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# Efficacy of transcutaneous electrical acupoint stimulation combined with diazepam for acute alcohol withdrawal syndrome: A double-blind randomized sham-controlled trial

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## Abstract

**Objective:** To compare the efficacy of transcutaneous electrical acupoint stimulation (TEAS) combined with diazepam against diazepam alone for treatment of acute alcohol withdrawal syndrome (AWS).

**Methods:** In this double-blind randomized sham-controlled trial, men with acute AWS were randomly allocated to either a group treated with TEAS combined with diazepam (n = 57) or a control group treated with sham TEAS combined with diazepam (n = 60). Treatment was performed at four acupoints twice a day for 14 days. The Clinical Institute Withdrawal Assessment for Alcohol Scale (CIWA-Ar), visual analogue scale (VAS), Pittsburgh Sleep Quality Index (PSQI) and modified Epworth Sleepiness Scale (mESS) were used to evaluate treatment efficacy.

**Results:** All scores improved significantly in both groups during the trial. CIWA-Ar scores were lower in the TEAS group than in the control group from day 3 until the end of observation. VAS and mESS scores were also lower in the TEAS group than in the control group on day 7. VAS and PSQI scores were lower in the TEAS group on day 14.

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**Conclusion:** Combining diazepam with TEAS may result in milder AWS symptoms than diazepam alone, improve sleep quality and reduce sleepiness.

**Keywords**
Transcutaneous electrical acupoint stimulation, diazepam, alcohol withdrawal syndrome, randomized controlled trial, sleep quality, daytime sleepiness

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## Introduction

Acute alcohol withdrawal syndrome (AWS) generally emerges 6 hours after reduction or cessation of alcohol intake. The symptoms of AWS can persist for 2 weeks or more and include physical and psychological effects, such as arrhythmia and hypertension, paroxysmal sweats, nausea, vomiting, diarrhoea, tremor, hallucination, delusion, anxiety, craving and sleep disorders.[1] These symptoms can be partly alleviated with benzodiazepines. However, it can be difficult to optimize benzodiazepine dose to maximize therapeutic effects while minimizing adverse effects such as sleepiness, poor sleep quality and respiratory inhibition.[2] Pregabalin, sodium oxybate and other anticonvulsant agents may alleviate AWS through the gamma-aminobutyric acid (GABA) pathway.[3–5]

Transcutaneous electrical acupoint stimulation (TEAS) is an electrical stimulation technique in which electrodes send electrical impulses into specific points of the body called acupoints. The technique is straightforward and non-invasive; therefore, there is no risk of cross infection, bleeding or hematoma (unlike in traditional acupuncture, which uses needles).[6] TEAS may work by selectively activating opioid receptors in the cerebrum,[7] which in turn modulate the neuroimmunological and neuroendocrinological systems.

TEAS is particularly well regarded by patients and clinicians in China, where acupuncture originated. Several studies have already demonstrated the efficacy of TEAS in treating diseases,[8–10] including drug addiction.[11,12] TEAS stimulates nerve endings or fibres and generates action potentials. Signals transmitted to the spinal cord and cerebrum activate the central nervous system to produce specific chemical mediators or neurotransmitters to induce specific physiological or psychological effects.[8,11] Han found that electroacupuncture and TEAS can increase the secretion of endogenous opioid peptides (which are partial substitutes for the exogenous opioids stimulated by drugs) in the central nervous system and can thus relieve AWS and pain.[12,13] However, the underlying mechanisms of TEAS remain to be fully clarified, and the use of TEAS for treating AWS is controversial.

The objective of the present study was to examine whether a combination of the benzodiazepine drug diazepam and TEAS can relieve AWS symptoms more effectively than diazepam alone.

## Patients and methods

### *Study design and population*

This was a prospective, double-blind, sham-controlled trial to compare the efficacy of TEAS with diazepam against diazepam alone for treating AWS. The study protocol was approved by the ethics committee of Shandong Mental Health Center

(2016R08), and written informed consent was obtained from all participants.

Male patients aged 18 to 60 years who were hospitalized for AWS in the substance abuse ward of Shandong Mental Health Center were consecutively recruited from May 2017 to December 2018. AWS was diagnosed according to the symptoms described in the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV).[14]

Potential participants were excluded if they (a) refused to provide consent or be randomly allocated in the study, (b) were dependent on other drugs (based on self-report), (c) had a major psychiatric disorder, history of acupuncture or history of anticoagulation therapy, or (d) had severe physical disease that required immediate treatment or prevented them from completing the study. Individuals were also excluded if they reported having stopped alcohol consumption more than 12 hours before hospitalization.

We used EpiCalc2000 software[15] and the results of a previous similar study[16] to estimate a minimum sample of 56 per group to detect a difference in alcohol craving,[17] assessed using a visual analogue scale (VAS), between the two groups with 95% power at a significance level of 5%. Therefore, we aimed to recruit at least 124 patients to the study.

## Randomization

Participants were randomly assigned to either the TEAS or control group in a 1:1 ratio using a random number table created by EpiCalc 2000 software. A clinical professional uninvolved in the study performed the randomization and provided a code for each patient. The group allocation and TEAS were performed using a partially double-blind method. Patients and clinical assessors were blinded to the assignment and the treatment. According to the patient's code and allocation, the trial manager directed nurses to complete TEAS or sham TEAS. Both sets of nurses had signed a confidentiality agreement and had agreed not to discuss the efficacy and details of the trial with others before unblinding.

## Interventions

On the day after enrolment, patients underwent a baseline assessment to gather information on age, alcohol dependence and alcohol consumption. Patients in both groups were instructed to take diazepam orally thrice daily, starting 1 hour after hospitalization. The dose was gradually reduced as per standard procedures at the participating hospital: patients were given 30 mg diazepam per day for 5 days, followed by 15 mg/day for 3 days, 10 mg/day for 2 days, and 5 mg/day for 3 days. Patients ceased treatment on day 14. Throughout the trial, all patients received the same nutritional regimen and oral vitamin B1 supplementation of 60 mg/day. Patients in both groups were treated with the same medications if they suffered electrolyte disturbance, transaminase elevation or other conditions.

Patients in the TEAS group were given TEAS twice daily at a regular time in a quiet room. Four acupuncture points, *Hegu* (LI4), *Laogong* (PC8), *Neiguan* (PC6), and *Waiguan* (SJ5), were stimulated concurrently using a HANs acupoint nerve stimulator (Beijing Huawei Industrial Development Co., Beijing, China) for 30 minutes at a frequency of 2 Hz and 100 Hz with automatic shifting and a current of 15 to 25 mA. Patients in the control group were given sham TEAS, which was performed using the same equipment but with no electrical output from the HANs stimulator. During the procedure, patients were asked to close their eyes and were not permitted to discuss their experiences of the therapy with other patients. Treatments

were administered by specially trained mental health nurses who were not blinded to treatment group.

Adverse events and abnormal examination results were recorded. Serious adverse events (SAEs) were defined according to the US Food and Drug Administration's definition.[18] Acceptable adverse events were those that patients and physicians classified as acceptable non-SAEs. Patients who experienced adverse events or whose results were abnormal were assessed by a qualified physician and permitted to continue the trial if it was judged safe to do so and if permission was granted by their guardians. Otherwise, such patients were exited from the study and their data were excluded from the final analysis.

### Primary outcomes

Severity of AWS symptoms was assessed using the Clinical Institute Withdrawal Assessment for Alcohol Scale (CIWA-Ar), which measures 10 parameters of physical and psychiatric symptoms of withdrawal.[19] Four trained psychiatrists completed the CIWA-Ar evaluations during eight interviews on days 1, 2, 3, 4, 5, 7, 10 and 14. At each interview, the severity of each symptom was scored. Higher scores on an item indicate more severe withdrawal symptoms. Evaluations by the five psychiatrists showed high consistency ($r = 0.86$, $P < 0.05$).

### Secondary outcomes

At the interviews on days 1, 7 and 14, patients were asked to rate their craving for alcohol, their sleep quality and their sleepiness during the day. Alcohol craving was measured using scores on a VAS scale of 0 to 10; higher scores indicate stronger cravings. Sleep quality was evaluated using the Pittsburgh Sleep Quality Index (PSQI),[20] and daytime sleepiness was evaluated using a modified Epworth Sleepiness Scale (ESS).[21] The modified ESS (mESS) evaluation asked patients to rate their chance of dozing off or falling asleep while engaged in different scenarios. Three scenarios poorly suited to our study population were modified as follows: 'Being a passenger in a car for an hour without a break' was changed to 'Playing in a poker or chess game for an hour without a break'; 'Sitting quietly after a lunch without alcohol' was changed to 'Sitting quietly after a meal'; and 'Being in a car, while stopped for a few minutes in traffic' was modified to 'Being in a line, while waiting a few minutes for check-out'. Higher scores indicate poorer sleep quality and increased sleepiness. VAS, PSQI and mESS scores were randomly retested in 10% of patients to assess accuracy.

### Statistical analysis

Statistical analysis was performed using SPSS version 14.0 (SPSS Inc., Chicago, IL, USA). Values were expressed as mean $\pm$ standard deviation and the homogeneity of variance was examined before performing *t*-tests. Intergroup differences in questionnaire scores and subject characteristics (age, duration of alcohol dependence and alcohol consumption per day) were assessed for significance using two-sample *t*-tests. Intergroup differences in categorical data such as follow-up and frequency of adverse events throughout the observation period were assessed using chi-squared tests or Wilcoxon tests. Differences between pre-treatment and post-treatment were assessed using analysis of variance and the least significant difference *t*-test. Differences associated with $P < 0.05$ were considered statistically significant.

## Results

A total of 173 patients were assessed for enrolment, and 125 were enrolled and

randomized into the two groups (Figure 1). Over the course of the study, eight patients were excluded because they withdrew consent (4), discontinued the intervention owing to adverse events (3), or were lost to follow-up (1). A final total of 117 patients completed the study and were included in the final analysis: 57 in the TEAS group and 60 in the control group. The rate of follow-up was similar between the two groups ($\chi^2 = 0.98$). The TEAS and control groups were similar, respectively, in their mean age ($45.51 \pm 9.75$ vs. $44.54 \pm 8.32$ years), self-reported years of alcohol dependence ($9.53 \pm 4.35$ vs. $10.14 \pm 5.16$ years) and self-reported daily alcohol consumption ($256.21 \pm 123.68$ vs. $238.49 \pm 109.36$ g/day).

### Reduction in AWS symptoms

CIWA-Ar scores did not differ between the TEAS group and controls on days 1 or 2, but they were significantly lower in the TEAS group on days 3 to 14 ($P = 0.02$, 0.02, 0.01, 0.03, 0.00, 0.00). In the TEAS group, CIWA-Ar scores were significantly lower on days 3 to 14 than on day 1 (all $P = 0.00$) (Table 1). In the control group, CIWA-Ar scores were lower on days 4 to 14 than on day 1 (all $P = 0.00$).

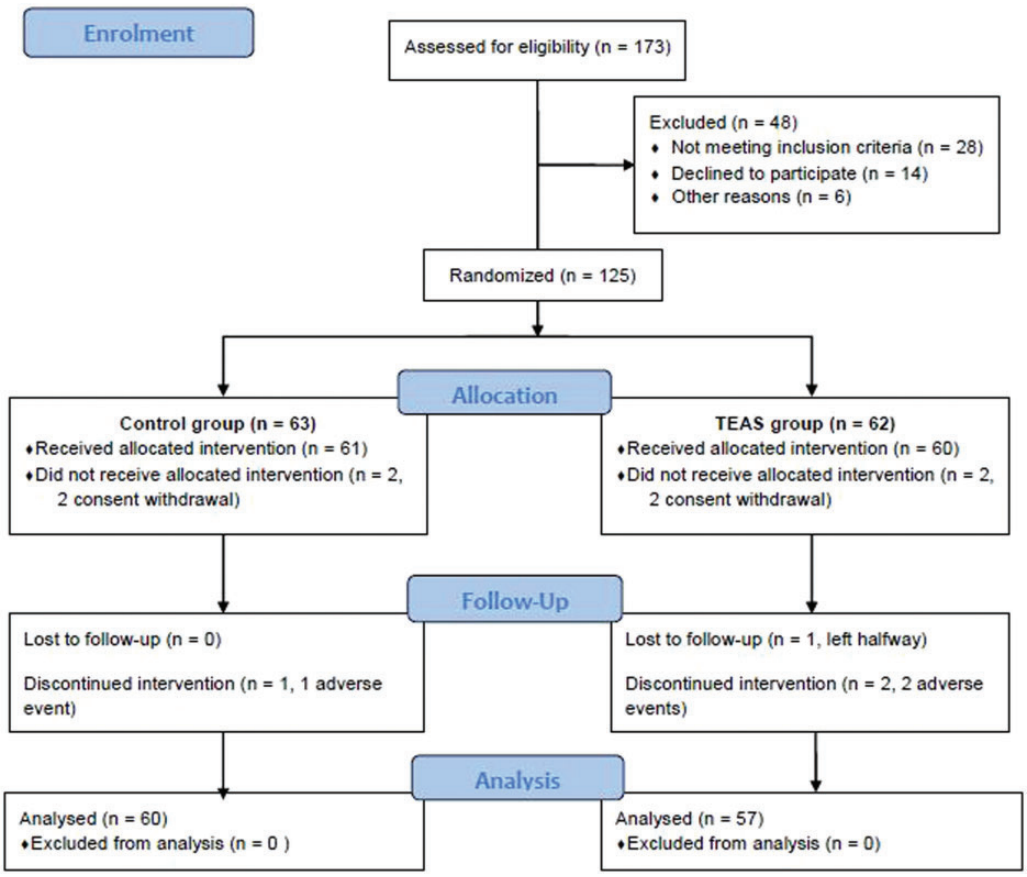


**Figure 1.** Flow of participants through the trial. TEAS: transcutaneous electrical acupoint stimulation.

**Table 1.** Scores on the Clinical Institute Withdrawal Assessment for Alcohol Scale in AWS patients treated with diazepam alone or combined with TEAS.

| Group | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 7 | Day 10 | Day 14 |
|---|---|---|---|---|---|---|---|---|
| Control (n = 60) | 18.25 ± 5.12 | 19.01 ± 5.10 | 16.84 ± 3.68 | 15.12 ± 3.71 | 13.20 ± 3.01 | 10.68 ± 3.25 | 9.92 ± 2.22 | 6.41 ± 2.03 |
| *t* (*P*) values* | – | 0.81 (0.42) | 1.73 (0.09) | 3.83 (0.00) | 6.59 (0.00) | 9.67 (0.00) | 11.56 (0.00) | 17.05 (0.00) |
| TEAS (n = 57) | 17.93 ± 6.01 | 17.28 ± 6.33 | 15.11 ± 4.15 | 13.21 ± 4.69 | 11.45 ± 4.27 | 9.35 ± 3.23 | 8.50 ± 1.99 | 4.97 ± 1.58 |
| *t* (*P*) values* | – | 0.58 (0.56) | 3.01 (0.00) | 4.85 (0.00) | 6.85 (0.00) | 9.82 (0.00) | 11.63 (0.00) | 16.28 (0.00) |
| *t* (*P*) values for the intergroup difference | 0.32 (0.76) | 1.64 (0.10) | 2.38 (0.02) | 2.45 (0.02) | 2.57 (0.01) | 2.22 (0.03) | 3.64 (0.00) | 4.40 (0.00) |

AWS: acute alcohol withdrawal syndrome; TEAS: transcutaneous electrical acupoint stimulation.
*For the given day *vs.* day 1.

### *Alcohol craving and sleep quality*

In both groups, VAS, PSQI and mESS scores decreased progressively over days 1, 7 and 14 (all $P = 0.00$) (Table 2). VAS scores were similar between the TEAS and control groups on day 1, but significantly lower in the TEAS group on days 7 and 14 ($P = 0.03$, 0.03). PSQI scores were similar between the two groups on days 1 and 7, but significantly lower in the TEAS group on day 14 ($P = 0.03$). The mESS scores were similar between the two groups on days 1 and 14, but significantly lower in the TEAS group on day 7 ($P = 0.04$). Scores on the VAS, PSQI and mESS on day 1 strongly correlated with retest results on day 2 (VAS, $r = 0.88$, $P = 0.00$; PSQI, $r = 0.91$, $P = 0.00$; mESS, $r = 0.89$, $P = 0.00$).

### *Adverse events*

No SAEs occurred during the 14-day treatment period. There were 19 acceptable adverse events in the control group: sleepiness (9), dizziness (4), headache (3), nausea (1), aggravation of sleep apnoea (1) and diarrhoea (1). There were 15 acceptable adverse events in the TEAS group: sleepiness (5), dizziness (2), light tingling (2), skin redness at contact sites (2), headache (1), nausea (1), insomnia (1) and temporary paralysis of hands (1). The incidence of adverse events was not significantly different between the two groups ($\chi^2 = 0.24$). Physician assessment indicated that six adverse events (2 cases of light tingling, 2 cases of skin redness at contact site, 1 case of insomnia and 1 case of temporary hand paralysis) were likely to be connected with TEAS, whereas the significantly greater number of 22 (14 cases of sleepiness, 6 cases of dizziness, 1 case of nausea and 1 case of aggravation of sleep apnoea) were likely to be caused by diazepam ($z = 3.01$, $P = 0.00$). Six adverse events were unrelated to either TEAS or diazepam.

**Table 2.** VAS, PSQI and mESS scores in AWS patients treated with diazepam alone or combined with TEAS.

| Scale | Group | Day 1 | Day 7 | Day 14 |
|---|---|---|---|---|
| VAS | Control (n = 60) | 9.15 ± 2.76 | 7.55 ± 2.05 | 4.55 ± 1.43 |
| | *t* (*P*) values* | | 3.65 (0.00) | 11.49 (0.00) |
| | TEAS (n = 57) | 9.40 ± 3.09 | 6.69 ± 2.23 | 3.95 ± 1.65 |
| | *t* (*P*) values* | | 5.52 (0.00) | 12.02 (0.00) |
| | *t* (*P*) values for the intergroup difference | 0.46 (0.64) | 2.18 (0.03) | 2.11 (0.03) |
| PSQI | Control (n = 60) | 14.69 ± 4.12 | 11.20 ± 2.88 | 7.91 ± 3.19 |
| | *t* (*P*) values* | | 5.49 (0.00) | 10.03 (0.00) |
| | TEAS (n = 57) | 15.01 ± 4.31 | 10.67 ± 3.50 | 6.83 ± 2.10 |
| | *t* (*P*) values* | | 6.04 (0.00) | 13.12 (0.00) |
| | *t* (*P*) values for the intergroup difference | 0.40 (0.68) | 0.90 (0.37) | 2.14 (0.03) |
| mESS | Control (n = 60) | 11.43 ± 2.80 | 8.97 ± 1.99 | 7.57 ± 2.76 |
| | *t* (*P*) values* | | 5.62 (0.00) | 7.62 (0.00) |
| | TEAS (n = 57) | 11.72 ± 3.11 | 8.10 ± 2.55 | 6.83 ± 2.02 |
| | *t* (*P*) values* | | 6.90 (0.00) | 10.16 (0.00) |
| | *t* (*P*) values for the intergroup difference | 0.52 (0.60) | 2.05 (0.04) | 1.65 (0.10) |

AWS: acute alcohol withdrawal syndrome; mESS: modified Epworth Sleepiness Scale; PSQI: Pittsburgh Sleep Quality Index; TEAS: transcutaneous electrical acupoint stimulation; VAS: visual analogue scale.
*For the given day *vs.* day 1.

## Discussion

TEAS has been reported to have a similar efficacy as acupuncture, electroacupuncture and transcutaneous electrical nerve stimulation,[11,22,23] and it can help to reduce anxiety and control stress by regulating the release of enkephalins and dynorphins and increasing GABA signalling in the brain.[24] Electroacupuncture can also normalize the activity of dopamine neurons in the ventral tegmental area[25] and relieve mental symptoms such as anxiety, depression and emotional exhaustion.[26] TEAS regulates vegetative nerve functions, which are related to acute withdrawal symptoms such as nausea and vomiting.[27–29] Importantly, many of these neurotransmitters and receptors also play roles in AWS, and may prompt the GABA system to produce direct or indirect inhibiting effects, similar to the functions of agents such as pregabalin and gabapentin.[3–5]

In this trial, we found that a combination of TEAS and diazepam suppressed alcohol cravings better than diazepam alone. This suppression may involve the release of endogenous enkephalins and dynorphins that stimulate dopaminergic neurons of the reward pathway in the brain, decreasing alcohol craving. Acupuncture can rapidly inhibit neuronal activity in brain regions involved in craving (e.g. the frontal lobe, precuneus, temporal lobe, cingulate gyrus) in heroin-addicted patients.[30] TEAS may produce similar effects in patients experiencing AWS.

We found that TEAS improved sleep quality in AWS patients, perhaps owing to the treatment's ability to reduce clinical AWS symptoms, physical discomfort and psychological stress. Similarly, electroacupuncture has been reported to improve sleep latency in patients with heroin addiction,[31] and acupuncture can increase nocturnal endogenous melatonin and improve sleep quality.[32]

Diazepam promotes sleep quality by prolonging non-rapid eye movement sleep, but this usually comes at the cost of increased daytime sleepiness.[2] However, the present combination of TEAS with

diazepam improved sleep quality while reducing the daytime sleepiness associated with diazepam alone. This result is similar to that of Dias et al.,[26] who found that electroacupuncture improved sleep quality and reduce sleepiness more than sham-electroacupuncture. These effects may be related to regulation of GABA receptor functions and altered vigilance levels.[33]

Our results should be interpreted with caution given the relatively short observation period and the fact that our patients were all men at a single medical centre. Nevertheless, our data provide evidence that TEAS can effectively improve AWS symptoms in patients taking diazepam. TEAS further improved sleep quality beyond diazepam alone, while reducing the daytime sleepiness associated with the drug. At the same time, TEAS was linked to far fewer adverse events than diazepam, consistent with previous suggestions that TEAS is safe and well-tolerated.[34]

Larger trials are needed to confirm and extend our findings. Future researchers may also wish to compare TEAS alone with diazepam or other therapies, such as acupuncture-based techniques, for patients experiencing acute AWS.

## Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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## Registration

Trial registration number: ChiCTR-ROC-17011117.

## Supplemental material

Supplemental material for this article is available online.

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