these interventions was not addressed in this study; a head-to-head comparison could be both informative and useful.[6] Certainly, the lack of a true sham device or placebo arm make the results of this study somewhat less compelling. Although the reasoning for the study design is explained, Starling et al noted this as a relative weakness. Future studies should include a true randomized sample with a control group.

The cost and availability of the device will be a factor for many prospective patients. Insurance may

require steps before approval, and it is not clear that any insurance plans will cover the device. The company offers an array of financial information on its website. With a $300 discount for new patients, the initial cost to rent a device is $450 for the first three months. Rentals can be arranged online with a convenient, downloadable form completed by a provider. The device comes with a SIM card that can be replaced when a prescription is renewed. There is also an online migraine diary for patients to track progress, and clinical education support specialists are available for consultation.[7]

The website offers a glimpse into a relatively new manner of reaching patients with medical information and offering treatment. There is a section for healthcare professionals and a link to obtain information on a certification process to prescribe the device. The bulk of the site appears devoted to marketing, education, and support for patients who desire to use the device. The commercialization of the prescribing process may be a barrier for some, but could be comfortable and convenient for others.

Notably, this device has not been studied or approved for children. Long-term effects are unknown. Contraindications to its use include the presence of any implanted device that could be affected by a magnetic field, including but not limited to metallic heart valves, stents, and plates.

The Starling et al study is interesting and provides an exploration of some of the evidence presented to FDA in approving and extending indications for use of the sTMS device to migraine prevention. Patients are very likely to ask about the device. Providers can assist in interpreting evidence, explaining limitations, and helping patients weigh risks and benefits. There is a secondary gain inherent in obtaining this information directly from the makers of the device; this may make some prospective users (and prescribers) wary or uneasy. A neutral medical provider who knows the patient and understands a holistic medical picture is a particularly valuable partner under these circumstances. Understanding that sTMS may help reduce the prevalence of migraines, that acute medication still may be needed, that there are specific contraindications, and that the long-term effect is unknown are important points for patients and providers to discuss as part of a comprehensive wellness plan. ■

REFERENCES

1. Diener HC, Steiner TJ, Tepper SJ. Migraine – the forgotten epidemic: Development of the EHF/WHA Rome Declaration on Migraine. *J Headache Pain* 2006;7:433-437.
2. GBD 2016. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017;390:1211-1259.
3. Chin JH, Vora N. The global burden of neurologic diseases. *Neurology* 2014;83:349-351.
4. Bhola R, Kinsella E, Giffin N, et al. Single-pulse transcranial magnetic stimulation (sTMS) for the acute treatment of migraine: Evaluation of outcome data for the UK post market pilot program. *J Headache Pain* 2015;16:535.
5. U.S. Food and Drug Administration. Treating Migraines: More Ways to Fight the Pain. Available at: https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm414707.htm. Accessed May 14, 2018.
6. Millstine D, Chen CY, Bauer B. Complementary and integrative medicine in the management of headache. *BMJ* 2017;357:j1805.
7. eNeura. Available at: http://www.eneura.com/. Accessed May 10, 2018.

STRESS

ABSTRACT & COMMENTARY

Emotional Freedom Technique and Post-traumatic Stress Disorder

By Rebecca L. Fahey, PhD, MD, MBA

Integrative Medicine Epidemiologist, Cary, NC

Dr. Fahey reports no financial relationships relevant to this field of study.

SYNOPSIS: The emotional freedom technique is a new approach to treating post-traumatic stress disorder in veterans that uses genomic science.

SOURCE: Church D, Yount G, Rachlin K, et al. Epigenetic effects of PTSD remediation in veterans using emotional freedom techniques: A randomized controlled pilot study. *Am J Health Promot* 2018;32:112-122.

The obstinate nature of post-traumatic stress disorder (PTSD) toward current treatments has been explored in the literature.[1] The prevalence of PTSD in the general population is about 6.8%.[2] According to the National Comorbidity Survey Replication (2001-2003), the prevalence of lifetime PTSD was around

9.7% in the female general population, 13.4% in female veterans, 3.6% in the male general population, and 7.7% in male veterans.[3] The numbers are higher in veterans who have served in wars or conflicts, especially Operation Iraqi Freedom and Operation Enduring Freedom (13.8%), the Gulf War (Operation Desert Storm, 10.1%), and the Vietnam War (26.9% for women and 30.9% for men). Women are more than twice as likely as men to develop PTSD.[3]

The emotional freedom technique (EFT) is a therapy that has emerged over the last 20 years. EFT is simple to learn. Videos demonstrating the therapy are available online, and a manual that is updated periodically can be downloaded for free.[4,5] EFT relies on a combination of techniques of tapping on or massaging acupuncture points (acupressure) while saying an activating phrase. The phrasing comes from cognitive behavioral therapy and is used to identify the issue. A sample phrase would be, "Even though I have this fear of spiders, I deeply and completely accept myself." While repeating the phrase (specific to the patient's specific issue), the patient taps on the points in the order shown in the figure available at: https://bit.ly/2xPaYT3.[6]

Despite its ease of use, EFT has had difficulty crossing the translational gap.[7] It takes an average of 17 years for a new approach to be incorporated into the medical model, with only about 20% of new techniques accepted. EFT is emerging in the literature, partly because it meets evidence-based standards set by the American Psychological Association.[7,8]

Church et al designed their study to understand the role EFT plays in the treatment of PTSD. Sixteen veterans were randomized to an EFT group or a treatment-as-usual (TAU) group. Patients in the EFT group participated in one-hour EFT sessions each week for 10 weeks. All participants were given several questionnaires (Symptom Assessment 45, Hospital Anxiety and Depression Scale, Insomnia Severity Scale, SF-12v.2 health survey, Brief Pain Inventory, Rivermead Post-concussion Symptoms Questionnaire) before, during, and after treatment. The researchers monitored 93 genes that encode the key regulators of glucocorticoid signaling, inflammation, and innate immune signaling, as well as the transporters and receptors for these key regulators linked to PTSD, using the Student *t* test and post-hoc analyses. They drew blood samples before and after EFT treatment, extracted mRNA, and measured the product levels (proteins) for the above genes. The premise was that EFT would act via epigenetics to influence gene expression to decrease the creation of proteins linked to inflammation, the immune system, and the cortisol cycle. These products were measured by recording the amount of the proteins and/or hormones in the blood before and after EFT treatment.

Summary Points

- Post-traumatic stress disorder (PTSD) notoriously is hard to treat. The emotional freedom technique (EFT) is a simple and potentially effective treatment for PTSD.
- EFT involves a sequence of repetitive tapping on acupuncture points while saying an activating phrase, which is based on cognitive behavior therapy.
- EFT addresses the fear behind patients' physical symptoms.

In the EFT group (n = 18), PTSD symptoms decreased (-53; $P < 0.0001$), with these results still present at the six-month follow-up. Six genes involved in stress response, cellular immunity, and inflammation had a strong signal-to-noise ratio ($P < 0.05$) when levels were compared before and after treatment with EFT. (*See Table 1.*) Post-hoc analyses were performed to detect any changes in gene expression pre- and post-EFT treatment; 12 genes were identified. (*See Table 2.*) Student *t* test and log transformed ratios ($P < 0.05$) found six genes with > 15%-fold changes, and two previously unidentified genes had significant differential gene expression. After both TAU and EFT groups received EFT treatments, a two-sample Student *t* test of the fold changes showed no significant differences ($P > 0.05$) in gene expression.

■ COMMENTARY

PTSD remains a difficult disorder to treat and has inspired the development of new treatment modalities, including EFT. Research about the mechanisms behind the success of EFT has been increasing. EFT has been shown to treat the phenomenon of recalled pain that causes chronic pain.[9,10] When a nerve has been injured, the damage may change epigenetic markers on the genes of these nerve cells. Denk et al identified nerve cells that performed normally but had genetic changes that showed the cell had a memory of the original injury. When this memory is triggered by epigenetic mechanisms, recall of the original trauma by the injured nerve cell could be the reason for apparently random attacks of pain that some patients with chronic pain experience.[10]

Swingle et al monitored electroencephalogram (EEG) patterns of patients before and after EFT treatment for injuries from motor vehicle collisions ($t = 7.25$;

$P < 0.01$).[11] Lambrou et al studied the EEG patterns of the effect of EFT on claustrophobia ($P < 0.001$).[12] EFT has been shown to be effective on fear, anxiety, and trauma-based symptoms.[13] In functional magnetic resonance imaging studies, Dhond et al demonstrated that acupuncture works by down-regulating neural output from the limbic system, which is triggered by fear.[14] EFT is the manual stimulation of 14 identified acupuncture points, using phrasing from cognitive behavioral therapy.[15] The practice of EFT has evolved over the years, and new practitioners are asked to add an element of their own personal work and rename the technique.

Researchers have explored the mechanism of action of EFT, such as in a triple-blind, randomized, controlled trial on how EFT affects the release of hormones from endocrine cells to target cells. Key psychological signs were compared with cortisol levels in 83 participants who were divided into three groups before and after one treatment of EFT.[16] Cortisol levels decreased in all three groups: The EFT group (-24.39%; standard error [SE], 2.62) had a larger decrease in levels than the supportive interview (-14.25%; SE, 2.61) and no treatment (-14.44%; SE, 2.67) groups ($P < 0.03$). The EFT group displayed statistically significant recoveries in anxiety (-58.34%; $P < 0.05$), depression (-49.33%; $P < 0.002$), total severity of indicators (-50.5%; $P < 0.001$), and symptom scope (-41.93%; $P < 0.001$).[16] Once again, fear was the underlying emotion addressed. PTSD is unique as an illness because a patient had to experience a trauma to develop the disorder.[17] The more traumas or fears experienced in childhood, the more likely someone will develop PTSD or other disorders as a result.

The link established between EFT and down-regulation of the limbic system created new areas of research into the epigenetic effects of EFT. Its mechanism of action may be that it interacts with the epigenetic process that controls the development and continuation of symptoms. Genetic structures are thought to be stable throughout the organism's lifetime while epigenetic activities are labile, continuously changing gene expression as a response to environmental stimuli. This discussion can get complicated because epigenetic responses vary from cell to cell and from organism to organism.[18] EFT therapy has been linked to the stress response and the limbic system, which is regulated by the epigenetic response to environmental stimuli.

Until now, the research on the epigenetic effects of EFT only focused on DNA methylation, the most investigated epigenetic mechanism in mammals, and its connection to the possibility of development of PTSD and conditioned fear.[19,20] A series of epigenetic studies have connected the onset of PTSD to effects of DNA methylation levels at specific points in the genome.[21,22] The literature supports the theory that there is communication among the inborn genes, the number of individual traumas experienced in childhood, and the development of PTSD.[23] Authors of further studies have suggested that the epigenetic processes of the stress response act via cortisol on the hypothalamic-pituitary-adrenal (HPA) axis. The increased risk of mental health issues in adulthood may be caused by the accumulated traumas of childhood that have induced DNA demethylation of the FK506 binding protein (FKBP5) gene, an important regulator of the stress hormone system. The results of the study indicated that demethylation amplified stress-dependent gene transcription and consequential continued impairment of HPA axis regulation.[24]

Table 1: Changes in Gene Expression From Pre- to Post-treatment

Gene	TAU (n = 9) mean fold change	EFT (n = 7) mean fold change	*P* value
IL-IORB	1.047	1.170	0.019
SELL	1.040	1.203	0.025
TNFAIP6	1.058	1.318	0.026
CXCR3	1.042	-1.467	0.45
IL-18	-1.062	1.177	0.046
IFITMI	1.006	1.151	0.48

TAU: treatment as usual; EFT: emotional freedom technique

The results confirm and advance the epigenetic research that three genes related to the immune system are under-expressed ($P < 0.05$) in the peripheral blood of individuals with PTSD.[25] A study on whole blood identified four genes in veterans with combat-induced PTSD and found four genes ($P < 0.05$) that were involved in the regulation of the inflammatory response.[26,27,28]

There were several limitations to the study, including a small sample size. Several studies cited issues with recruiting yields of 3-5.5% when targeting veterans with PTSD to obtain an appropriate sample size,[29] illustrating issues identified with getting members of this target group to complete an entire study. The TAU group was treated with EFT after the study ended, which ruled it out as a long-term comparison group. Another control group should be added for cognitive behavioral therapy or other similar treatment modality to establish a proper comparison with a current successful therapy. Two pilot studies

Table 2: Gene Expression Between Treatment Groups From Pre- to Post-treatment						
	EFT		TAU (With EFT)		Pooled	
Gene	**MFC**	***P***	**MFC**	***P***	**MFC**	***P***
IL-IORB	1.17	0.002	1.093	0.01	1.128	< 0.001
SELL	1.203	0.009	1.064	0.097	1.127	0.002
TNFAIP6	1.318	0.001	1.033	0.698	1.047	0.431
CXCR3	-1.467	0.087	-1.279	0.095	-1.364	0.012
IL-18	1.177	0.106	1.09	0.241	1.13	0.036
IFITMI	1.151	0.026	1.051	0.103	1.096	0.006
CANX	-1.098	0.019	-1.008	0.765	-1.049	0.047
NFIL3	1.206	0.048	1.067	0.425	1.13	0.042
CXCLI	1.312	0.097	1.121	0.32	1.206	0.046
GPR65	1.265	0.164	1.118	0.243	1.184	0.058
EDGI	-1.244	0.208	-1.042	0.441	-1.132	0.133
CASP2	-1.235	0.066	-1.039	0.49	-1.126	0.049
IFNGRI	1.185	0.075	1.116	0.004	1.148	0.003
IFITM3	1.176	0.235	-1.007	0.928	1.075	0.317

comparing cognitive behavioral therapy with EFT in adolescents and adults indicate that EFT is credible enough to merit additional study.[30,31]

Among the patients studied, 83% reported a prior diagnosis of PTSD. Although this can be verified through medical records, it would have benefited the study to have a mental health practitioner evaluate each participant for PTSD before and after each treatment. Another limitation was the inability to control for analgesics in the study.

There are potential harms associated with EFT when working with veterans diagnosed with PTSD. The adverse effects mentioned in the literature surrounding EFT identify issues with negative emotions, a resurgence of symptoms, and not responding to EFT at all. Patients should work with certified EFT practitioners within the context of a holistic team led by a mental health practitioner.

CONCLUSION

PTSD is a serious, sometimes labile, condition, and practitioners should work within teams in the healthcare system to provide a holistic, interdisciplinary approach to treat PTSD patients. Some of the emerging evidence, including the findings from this study, shows that EFT might be part of an integrative treatment plan that also continues with proven conventional therapies. ■

REFERENCES

1. Church D, Yount G, Rachlin K, et al. Epigenetic effects of PTSD remediation in veterans using emotional freedom techniques: A randomized controlled pilot study. *Am J Health Promot* 2018;3:112-122.
2. U.S. Department of Veterans Affairs. PTSD: National Center for PTSD. Gradus J. Epidemiology of PTSD. Available at: https://www.ptsd.va.gov/professional/PTSD-overview/epidemiological-facts-ptsd.asp. Accessed June 1, 2018.
3. Kessler RC, Berglund P, Demler O, et al. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005;62:593-602.
4. Lehavot K, Katon JG, Chen JA, et al. Post-traumatic stress disorder by gender and veteran status. *Am J Prev Med* 2018;54: e1-e9.
5. Church D. *The EFT Manual*. 3rd ed. Santa Rosa, CA: Energy Psychology Press; 2013.
6. Burk L. EDANVIR tapping. Available at: https://bit.ly/2xPaYT3. Accessed June 1, 2018.
7. Church D, Feinstein D, Palmer-Hoffman J, et al. Empirically supported psychological treatments: The challenge of evaluating clinical innovations. *J Nerv Ment Dis* 2014;202:699-709.
8. Feinstein D. Acupoint stimulation in treating psychological disorders: Evidence of efficacy. *Rev Gen Psychol* 2012;16:364-380.
9. Callahan RJ, Callahan J. *Stop the Nightmares of Trauma: Thought Field Therapy, the Power Therapy for the 21st Century*. Indian Wells, CA: Professional Press; 2000.
10. Denk F, Crow M, Didangelos A, et al. Persistent alterations in microglial enhancers in a model of chronic pain. *Cell Rep* 2016;15:1771-1781.
11. Swingle PG, Pulos L, Swingle MK. Neurophysiological indicators of EFT treatment of post-traumatic stress. *Subtle Energies Energy Med*, 2005;15:75-86.
12. Lambrou P, Pratt G, Chevalier G. Physiological and psychological effects of a mind/body therapy on claustrophobia. *Subtle Energies Energy Med* 2005;14:239-251.
13. Flint G, Lammers W, Mitnick DG. Emotional freedom techniques: A safe treatment intervention for many trauma based issues. *J Aggression*

Maltreatment Trauma 2008;12:125-150.
14. Dhond RP, Kettner N, Napadow V. Neuroimaging acupuncture effects in the human brain. *J Altern Complement Med* 2007;13:603-616.
15. Church D, Feinstein D. The manual stimulation of acupuncture points in the treatment of post-traumatic stress disorder: A review of clinical emotional freedom techniques. *Med Acupunct* 2017;29:194-205.
16. Church D, Yount G, Brooks AJ. The effect of emotional freedom techniques on stress biochemistry: A randomized controlled trial. *J Nerv Ment Dis* 2012;200:891-896.
17. Xie P, Kranzler HR, Poling J, et al. Interaction of FKBP5 with childhood adversity on risk for post-traumatic stress disorder. *Neuropsychopharmacology* 2010;35:1684-1692.
18. Klengel T, Mehta D, Anacker C, et al. Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions. *Nat Neurosci* 2013;16:33-41.
19. Zhang TY, Meaney MJ. Epigenetics and the environmental regulation of the genome and its function. *Annu Rev Psychol* 2010;61:439-466.
20. Novik K, Nimmrich I, Genc B, et al. Epigenomics: Genome-wide study of methylation phenomena. *Curr Issues Mol Biol* 2002;4:111-128.
21. Chang SC, Koenen KC, Galea S, et al. Molecular variation at the SLC6A3 locus predicts lifetime risk of PTSD in the Detroit Neighborhood Health Study. *PLoS One* 2012;7:e39184.
22. Wilker S, Kolassa I-T. The formation of a neural fear network in posttraumatic stress disorder: Insights from molecular genetics. *Clin Psychol Sci* 2013;1:452-469.
23. Zovkic IB, Meadows JP, Kaas GA, Sweatt JD. Interindividual variability in stress susceptibility: A role for epigenetic mechanisms in PTSD. *Front Psychiatry* 2013;4:1-22.
24. Hollifield M, Moore D, Yount G. Gene expression analyses in combat veterans with and without post-traumatic stress disorder. *Mol Med Rep* 2013;8:238-244.
25. Neylan TC, Sun B, Rempel H, et al. Suppressed monocyte gene expression profile in men versus women with PTSD. *Brain Behav Immun* 2011;25:524-531.
26. Logue MW, Smith AK, Baldwin C, et al. An analysis of gene expression in PTSD implicates genes involved in the glucocorticoid receptor pathway and neural responses to stress. *Psychoneuroendocrinology* 2015;57:1-13.
27. Breen MS, Maihofer AX, Glatt SJ, et al Gene networks specific for innate immunity define post-traumatic stress disorder. *Mol Psychiatry* 2015;20:1538-1545.
28. Church D. *The Genie in Your Genes: Epigenetic Medicine and the New Biology of Intention.* Santa Rosa, CA: Energy Psychology Press; 2007.
29. Bayley PJ, Kong JY, Helmer DA, et al. Challenges to be overcome using population-based sampling methods to recruit veterans for a study of post-traumatic stress disorder and traumatic brain injury. *BMC Med Res Methodol* 2014;14:48.
30. Chatwin H, Stapleton P, Porter B, et al. The effectiveness of cognitive behavioral therapy and emotional freedom techniques in reducing depression and anxiety among adults: A pilot study. *Integr Med* (Encinitas) 2016;15:27-34.
31. Gaesser AH, Karan OC. A randomized controlled comparison of emotional freedom technique and cognitive-behavioral therapy to reduce adolescent anxiety: A pilot study. *J Altern Complement Med* 2017;23:102-108.

CME QUESTIONS

1. In a study of women receiving acupuncture treatment vs. sham treatment for stress urinary incontinence, what percentage of those who received sham treatment incorrectly thought that they were receiving real acupuncture?
a. 64-69%
b. 50-54%
c. 75-78%
d. 45-49%

2. Which of the following statements regarding single-pulse, transcranial stimulation (sTMS) is true?
a. sTMS is a cost-effective, well-studied, minimally invasive technique to combat migraines and is FDA approved.
b. sTMS was approved for acute treatment of migraine with aura initially and now is approved for prevention and treatment of migraine with and without aura.
c. sTMS is FDA approved for treatment and prevention of migraines for patients ages 12 and older.
d. sTMS must be used under direct supervision of a medical professional in a clinic setting.

3. The suggested mechanisms of action of the emotional freedom technique is to act via which of the following?
a. Limbic system and the hypothalamic pituitary adrenal axis
b. Endocrine system
c. Immune system
d. All of the above

[IN FUTURE ISSUES]

Traditional Chinese Medicine for Cardiovascular Disease

Common Adaptogens for Exercise Performance

Vitamin D and Glycemic Control in Diabetes

Exercise and Depression