Acupuncture for Treatment of Persistent Disturbed Sleep: A Randomized Clinical Trial in Veterans With Mild Traumatic Brain Injury and Posttraumatic Stress Disorder

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ABSTRACT

Objective: To evaluate real, as compared with sham, acupuncture in improving persistent sleep disturbance in veterans with mild traumatic brain injury (mTBI) and posttraumatic stress disorder (PTSD).

Methods: This sham-controlled randomized clinical trial at a US Department of Veterans Affairs Medical Center (2010–2015) included 60 veterans aged 24–55 years (mean of 40 years) with history of mTBI of at least 3 months and refractory sleep disturbance. Most of these participants (66.7%) carried a concurrent *DSM-IV* clinical diagnosis of PTSD. For the present study, they were randomized into 2 groups and stratified by PTSD status using the PTSD Checklist–Military Version. Each participant received up to 10 treatment sessions. The primary outcome measure was change in baseline-adjusted global Pittsburgh Sleep Quality Index (PSQI) score following intervention. Secondary outcomes were wrist-actigraphy–assessed objective sleep measurements. Comorbid PTSD was analyzed as a covariate.

Results: Mean (SD) preintervention global PSQI score was 14.3 (3.2). Those receiving real acupuncture had a global PSQI score improvement of 4.4 points (relative to 2.4 points in sham, $P = .04$) and actigraphically measured sleep efficiency (absolute) improvement of 2.7% (relative to a decrement of 5.3% in sham, $P = .0016$). Effective blinding for active treatment was maintained in the study. PTSD participants presented with more clinically significant sleep difficulties at baseline; acupuncture was effective for both those with and without PTSD.

Conclusions: Real acupuncture, compared with a sham needling procedure, resulted in a significant improvement in sleep measures for veterans with mTBI and disturbed sleep, even in the presence of PTSD. These results indicate that an alternative-medicine treatment modality like acupuncture can provide clinically significant relief for a particularly recalcitrant problem affecting large segments of the veteran population.

Trial Registration: ClinicalTrials.gov identifier: NCT01162317

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Mild traumatic brain injury (mTBI) is a brain injury associated with loss of consciousness or alteration of mental status for less than 30 minutes. It was the "signature" injury in recent military conflicts.[1,2] Although most mTBI patients recover within 3 months,[3] symptoms associated with delayed recovery have not only affected the quality of life of these patients, preventing them from returning to routine daily activities and work, but also put a huge price tag on health care. The financial cost for the health system of deployment-related mTBI has been estimated to be $25,000 to $30,000 per case annually.[4] While multiple symptoms are associated with brain injury, sleep disturbance is one of the most highly prevalent,[5] found in 37%–80%[6–8] of the TBI population. Sleep problems in these patients are associated with increased daytime sleepiness, chronic fatigue, behavioral and neurocognitive problems, depressed mood, poorer self-reported overall health, and delay of recovery or return to work.[5,9–11] The mTBI veteran population frequently presents with coexisting and significant posttraumatic stress disorder (PTSD),[12] which is one of the major comorbidities in persistent sleep difficulties,[11] making the condition even harder to treat.

Effective treatments for sleep difficulties in the mTBI population, especially for those with concurrent PTSD, are limited.[13,14] The use of hypnotic medications is associated with a number of risks and limitations, including drowsiness, dizziness, light-headedness, cognitive and psychomotor impairments, and risks for tolerance and dependence.[5] These side effects are especially worrisome in the population with mTBI. From previous small sample studies,[15,16] melatonin and trazodone are the products that were found to have limited success in TBI patients. However, while a melatonin receptor agonist (ramelteon) was reported to increase total sleep time, it also increased sleep latency with no improvement in sleep efficiency.[15] Trazodone studies[16] presented even more mixed results. Alternatively,

Clinical Points

- It is challenging to treat persistent disturbed sleep in veterans with traumatic brain injury, especially those with posttraumatic stress disorder, by using currently available pharmaceutical therapies.
- Acupuncture presents a viable alternative in this difficult population, being well tolerated and effective in improving sleep quality.

acupuncture can be a potentially useful treatment modality capable of addressing the need to treat these patients with a holistic approach and relatively few side effects. The findings about the efficacy of acupuncture for insomnia have been controversial in several systematic reviews.[17,18] Additionally, we know little about whether poor sleep would respond favorably to acupuncture in an mTBI veteran population, especially in those with PTSD. These issues make our attempt to evaluate the feasibility and efficacy of acupuncture in this difficult population timely and meaningful.

METHODS

This sham-controlled randomized clinical trial (RCT) was registered at ClinicalTrials.gov, identifier NCT01162317. The study protocol was approved by the Emory University Institutional Review Board (IRB) and by the Atlanta Veterans Affairs Medical Center (VAMC) Research and Development Committee. Written informed consents were obtained from all participants entering the sleep education phase of the protocol (Figure 1).

Participants

Veterans receiving care from the Atlanta VAMC TBI clinic from 2007 to 2014 were the source of participants for the study, which was conducted from 2010 to 2015. The IRB authorized an opt-in recruitment strategy in which veterans in clinical care could be mailed information about the study. Of 847 veterans who were contacted, 384 expressed initial interest, with 347 available for screening. A flowchart for entry into the trial is provided in Figure 1; Table 1 summarizes the inclusion and exclusion criteria.

Baseline Measures

All participants meeting the inclusion criteria were administered the following questionnaires at baseline: Pittsburgh Sleep Quality Index (PSQI),[22] Beck Depression Inventory (BDI),[23] Beck Anxiety Inventory (BAI),[24] Brief Pain Inventory (BPI),[25] Impact of Event Scale–Revised (IES-R),[26] and the PTSD Checklist–Military Version (PCL-M).[27]

Sleep Education Run-In Period

Eligible study participants (n = 70) gave informed consent and underwent a 4-week sleep education run-in. During this period, they attended a session of 60 minutes or less on improving sleep using conventional sleep hygiene techniques[28] provided by a study coordinator (S.N.H. or Gwendolyn Agbaere, BS). Written instructions (Supplementary Appendix 1) were provided, and the participants were asked to apply these techniques over the following 4 weeks, after which sleep was reassessed with the PSQI. Participants whose PSQI global score was ≤ 5 or whose score decreased by ≥ 4 points were excluded. This conservative approach allows for participants' modification of their own behavior in advance of formal randomization for acupuncture.

Stratification, Randomization, and Blinding

Ten participants were excluded (Figure 1) after the 4-week run-in. The remaining 60 participants were randomized (using SAS version 9.4, SAS Institute, Cary, North Carolina) into active or sham acupuncture arms. Although 66.7% of these participants carried a *DSM-IV* clinical diagnosis of PTSD, to stratify by comorbid PTSD, we used a PCL-M score of ≥ 50.[27] Study participants and study coordinators were blinded to the group assignment. The interventionist (W.H.) was blinded to all primary and secondary assessments except for side effects. All data were collected and entered into a database by study coordinators and were scrubbed of personal identifiers.

Intervention

The first author (W.H.), a board-certified physiatrist with advanced training in acupuncture, was the interventionist for all participants. All participants were scheduled individual visits twice weekly over 5 weeks, aiming for 10 sessions as full completion. Although there were some variations in visit frequency due to participants' schedules (see Figure 1 and Supplementary Appendix 2), all participants underwent at least 6 sessions. Participant/provider interaction time was approximately 50–60 minutes per session.

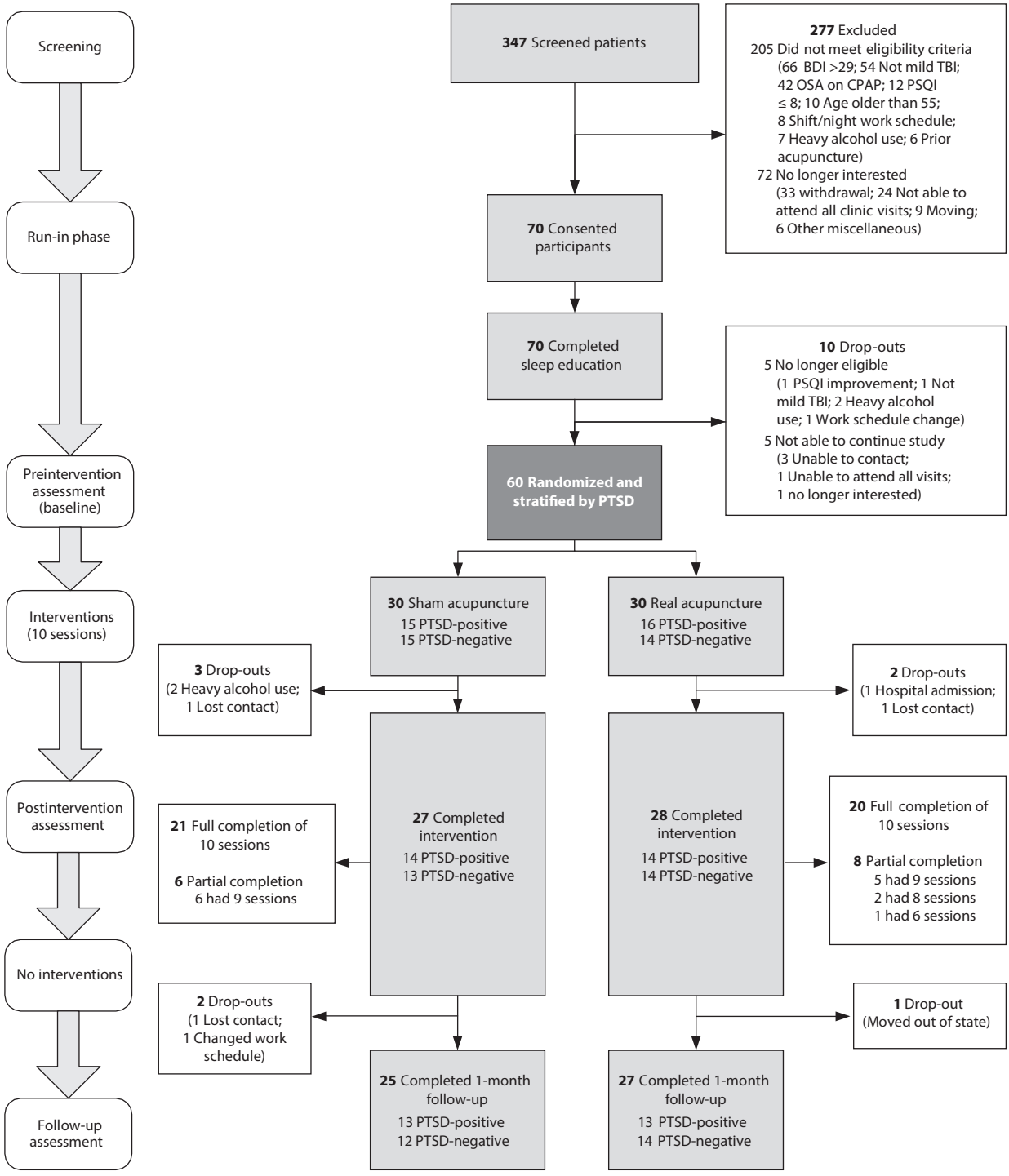
The participants received either real or sham acupuncture (Supplementary Appendix 2). In brief, acupoints used in this clinical trial comprised standardized and individualized points (Supplementary Appendix 2: Table 1). Sham acupuncture involved the use of sham needles without skin penetration and needle placements at sites proximal (ie, within 1 inch) to active acupoints. No needle manipulations were performed to elicit de-qi sensation in either group.

No additional psychiatric or sleep medications other than those at baseline were allowed, and no subjects were receiving psychotherapy or behavioral therapy for sleep during their time in the study. Participants' medication use was confirmed and recorded at each encounter. We encouraged participants to maintain stable usage of caffeine and alcohol during the study and had them record such use (Table 2). Participants were excluded if consumption exceeded baseline (Figure 1).

Outcome Measures

The primary outcome was change in PSQI global score from baseline to postintervention. The PSQI is a well-validated measure to assess subjective sleep quality and quantitative sleep-wake parameters over the preceding month. Responses to 19 items are scaled onto 7 component

Figure 1. Study Flowchart



Abbreviations: BDI = Beck Depression Inventory, CPAP = continuous positive airway pressure, OSA = obstructive sleep apnea, PSQI = Pittsburgh Sleep Quality Index, PTSD = posttraumatic stress disorder, TBI = traumatic brain injury.

scores, which are totaled to provide a global PSQI score ranging from 0 to 21; higher scores represent worse sleep. On the basis of the empirically derived distribution of global PSQI scores in patients with TBI, a global PSQI score greater than 8 has 93% sensitivity and 100% specificity rates to the clinical diagnosis of insomnia in the TBI population.[20] The PSQI also has been shown to be sensitive to improved sleep in populations with insomnia in response to interventions such as aerobic exercise,[29] tai chi,[30] Cognitive Behavioral Therapy for Insomnia (CBT-I),[31] and medications,[32] with baseline-subtracted treatment versus control differences typically in the 1.9- to 2.8-point range.

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
1. Diagnosis of at least 1 episode of mild TBI on the basis of the following: a. Loss of consciousness or alteration of mental status, eg, slow thinking, disorientation, confusion, etc, for < 30 min (if evaluated after 30 min, must have a GCS[19] score of 13–15) b. Pre- or posttraumatic amnesia for < 24 h c. Focal neurologic deficit(s) that may or may not be transient, eg, weakness, paresis, loss of coordination, speech difficulties, or double vision[19] 2. Aged 18–55 3. ≥ 3 Months after brain injury 4. PSQI global score[20] > 8 5 Self-report of "disturbed sleep" at least 4 nights per week in the past month 6. Self-report of average sleep duration of ≤ 6 h nightly	1. Disturbed sleep present prior to TBI 2. Diagnosis of obstructive sleep apnea prior to this study 3. Shift/night work-schedule 4. Moderate and severe alcohol use of > 14 alcoholic beverages per week. Alcoholic beverage defined as a. 1 drink of beer = 12 oz/1 can b. 1 drink of wine = 5 oz/1 glass c. 1 drink of liquor = 1.5 oz/1 shot 5. History of bleeding diathesis or currently on anticoagulation therapy, with an INR > 2.5 6. Prior acupuncture experience 7. Severe depression with a BDI score ≥ 29[21] 8. Taking β-blockers, digitalis, or other autonomic, heart-rate modifying agents

Abbreviations: BDI = Beck Depression Inventory, GCS = Glasgow Coma Scale, INR = International Normalized Ratio, PSQI = Pittsburgh Sleep Quality Index, TBI = traumatic brain injury.

Secondary outcomes included sleep variables derived from wrist actigraphy, a noninvasive objective sleep measure, performed at baseline and at the end of interventions. Actigraphy monitors gross body activities via an accelerometer worn on the nondominant wrist. Algorithms have been developed to assess sleep/wake behavior. We used Respironics Actiwatches (Philips Respironics, Murrysville, Pennsylvania) for 7 consecutive days at baseline and postintervention. Actiwatches were taken off only during showers. We employed the threshold-based method algorithm for data interpretation (Respironics Actiware Software; Supplementary Appendix 3), from which the participants' time in bed (in minutes), sleep latency (in minutes), sleep efficiency (percentage), sleep duration (in minutes) and wake after sleep onset (WASO; in minutes) were derived.

Other assessments. We assessed adequacy of participants' blinding by asking whether they believed they were receiving real or sham acupuncture on 3 occasions (ie, after the first, fifth, and final treatment session). "Not sure" was also considered an allowable response. On these same 3 occasions, participants were also asked a question regarding the experience of needle stick: "Do you feel the needle pricks?" Possible responses to this question were "yes" or "no."

To monitor side effects of acupuncture, following each interventional session, we asked participants if they experienced any ill effects from the treatment; their responses were recorded verbatim and later categorized. Observations of needle site bleeding/hematoma, if any, were recorded at this time.

Finally, all participants were contacted 4 weeks after the end of the intervention, and a subset agreed to complete the PSQI a third time.

Statistical Analyses

Descriptive statistics included means (standard deviations) for continuous variables and frequencies (percentages) for categorical variables. Simple group comparisons used Fisher exact tests for categorical variables and unpaired *t* tests with Levene's test of unequal variances for continuous variables. We employed a 2-sided α level of .05.

On the basis of our preliminary data employing acupuncture for disturbed sleep in 6 TBI patients showing a mean decrease in PSQI global score of 3 points subsequent to treatment, we estimated a sample size of 60 was required to achieve 0.80 statistical power to detect an effect of that magnitude using a 2-tailed α of .05.

For primary and secondary outcomes, we used intent-to-treat principles and employed linear mixed effect models to measure the effects of change in sleep outcomes over time by treatment. PTSD status (positive/negative) was included as a covariate in these models. Because actigraphy data were collected for multiple nights, the number of which may have differed by participant and condition (Supplementary Appendix 3), analyses of repeated effects for overall study weeks (baseline, postintervention) and day within week were required. Analyses were completed using the MIXED procedure in SAS 9.4. This procedure allowed us to fit the multiple nested model with 2 sets of repeated measures and adjust accordingly for the missing actigraphic data within a study week. All models included main effects for study week, study day nested within week, and study group, as well as interaction terms to assess the change over a week in sleep outcomes by treatment group and PTSD status.

RESULTS

After sleep education, only 1 participant decreased PSQI global score by more than 4 points and was dropped. An additional 9 discontinued for a variety of reasons (Figure 1), leaving 60 participants to enter randomization (30 real acupuncture; 30 sham acupuncture). Fifty-five (91.7%) participants completed interventions (28 real, 27 sham). Those who dropped out did not differ significantly from those who completed the study in any of the baseline demographics and clinical characteristics provided in Table 2 (data not shown).

Demographic and baseline clinical characteristics of the 60 study participants are summarized in Table 2. Overall, the sample was middle-aged (mean age 39.8 [SD = 9.9] years), predominantly male (76.7%), and included approximately equal numbers of whites (45.0%) and African Americans (55.0%).

Table 2. Participants' Baseline Demographic and Clinical Characteristics Prior to Intervention

Characteristic	Real Group (n = 30)		Sham Group (n = 30)	
	PTSD-Negative (n = 14)	PTSD-Positive (n = 16)	PTSD-Negative (n = 15)	PTSD-Positive (n = 15)
Age, y, mean (SD)	38.3 (8.6)	40.7 (10.8)	39.7 (10.8)	40.3 (10.1)
	n (%)	n (%)	n (%)	n (%)
Sex				
Male	11 (78.6)	11 (68.8)	11 (73.3)	13 (86.7)
Female	3 (21.4)	5 (31.3)	4 (26.7)	2 (13.3)
Race				
White	6 (42.9)	7 (43.8)	7 (46.7)	7 (46.7)
African American	8 (57.1)	9 (56.3)	8 (53.3)	8 (53.3)
Marriage status				
Single	4 (28.6)	5 (31.3)	4 (26.7)	6 (40.0)
Married	8 (57.1)	2 (12.5)	6 (40.0)	7 (46.7)
Divorced or separated	2 (14.3)	9 (56.3)	4 (26.7)	2 (13.3)
Widowed	0 (0)	0 (0)	1 (6.7)	0 (0)
Education				
≤ High school	7 (50.0)	11 (68.8)	5 (33.3)	5 (33.3)
Associate degree	7 (50.0)	2 (12.5)	4 (26.7)	7 (46.7)
Bachelor degree	0 (0)	3 (18.8)	4 (26.7)	2 (13.3)
Graduate degree	0 (0)	0 (0)	2 (13.3)	1 (6.7)
Work status				
Full-time employment	5 (35.7)	4 (25.0)	5 (33.3)	4 (26.7)
Part-time employment	1 (7.1)	1 (6.3)	0 (0)	2 (13.3)
Disabled	3 (21.4)	7 (43.8)	2 (13.3)	4 (26.7)
Unemployed	3 (21.4)	3 (18.8)	6 (40.0)	3 (20.0)
Self-employed, retired, or other	2 (14.3)	1 (6.3)	2 (13.3)	2 (13.3)
Medication use				
Benzodiazepines	0 (0)	5 (31.3)	2 (13.3)	5 (33.3)
Other hypnotics	7 (50.0)	8 (50.0)	4 (26.7)	5 (33.3)
Antipsychotics	1 (7.1)	5 (31.3)	0 (0)	0 (0)
Antidepressants	5 (35.7)	7 (43.8)	3 (20.0)	2 (13.3)
Anxiolytics	0 (0)	1 (6.3)	0 (0)	0 (0)
Living situation				
Live with family	11 (78.6)	9 (56.3)	8 (53.3)	13 (86.7)
Live with friend(s)	2 (14.3)	2 (12.5)	1 (6.7)	2 (13.3)
Live alone	1 (7.1)	5 (31.3)	5 (33.3)	0 (0)
Homeless	0 (0)	0 (0)	1 (6.7)	0 (0)
Household income				
< $10,000	0 (0)	2 (12.5)	2 (13.3)	1 (6.7)
$10,000–$24,999	4 (28.6)	4 (25.0)	2 (13.3)	4 (26.7)
$25,000–$49,999	4 (28.6)	2 (12.5)	4 (26.7)	5 (33.3)
$50,000–$99,999	3 (21.4)	6 (37.5)	6 (40.0)	5 (33.3)
≥ $100,000	3 (21.4)	2 (12.5)	1 (6.7)	0 (0)
Substance use				
Tobacco				
Current use	7 (50.0)	7 (43.8)	4 (26.7)	6 (40.0)
First-hour use in the morning	0 (0)	3 (18.8)	0 (0)	5 (33.3)
Recreational drugs[a]	1 (7.1)	0 (0)	1 (6.7)	1 (6.7)
Caffeinated drinks	12 (85.7)	15 (93.8)	11 (73.3)	12 (80.0)
Alcohol, current use	6 (42.9)	9 (56.3)	10 (66.7)	11 (73.3)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Alcohol, number of drinks[b] per month	5.0 (4.8)	12.2 (21.5)	12.9 (12.6)	15.1 (15.7)
PSQI global score	12.4 (2.9)	15.8 (3.1)	12.5 (3.0)	16.1 (2.0)
PSQI component scores				
Sleep quality	1.6 (0.8)	2.2 (0.8)	1.8 (0.7)	2.3 (0.6)
Sleep latency	2.4 (0.9)	2.8 (0.5)	2.2 (0.9)	2.7 (0.5)
Sleep duration	2.1 (1.0)	2.3 (1.0)	1.9 (1.1)	2.6 (0.8)
Sleep efficiency	1.8 (1.2)	2.7 (0.8)	2.1 (1.1)	2.5 (1.0)
Sleep disturbance	1.7 (0.6)	2.1 (0.7)	1.7 (0.5)	2.3 (0.7)
Sleep medication	1.6 (1.3)	1.9 (1.4)	1.1 (1.4)	2.1 (1.3)
Daytime dysfunction	1.2 (0.6)	1.9 (0.7)	1.6 (0.9)	1.7 (0.9)
Sleep duration, h[c]	4.8 (1.3)	4.9 (1.4)	5.0 (1.2)	4.1 (1.0)
BDI score	16.5 (5.6)	22.7 (8.8)	11.3 (5.6)	23.5 (6.4)
BAI score	18.0 (10.5)	27.7 (13.4)	13.7 (6.5)	26.1 (10.4)
BPI score				
Least pain in the past 24 h	3.2 (1.6)	4.2 (2.4)	2.8 (3.1)	3.3 (1.8)
Worst pain in the past 24 h	6.2 (2.2)	6.9 (2.5)	5.3 (2.5)	5.6 (1.9)
Average pain	5.4 (1.6)	6.1 (2.3)	4.1 (2.2)	5.4 (1.7)
Current pain	3.5 (2.2)	5.7 (2.6)	3.3 (3.1)	4.6 (2.5)

(continued)

Features of PTSD at Baseline

Comparison of patients with versus without PTSD showed those with PTSD having higher PSQI global scores ($P < .00001$), longer actigraphically recorded baseline sleep-onset latency ($P < .03$), and lower actigraphically recorded sleep efficiency ($P < .04$). Differences in total sleep time ($P = .31$) and WASO ($P = .14$) did not reach statistical significance. Other variables significantly differentiating the PTSD positive versus PTSD negative participants included: higher BDI ($P < .0001$), BAI ($P < .0001$), BPI average pain ($P = .037$), BPI current pain ($P = .008$), and IES-R total ($P < .0001$) scores. All were higher in the PTSD positive group.

Primary Outcome (PSQI)

The mixed model demonstrated a statistically significant time-by-group interaction in PSQI global score ($F = 4.51$, $P = .04$). Mean (SD) scores improved in both real and sham groups by 4.4 (3.9) and 2.4 (3.4) points, respectively, by the end of treatments (Figure 2A). PTSD status did not interact with this effect ($F = 0.07$, $P = .79$), indicating benefit was achieved regardless of the presence or absence of PTSD.

Secondary Outcomes (Wrist Actigraphy)

Wrist-actigraphy–measured sleep efficiency (Figure 2B) also showed a similar time by group interaction ($F = 12.25$, $P = .0016$). Among the real acupuncture group, sleep efficiency improved by a mean (SD) of 2.7% (0.17%), whereas among the sham group, sleep efficiency decreased by 5.3% (0.28%). No interaction of treatment with PTSD was observed. No time-by-group interactions were noted for time in bed, sleep latency, WASO, or sleep duration, nor were 3-way interactions (ie, with PTSD) noted for any of these variables.

Other Assessments

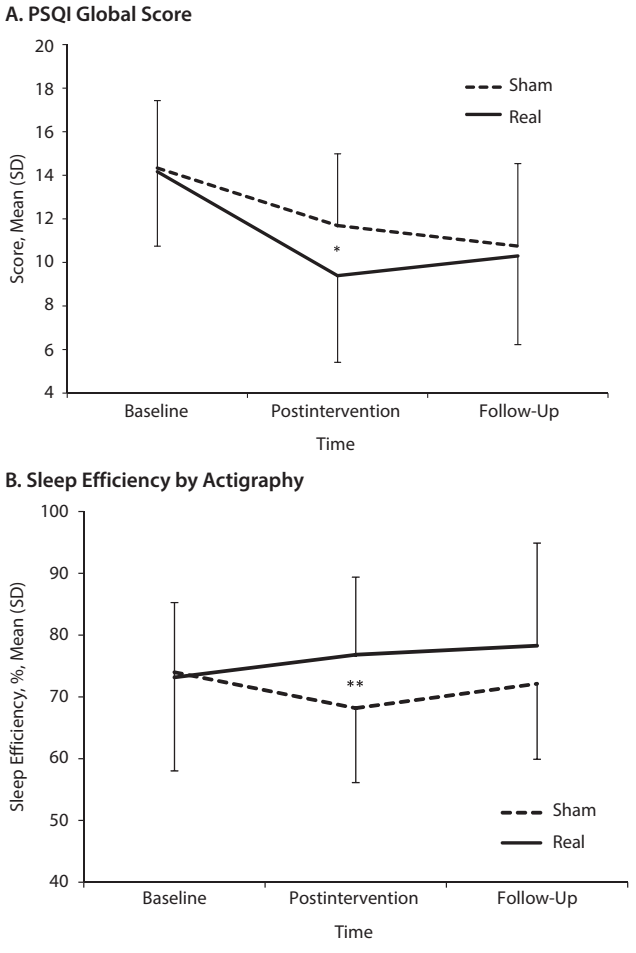
All participants in the real and sham groups answered "yes" to the question regarding needle prick at every time of assessment. The majority of participants (80% at the beginning, 71.4% middle, and 67.9% end) were unable to guess correctly whether they had been assigned to an

Table 2 (continued).

Characteristic	Real Group (n = 30)		Sham Group (n = 30)	
	PTSD-Negative (n = 14)	PTSD-Positive (n = 16)	PTSD-Negative (n = 15)	PTSD-Positive (n = 15)
IES-R score				
Total score	32.8 (17.2)	53.6 (14.2)	26.1 (12.6)	51.4 (17.4)
Subscale scores				
Intrusion	12.5 (5.8)	20.4 (6.2)	7.6 (6.3)	18.1 (7.6)
Avoidance	9.9 (5.4)	16.9 (5.7)	8.3 (6.3)	16.9 (8.0)
Hyperarousal	10.4 (6.8)	16.4 (4.3)	9.3 (4.2)	16.4 (3.3)
PCL-M score	45.1 (14.0)	61.3 (7.8)	39.6 (8.4)	58.5 (9.6)
Wrist actigraphy				
Sleep onset latency, min	11.0 (17.3)	26.5 (36.7)	18.7 (34.4)	31.3 (52.2)
Sleep efficiency, %	80.8 (15.0)	68.3 (18.2)	77.8 (14.8)	72.1 (13.6)
Wake after sleep onset, min	72.6 (74.2)	105.1 (72.6)	76.7 (72.6)	104.0 (83.7)
Total sleep time, min	370.8 (92.3)	316.5 (106.0)	375.7 (106.2)	379.1 (94.1)

[a]All marijuana.
[b]Refers to those with current alcohol use. The number of drinks was obtained from a baseline questionnaire of alcohol consumption and converted to monthly intake. One alcoholic beverage was defined as 1 drink of beer = 12 oz/1 can, 1 drink of wine = 5 oz/1 glass, or 1 drink of liquor = 1.5 oz/1 shot.
[c]Sleep duration was calculated from PSQI item 4.
Abbreviations: BAI = Beck Anxiety Inventory, BDI = Beck Depression Inventory, BPI = Brief Pain Inventory, IES-R = Impact of Event Scale-Revised, PCL-M = PTSD Checklist–Military Version, PQSI = Pittsburgh Sleep Quality Index, PTSD = posttraumatic stress disorder.

Figure 2. Treatment Effects by Time for PSQI Global Score and Actigraphically Measured Sleep Efficiency[a]



[a]Significant group × time interaction comparing baseline and post-intervention scores. Follow-up occurred 1 month after intervention.
*P = .04. **P = .0016.
Abbreviation: PSQI = Pittsburgh Sleep Quality Index.

active or sham placebo intervention. Although the participants became more accurate by the end of the study versus at the beginning (33.1% vs 20%), Fisher exact test indicated that the perceived group assignment was independent of actual real versus sham group assignment (P = .58, .30, and .07 at the beginning, middle, and end, respectively).

During intervention, of 545 total treatment sessions across all participants, adverse reactions were reported in 55 (10.1%) sessions, with 34.5% originating from the sham group (15 individuals) and 65.5% originating from the real group (23 individuals). Among the 55 sessions, the most common side effects were needle site pain or discomfort (30.9%), fatigue or drowsiness (20.0%), and mild bleeding at needle site with needle removal (18.2%). More serious vasovagal reactions (ie, presyncope) to needle stick were reported by 3 participants in 4 sessions (7.2%), all in the real acupuncture group. Other reported uncommon side effects included subcutaneous hematoma (5.5%), light-headedness (5.5%), needle site swelling (1.8%), or skin itchiness (1.8%).

At 4-week follow-up, 52 participants (27 real, 25 sham) returned the PSQI (Figure 1). Compared to PSQI global score postintervention, there was no significant difference (P = .68), although the real acupuncture group showed a trend for slight worsening in overall sleep quality at follow-up (+1.0 [2.8], P = .08), without change in the sham acupuncture group (–0.7 [4.1], P = .40). There was no significant difference in PSQI global score between real and sham acupuncture groups at the 4-week follow-up (P = .68).

DISCUSSION

This RCT demonstrated that real acupuncture was more efficacious than sham acupuncture in veterans with mTBI and poor sleep who were previously naïve to this treatment modality. Although the absolute improvements were modest, both subjective and objective (actigraphic) measures of disturbed sleep reflected statistically significant improvements. Given the low dropout rate (8.3%), this modality provides a feasible treatment alternative for this population. Other features of this trial included the effective maintenance of blinding of real versus sham acupuncture throughout the protocol and the inclusion of a substantial number of patients with comorbid PTSD (31 of 60 participants), a condition known to be associated with markedly disturbed sleep. Prior to entry in the trial, these patients' impaired sleep was refractory to treatments previously offered under regular care and it did not respond to basic sleep hygiene education during the run-in phase.

Interestingly, there was some indication that although exposure to the course of acupuncture treatment improved sleep during active treatment, efficacy was not sustained on follow-up. This differentiates acupuncture treatment for insomnia from interventions such as CBT-I,[33] which has demonstrated sustained and, possibly, even enhanced benefits months and years after trial completion.

Several aspects of the treatment used here deserve comment. The most difficult component of any acupuncture RCT is the design of a credible control intervention. This is a problem for acupuncture trials generally,[34] and elsewhere we have reviewed this issue specifically as it applies to acupuncture trials targeting poor sleep.[17] In this study, we employed sham acupuncture needles that mimicked needle insertion but did not penetrate the skin. Nevertheless, all participants assigned to the sham condition reported needle prick sensation, arguing for the credibility of the sham. A second feature of the sham intervention was that we selected acupoints as proximal (but not overlapping) to real acupoints, thus essentially controlling for possible effects of manually applied acupressure, relative to needle insertion per se. Third, even with active needle insertion, we made no attempt to elicit the sensation typically known as de-qi, which represents soreness, numbness, heaviness, or radiation of needle sensation that typically occurs with needle manipulation, such as thrusting and twisting. Although traditional acupuncture emphasizes elucidation of de-qi sensation, 1 precedent study[35] on acupuncture for hip and knee osteoarthritic pain suggested that the presence and intensity of de-qi had no effect on the pain relief. Therefore, we opted not to conduct needle manipulation in order to minimize the possibility of unblinding. A fourth consideration is that we used both standard (for sleep) and customized (for other conditions, such as pain) locations that were determined individually for participants at each visit (Supplementary Appendix 2). Despite that selection of combinations of customized sites could be perceived as a source of uncontrolled treatment variance, this individualized procedure most closely reflects how acupuncture is typically performed in clinical practice and has been proposed as a preferred research method not only for acupuncture but also for other alternative medicine modalities.[34,36] Finally, because of limitations of funding, a single acupuncturist performed all treatments, which could have influenced both specific aspects of the acupuncture procedures and nonspecific aspects of each participant's treatment experience. Arguments against sources of such potential bias were that the participants were unable to identify whether they were receiving real or sham acupuncture. Moreover, the outcomes were independent of participants' satisfaction rate (see Supplementary Appendix 2).

Limitations of our study include the absence of polysomnography to confirm our actigraphic measurements, a single-center/single-provider design, and an assumption of data loss at random for imputation analyses. Additionally, actigraphy proved challenging to obtain, and as evidenced by missing data (see Supplementary Appendix 3), technical failure rates were considerable. These difficulties have been reported previously for overnight actigraphy in the context of other clinical trials as well.[37] However, comparisons of study participants with and without usable actigraphy in our study were unremarkable (Supplementary Appendix 3: Table 2).

Why acupuncture improves poor sleep in this population was unaddressed in this study. As a treatment modality of traditional Chinese medicine, acupuncture has been practiced for over 3,000 years with beneficial clinical effects for many disorders. Since the 1970s, multiple research studies have associated acupuncture with regulation of various neurotransmitters and humoral factors.[38,39] Although the physiologic changes associated with acupuncture are complex, a unifying theme emerges across much of this literature, ie, the positive effects of acupuncture on autonomic nervous system measures.[38] The autonomic nervous system plays an essential role in maintaining biological stability and equilibrium, via coordinated regulation of the neuroendocrine system and various neurotransmitters, and sustains homeostasis.[40] Because insomnia is often considered to reflect heightened autonomic arousal,[41,42] acupuncture's ability to down-regulate such physiologic functions may play a role in reinstituting improved sleep, this being especially true in a veteran population with mTBI and PTSD overlay.

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Supplementary material: Available at PSYCHIATRIST.COM.

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Supplementary Material

Article Title: Acupuncture for Treatment of Persistent Disturbed Sleep: A Randomized Clinical Trial in Veterans With Mild Traumatic Brain Injury and Posttraumatic Stress Disorder

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List of Supplementary Material for the article

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This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

eAPPENDIX 1: Sleep Education Written Information

Why Sleep Is Important

Scientists aren't sure about everything why we sleep. But they do know that sleep is a necessary part of life. If you're not getting enough sleep, then you know just how important it is. In fact, even sleep that is disrupted can leave you feeling tired and unrested. Life is harder to deal with when you do not sleep well. Without sleep, your reactions may be slower and you may have trouble concentrating. Sometimes, not getting enough sleep can be dangerous if you are operating machinery or driving. Poor sleep has also been associated with chronic pain and depression; both can further decrease your quality of life.

Getting Restful Sleep

If you're frustrated because of sleep troubles, you're not alone. Many people struggle with sleep disorders that keep them from getting enough sleep. Others have poor sleep habits that don't allow them to feel rested. We hope to give you some tips to help you get restful sleep. For example, your actions throughout the day and during the evening can affect your sleep. Relaxing before bedtime, creating a comfortable sleep environment, getting enough exercise during the day, and smoking cessation can improve your chances for a good night's sleep. These are part of good sleep habits (also called sleep hygiene). Making these changes part of your routine takes time and effort. But your goal of getting restful sleep is well worth it.

Sleep Hygiene Instructions

- Set up regular sleep/wake cycle, eliminating so called "catch-up sleep"
- Limit daytime napping to no more than 40 minutes and only at noon or in early afternoon

- Engage proper light exposure, i.e. increase bright light exposure during daytime and keep bedroom dark during nighttime
- If your mind is occupied before bedtime, write down any worries in a diary. Put it away and then try to fall asleep.
- Eliminate behaviors that focus too much on the time, e.g. clock monitoring during sleep
- Exercise regularly, but limited to morning or afternoon
- Avoid heavy meals less than 3 hours before bedtime
- No more than two caffeinated beverages per day with none after 3 PM
- Limited alcohol intake of at most 1 glass of wine or 1 beer, at least 3 hours prior to sleep
- Smoking cessation if possible; otherwise, limit smoking to none less than 3 hours before bedtime, because nicotine is a stimulant that can keep you awake
- Enhance sleep environment, e.g. do not read, use computer, play video or watch TV in bed. They can stimulate you and keep you awake.
- Create some relaxation routine prior to bedtime, e.g. relaxation session (e.g. deep breathing, progressive muscle relaxation, meditation), yoga, a cup of warm milk, or a warm bath/shower. Avoid playing games or watching TV that stimulate your mind or into late night.
- Limit wake time in bed to less than half an hour. Get up and do something relaxing until you feel sleepy. As one says, “use the bed only for 3‘s’: sleeping, sexual activity, and resting when sick”.

eAPPENDIX 2: Acupuncture

(a) Acupoint selection

The efficacy of acupuncture for insomnia has been evaluated in several systematic reviews;[1-4] we applied most commonly used acupoints in prior sleep studies for treatments (Appendix 2, Table 1).[1] To customize treatment of each individual subject's sleep disturbance, which could be associated with anxiety, pain, or depression, the *standardized* acupoints were supplemented by more *individualized* acupoints. Acupoints with dual action or triple action were preferred. Each treatment session could be comprised of different acupoints, if the participants' main complaints changed. This combination of standardization and individualization was intended to reflect real world acupuncture treatments. The acupoints were validated before initiation of the trial by a panel of 3 local acupuncture practitioners with an average of 20 years of clinical experience.

(b) Acupuncture schedule

Ten sessions were scheduled for each subject after randomization, targeting twice a week treatment for five weeks. If a subject missed a scheduled treatment, efforts were made to reschedule and make up for the missed appointment. If a subject missed three appointments in a row with more than two weeks apart between any two treatments, the intervention phase was terminated; he/she was considered as a partial completer. All cases were included in the analyses using intent-to-treat principles (see text under Statistical Analyses).

(c) Acupuncture procedure

Sterile, 34-gauge single-use disposable metal real or sham acupuncture needles were used. Skin areas designated as acupoints on a given visit were sterilized with alcohol swabs regardless of whether the participant was assigned to real or sham acupuncture. For **real** acupuncture treatment, all needles were inserted into appropriate depths and left in place for 30 minutes. There were no attempts to elicit needle De-Qi sensation by manipulating, turning or twisting the needles in order to minimize the chance of un-blinding participants. For **sham** acupuncture treatment, sham acupoints selected were 3-5mm distal from the real acupoints. Placebo sham research needles were used (AcuPrime® Marsh Barton, Exeter). The sham needle tips are blunted; although they simulate skin contact, no needle penetration occurs. When tapped at the end, the needle handles retract. The needles were stabilized with a disc (Appendix 2, Figure 1) and remained in place for 30 minutes as well. The number of needles used for each treatment was recorded. For real acupuncture group, the participants received an average of 11.7 ± 4.4 needles and for sham group, 11.1 ± 3.2 ($p=0.28$).

(d) Other Considerations

1. Environmental control: Same exam room was used and soft relaxing music was played throughout each treatment session.
2. Expectation control[5-8]: All participants were informed that the treatments, if effective, may improve other symptoms such as pain, anxiety or depression, as well as sleep. Participants were also consulted that real acupuncture may not be effective in all individuals and that sham acupuncture could be effective via various mechanisms, such as mind-body interaction, sensory enhancement etc.

3. Participant-provider interaction control: The duration (approximately 50-60 minutes per session) and extent of participant-provider interaction were attempted to be kept at the same level among all participants.

(e) Satisfaction:

At baseline and post-last intervention, the participants were asked to complete a satisfaction questionnaire with the following questions, "What is your satisfaction with the study staff so far?", and "What is your satisfaction with the clinical results so far?" Possible responses included "unsatisfied", "neutral", or "good satisfaction".

Surveys of participants' satisfaction with staff showed "good satisfaction" at the beginning (93.3% sham, 80% real), middle (100% sham, 96.3% real) and end of the study (95.7% sham, 88.9% real). For clinical results, the "good satisfaction" rates were 73.3%, 84.6%, 87.0% in sham and 60%, 88.9%, 77.8% in real at the beginning, middle and end of the study respectively.

eAppendix 2 References:

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eAppendix 2, Table 1: Listing of all acupoints used in the trial

Standardized Acupoints for Sleep	Location
Auricular shenmen	At the bifurcation of the crura of antihelix
PC-6 (Neiguan)	On the anterior forearm, 2 cun* proximal to the transverse wrist crease, between 7almaris longus and flexor carpi radialis tendons
SP-6 (Sanyinjiao)	Above the medial ankle, 3 cun* superior to the medial malleolus on the posterior border of the tibia

Other Acupoints of Selection	Treatment	Location
HT-7 (Shenmen)	Sleep, depression, anxiety with heart palpitation, panic attack	On the ulnar end of the transverse wrist crease, a depression between the pisiform and ulnar bones
GV-20 (Baihui)	Sleep, headache, anxiety with dizziness, irritability, tinnitus	On the midline scalp, intersects the line connecting right and left ear apices
LR-3 (Taichong)	Sleep, anxiety, anger, irritability, headache, dizziness, visual complaints	On the dorsum of the foot, between the first and second metatarsal bones, approximately 2 cun* proximal to the web margin
Ex HN-3 (Yintang)	Sleep, anxiety, stress, headache, sinusitis	On the face, midpoint between the eyebrows
KI-6 (Zhaohai)	Sleep, nightmare, night sweats, sore throat, anxiety with fear/fright	In the depression directly below the medial malleolus
Ex HN-5 (Anmian)	Sleep, dreams that disturb sleep	Midpoint between TH17 (Yifeng, behind the earlobe in depression between the mandible and mastoid process) and GB20 (see below)
GV-24 (Shenting)	Sleep, anxiety or depression with some mania, panic attack, headache	On the midline scalp, 0.5 cun* posterior to the anterior hairline
ST-36 (Zusanli)	Sleep, knee or leg pain, restless leg syndrome, gastro-intestinal complaints, depression	On the leg, one finger breadth lateral to the tibia's anterior crest, and 3 cun* inferior to the depression of the lateral side of patella

Other Acupoints of Selection	Treatment	Location
KI-3 (Taixi)	Sleep, anxiety, low back pain, headache, dizziness, tinnitus, ankle/foot pain	On the medial ankle, midpoint between the prominence of medial malleolus and the Achilles' Tendon
GB-20 (Fengchi)	Sleep, headache, neck pain, dizziness, vertigo, eye complaints	In the depression between the upper portion of the sternocleidomastoid muscle and the trapezius, below the tuberosity of the occipital bone at the back of the head
PC-7 (Daling)	Sleep, excessive sweat such as in post-menopausal syndrome	In the middle of the wrist crease between the tendons of palmaris longus and flexor carpi radialis
BL-62 (Shengmai)	Sleep, anxiety, headache, back and neck pain	In the depression directly below the lateral malleolus
Auricular HT	Sleep, depression	At the center of the deepest portion of the inferior conchae
Auricular sympathetic	Sleep, anxiety	At the border line between the brim of the inferior crus of antihelix and curved brim of the anterior portion of helix
LI-4 (Hegu)	Headaches, pain in facial region	On the radial side of the middle of the 2nd metacarpal bone
GB-21 (Jianjing)	Neck and shoulder pain	At the highest point of the shoulder, at the midpoint of a line connecting the 7th cervical vertebra and the lateral end of the acromion
LI-14 (Binao)	Shoulder and arm pain, radiating pain from neck	On the lateral side of the upper arm, in a depression between the lower pointed insertion area of the deltoid and the brachialis muscle
LI-11 (Quchi)	Shoulder pain, headache, depression, irritability	With the elbow flexed, the point is on the lateral end of the transverse cubital crease
HT-3 (Shaohai)	Arm pain, depression	When the elbow is flexed, the point is at the midpoint of the line connecting the medial end of the transverse cubital crease and the medial epicondyle of the humerus
GV-4 (Mingmen)	Low back pain, excessive nocturia, chronic fatigue, dizziness, tinnitus	On the posterior midline, below the spinous process of the 2nd lumbar vertebra

Other Acupoints of Selection	Treatment	Location
BL-23 (Shenshu)	Low back pain, chronic fatigue, depression, anxiety, tinnitus, restless leg syndrome	1.5 cun* lateral to the lower border of the spinous process of the 2nd lumbar vertebra
BL-52 (Zhishi)	Low back pain, nocturia	1.5 cun* lateral to BL-23
GB-25 (Jingmen)	Low back pain, urinary complaints	On lateral side of abdomen, below the lower border of the free end of the 12th rib
SP-9 (Yinlingquan)	Knee pain, low extremity edema, restless leg syndrome	On the lower border of the medial condyle of the tibia in the depression posterior and inferior to the medial condyle of the tibia
GB-34 (Yanglingquan)	Knee pain, depression, irritability, sciatica, lower extremity spasm, restless leg syndrome	In a depression anterior and inferior to the head of the fibular
BL-40 (Weizhong)	Posterior knee pain, sciatica, restless leg syndrome	Midpoint of the transverse crease of the popliteal fossa, between the tendons of biceps femoris and semitendinosis
BL-57 (Chengshan)	Sciatica, leg cramps, restless leg syndrome	In the depression below the gastrocnemius when heal is lifted, between the medial and lateral bellies of gastrocnemius
GB-39 (Xuanzhong)	Restless leg syndrome, headache, stiffness and pain in neck	At the anterior border of the fibula, 3 cun* proximal to the highest prominence of the lateral malleolus
Ex-LE-4 (Neixiyan)	Knee pain	Inferior to the patella, in a depression medial to the patellar ligament
Ex-LE-5 (Waixiyan)	Knee pain	Inferior to the patella, in a depression lateral to the patellar ligament

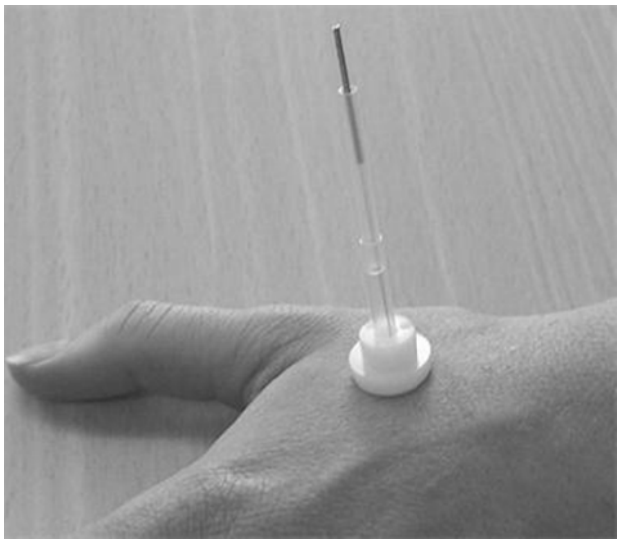
*Cun: a measurement used in acupuncture to find acupoints in relation to the patient's own body size.

- 1 cun equals the width of the thumb at distal interphalangeal joint, or the distance between the distal interphalangeal joint and the proximal interphalangeal joint on the middle finger.
- 1.5 cun equals the combined width at the level of the proximal interphalangeal joints when the index and middle fingers are held together.

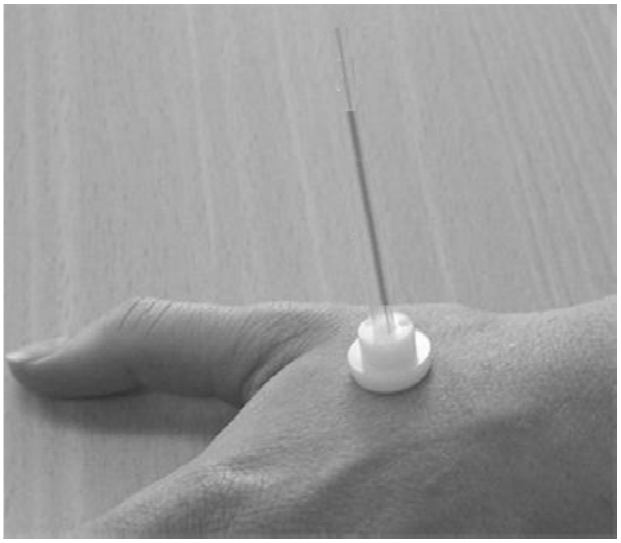
- 2 cun equals the combined width at the level of the proximal interphalangeal joints when the index, middle and ring fingers are held together.
- 3 cun equals the combined width at the level of the proximal interphalangeal joints when the index, middle, ring and little fingers are held together.

eAppendix 2, Figure 1: Sham Acupuncture Needle

A. Pre-insertion



B. Post-insertion



eAPPENDIX 3: Wrist Actigraphy

As the secondary outcome in this trial, wrist actigraphy data were collected by Actiwatches (Phillips Respironics® model IPX7, Murrysville, PA). Signals were processed using the time above threshold algorithm which has undergone validation with polysomnography.[1] A medium level threshold was set to detect Wake and Sleep; sleep interval detection algorithm was set for 3 minutes of immobile minutes for Sleep Onset and 5 minutes of immobile minutes for Sleep End. As is conventional for interpretation of wrist actigraphy,[2] each night's output was adjudicated by reference to a sleep diary that participants were asked to keep on the nights that they wore the actigraph. Based on the participants' sleep diary, the beginning and the end of sleep period were used to determine time-in-bed duration and then manually entered into the Respironics software.

(a) Data Completeness of Actigraphy

Due to various reasons, such as participants not returning wrist actigraphy watches, participants accidentally not wearing the watch on some days/nights, failure of the actigraph to record, or software malfunction during downloading, actigraphy data were incomplete in both groups. Conversely, although our goal was to collect 7 nights of sleep data, some participants wore the watches for longer intervals, therefore, enabling more nights of recording. Of the participants with valid actigraphic data, the modal number of nights of collected data was 7; a few participants wore the device for up to 9 nights and a relatively small number of participants for less than 4 nights (Appendix 3, Table 1). When combining both real and sham acupuncture groups, only 6 participants did not have any actigraphy data at both baseline and post-intervention (Appendix 3, Table 2), however only 13 patients in the real acupuncture group and 16 patients in the sham acupuncture group had actigraphic data at both times of measurement. As described in our Methods, the mixed model regression analyses included all actigraphy-recorded nights for all 54

patients. We observed no meaningful differences in their demographic and selected clinical features from those with actigraphy data used in the analyses (Appendix 3, Table 2).

eAppendix 3 References:

1. Blackwell T, Redline S, Ancoli-Israel S, et al. Comparison of sleep parameters from actigraphy and polysomnography in older women: the SOF study. Sleep. Feb 2008;31(2):283-291.
2. Blackwell T, Ancoli-Israel S, Gehrman PR, Schneider JL, Pedula KL, Stone KL. Actigraphy scoring reliability in the study of osteoporotic fractures. Sleep. 2005;28(12):1599-1605.

eAppendix 3, Table 1: Numbers of participants with valid actigraphy nights in sham versus real acupuncture groups.

Number of Valid Nights	**Real Group** (number of participants)	**Sham Group** (number of participants)
Baseline	N=20	N=24
9	4	1
8	1	6
7	9	8
6	4	4
5	1	3
4	1	0
3	0	1
2	0	1
Post-intervention	N=21	N=19
9	3	2
8	1	1
7	10	8
6	2	2
5	1	2
4	3	2
3	0	0
2	1	2

eAppendix 3 Table-2: Demographic and clinical features of participants with or without actigraphy

	With Actigraphy N=54		Without Actigraphy N=6		P value
	Mean	**SD**	**Mean**	**SD**	
Age, years	40.3	9.7	35.5	11.9	0.19
	N	**%**	**N**	**%**	
Sex					0.54
Male	42	77.8	4	66.7	
Female	12	22.2	2	33.3	
Race					0.80
Caucasian	24	44.4	3	50.0	
African American	30	55.6	3	50.0	
Marriage status					0.63
Single	18	33.3	1	16.7	
Married	21	38.9	2	33.3	
Divorced or Separated	14	25.9	3	50.0	
Widowed	1	1.9	0	0	
Education					0.95
High school and lower	25	46.3	3	50.0	
Associate degree	18	33.3	2	33.3	
College degree	8	14.8	1	16.7	
Graduate degree	3	5.6	0	0	

	With Actigraphy N=54		Without Actigraphy N=6		P value
	N	**%**	**N**	**%**	
Work Status					0.31
Full-time employment	16	29.6	2	33.3	
Part-time employment	3	5.5	1	16.7	
Disabled	13	24.1	3	50.0	
Unemployed	15	27.8	0	0	
Self-employed, retired, or other	7	13.0	0	0	
Substance Use					
Use of tobacco	23	42.6	1	16.7	0.22
Use of alcohol	32	59.3	4	66.7	0.81
Use of marijuana	2	3.7	1	16.7	0.17
Living Situation					0.38
Live with family	35	64.8	6	100.0	
Live with friend(s)	7	12.9	0	0	
Live alone	11	20.4	0	0	
Homeless	1	1.9	0	0	

	With Actigraphy N=54		Without Actigraphy N=6		P value
	N	**%**	**N**	**%**	
Household Income					0.08
Below $10,000	5	9.3	0	0	
$10,000-$24,999	13	24.1	1	16.7	
$25,000-$49,999	12	22.2	3	50.0	
$50,000-$99,999	20	37.0	0	0	
$100,000 and above	4	7.4	2	33.3	
	Mean	**SD**	**Mean**	**SD**	
Pittsburgh Sleep Quality Index Global Score	14.3	3.2	13.5	3.4	0.59
Beck Depression Inventory Score	18.6	8.7	17.2	4.4	0.76
Beck Anxiety Inventory Score	21.5	12.3	22.7	8.3	0.07
Brief Pain Inventory					
Worst pain in the past 24 hours	6.0	2.4	6.0	2.1	0.97
Least pain in the past 24 hours	3.5	2.4	2.3	1.5	0.12
Average pain	5.3	2.1	4.5	1.6	0.30
Current pain	4.4	2.7	4.2	3.3	0.90
Impact of Event Scale total score	41.5	19.4	44.0	19.5	0.77
PTSD Check List-Military version total score	51.4	13.9	52.7	9.5	0.77