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Electroacupuncture for tapering off long-term benzodiazepine use: A randomized controlled trial

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ABSTRACT

Objective: To evaluate the efficacy of using electroacupuncture as an adjunct treatment in enhancing the benzodiazepine cessation rate in long-term benzodiazepine users.

Methods: This was a randomized, assessor- and subject-blinded, controlled trial. One hundred and forty-four long-term benzodiazepine users were randomly assigned to receive either electroacupuncture or placebo acupuncture (a sham itervention using non-invasive placebo needles) combined with a gradual benzodiazepine tapering schedule for 4 weeks. The primary outcome was the cessation rate of benzodiazepine use. Subjects were assessed on their benzodiazepine usage, benzodiazepine withdrawal symptoms, insomnia severity, and anxiety and depressive symptoms at baseline, week 6 and week 16.

Results: The cessation rates of the electroacupuncture and placebo acupuncture groups at 12 weeks post-treatment were 9.17% and 10.83%, respectively. Both groups showed a reduction in benzodiazepine usage by a self-completed drug record at week 16 (compared to baseline: electroacupuncture group −40.23% versus placebo acupuncture group −48.76%). However, no significant between-group differences were found in the benzodiazepine cessation rate, reduction in benzodiazepine usage, and other secondary measures across all the study time points.

Conclusions: Electroacupuncture showed a similar cessation rate in benzodiazepine use to that of non-invasive placebo acupuncture in long-term users during a 4-week gradual tapering schedule. The evidence did not support advantages of electroacupuncture over non-invasive placebo acupuncture on reducing insomnia, anxiety, depression, or other withdrawal symptoms during the gradual tapering schedule. Despite a 40% decrease in the benzodiazepine usage in both groups, the effects may be attributed to the non-specific effects of acupuncture.

Trial Registration: ClinicalTrials.gov # NCT02475538.

1. Introduction

Benzodiazepines are promising in short-term relief of anxiety and insomnia symptoms; however, their long-term use is controversial due to concerns about effectiveness, tolerance, dependence and withdrawal syndrome upon cessation of use (Lader et al., 2009). It is not uncommon for some patients to continue to take benzodiazepine and become long-term users (Australian Bureau of Statistics, 1996; Holden et al., 1994; Petitjean et al., 2007). Long-term benzodiazepine use may carry a risk of dependence, overdose, abuse, cognitive impairment, household falls, work and road accidents, mortality, as well as withdrawal symptoms following discontinuation (Charlson et al., 2009; Kan et al., 1997; Lader et al., 2009; Verwey et al., 2000).

A high proportion of long-term benzodiazepine users failed to stop

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or reduce taking the benzodiazepine due to withdrawal symptoms (Chung et al., 1999). Benzodiazepine withdrawal symptoms include insomnia, anxiety, hand tremors, tachycardia, sweating, muscle pain and irritability, which are commonly reported upon discontinuation of benzodiazepines (Schweizer and Rickels, 1998). Gradual reduction is effective for tapering benzodiazepines (Parr et al., 2009). A meta-analysis found that gradual reduction provided superior cessation rates at post-treatment to routine care (OR = 5.96, 95% CI = 2.08–17.11). When gradual reduction used in combination with psychological intervention, it was more effective than gradual reduction alone (OR = 1.82, 95% CI = 1.25–2.67) (Parr et al., 2009). A Cochrane review also indicated that moderate quality of evidence supported the use of gradual reduction in combination with cognitive behavioural treatment in reducing benzodiazepine use (Darker et al., 2015). Other approaches such as individualized letters by a general practitioner to reduce benzodiazepine use, standardized interview and relaxation are also suggested to have emerging evidence to be effective for benzodiazepine reduction (Darker et al., 2015).

Acupuncture, one of the most commonly used complementary and alternative therapies, can be an adjunct treatment for benzodiazepine tapering. During acupuncture treatment, acupuncturists insert fine needles at special acupoints on the body according to the traditional Chinese meridian theory (Kaptchuk, 2002). The inserted acupuncture needles can be connected by an electric-stimulator to deliver electric-stimulation and is termed as electroacupuncture. Emerging evidence suggested that acupuncture could be effective for relieving insomnia (Cheuk et al., 2012; Yeung et al., 2009) and alleviating anxiety symptoms (Pilkington et al., 2007), which may be useful for reliving the benzodiazepine withdrawal symptoms and hence facilitate tapering. However, only a handful of case-series studies had examined the use of acupuncture to enhance benzodiazepine discontinuation rates (Qiao, 2002; Ruan and Zheng, 2002; Zhang et al., 2001). These studies suggested that acupuncture can reduce the frequency of using hypnotics (Ruan and Zheng, 2002), and facilitate the discontinuation of hypnotics (Zhang et al., 2001) and benzodiazepine (Qiao, 2002) after the acupuncture treatment.

Apart from these uncontrolled studies, to the best of our knowledge, no randomized placebo-controlled study has been performed for the efficacy and safety of acupuncture for benzodiazepine tapering. Therefore, we conducted a randomized controlled trial to examine the efficacy and safety of electroacupuncture as an adjunct treatment to gradual benzodiazepine tapering in long-term benzodiazepine users. We hypothesized that subjects receiving electroacupuncture would have a higher benzodiazepine cessation rate than those receiving non-invasive placebo acupuncture.

2. Methods

2.1. Setting design

This study was a two-arm, randomized, assessor- and subject-blinded controlled trial. The study was approved by the University's Institutional Review Board. The details of the trial protocol have been published elsewhere (Yeung et al., 2017). There was no deviation from the study protocol. This study was registered in the ClinicalTrials.gov (identifier: NCT02475538) and conducted according to the latest version of Declaration of Helsinki. The design and reporting of the study followed the CONSORT (Moher et al., 2012) and STRICTA (MacPherson et al., 2010) recommendations.

2.2. Setting and participants

Participants who were long-term benzodiazepine users were recruited from psychiatric outpatient clinics through doctor referral and advertisements at three regional hospitals in Hong Kong and an integrative health clinic between July 2015 and July 2017.

Included subjects were aged 18 years or over, had at least one of the psychiatric diagnoses listed in Table 1; were taking benzodiazepines, coded as N05BA (benzodiazepine derivatives, anxiolytics, e.g. diazepam, lorazepam), N05CD (benzodiazepine derivatives, hypnotics and sedatives, e.g. flurazepam, estazolam), N05CF (benzodiazepine related drugs, hypnotics and sedatives, e.g. zopiclone, zolpidem), and M03BX07 (benzodiazepine derivatives, muscle relaxants e.g. tetrazepam), according to the World Health Organization Anatomical Therapeutic Chemical classification system (World Health Organisation Collaborating Centre for Drug Statistics Methodology, 2002), on more than 50% of days for at least 3 months and during a prospective 2-week period prior to baseline; and willing to taper benzodiazepines as per protocol.

We excluded patients if they had any increase by ≥ 50% in the dosage of antidepressants or anxiolytics in the previous year; ≥ 8 score in either the depression or anxiety subscale of the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983); any concurrent psychiatric disorders or medical condition on the exclusion list (Table 1). Informed written consents were obtained from participants prior to any study procedures.

2.3. Procedure

Eligible subjects were randomized in a 1:1 ratio to receive either electroacupuncture combined with gradual tapering or placebo acupuncture combined with gradual tapering using the block

Table 1
Supplemented information of inclusion/exclusion criteria.

Psychiatric conditions listed in inclusion criteria	Other exclusion criteria
The ICD-10 code for psychiatric conditions considered as suitable for participation: - F32.0 Mild depressive episode; - F32.1 Moderate depressive episode; - F32.8 Other depressive episodes; - F32.9 Depressive episode, unspecified; - F33.0 Recurrent depressive disorder, current episode mild; - F33.4 Recurrent depressive disorder, currently in remission; - F33.1 Recurrent depressive disorder, current episode moderate; - F33.8 Other recurrent depressive disorders; - F33.9 Recurrent depressive disorder, unspecified; - F41.0 Panic disorder; - F41.1 Generalized anxiety disorder; - F41.2 Mixed anxiety and depressive disorder; - F43.2 Adjustment disorders; - F51.0 Nonorganic insomnia	The ICD-10 code of psychiatric conditions considered as unsuitable for participation: - F31.0 Bipolar affective disorder; - F42.0 Obsessive-compulsive disorder; - F43.1 Post-traumatic stress disorder; - F20.0 Schizophrenia; - F21-29 Other schizotypal and delusional disorders; - F55.0 Abuse of non-dependence-producing substances; - F10-12, F14-19 Abuse of other psychoactive substances Other conditions: - Serious physical conditions considered as unsuitable for participation; - Had valvular heart defects or bleeding disorders, were taking anticoagulant drugs, or had been fitted with any implanted electrical device; - Received acupuncture treatment within 6 months; - Being pregnant or breastfeeding, or had childbearing potential without adequate contraception; - Had infection or abscess close to the selected acupoints rendered unsafe; - Significant suicide risk as rated by the Hamilton Depression Rating Scale item on suicide (scored ≥ 3)

randomization method administered by an independent administrator. The group allocation was kept in sequentially numbered, sealed and opaque envelopes, and the acupuncturist opened the envelope only after the blinded research assistant confirmed that the participant had completed all the baseline assessments.

2.4. Intervention

2.4.1. Electroacupuncture combined with gradual tapering (electroacupuncture group)

Electroacupuncture was delivered twice per week for 4 consecutive weeks. Subjects were needled at preselected acupoints on head, hands and legs by sterile, disposable acupuncture needles (Dong Bang, Korea, 0.25 × 30 mm) until "Deqi", an indicator of "effective needling" in traditional Chinese medicine (TCM) theory, was obtained. The acupoints included bilateral EX-HN1 (Sishencong), EX-HN22 (Anmian), GB8 (Shuaigu), ST8 (Touwei), EX-HN5 (Taiyang), GB15 (Toulinqi), PC6 (Neiguan), HT7 (Shenmen), SP6 (Sanyinjiao), LV3 (Taichong), unilateral EX-HN3 (Yintang), GV24 (Shenting), and GV20 (Baihui). The inserted needles were retained for 30 min and four pairs of needles were connected to an electric stimulator (AWQ 104L, Electronic Acupunctoscope, Hong Kong) to deliver continuous and constant electrical stimulation at 4 Hz. The amplitude of electrical stimulation will be adjusted to a comfortable level. Further details of the intervention please refer to the published protocol (Yeung et al., 2017). The baseline equivalent benzodiazepine dose in diazepam was calculated with the average benzodiazepine consumption recorded in the 2 weeks prior to the baseline (Zitman and Couvée, 2001). There are no standard tapering regimens and the rate of tapering (Brett and Murnion, 2015) and the tapering schedule can range from a month to year (Dou et al., 2018). The 4-week benzodiazepine tapering schedule, based on the protocol used in previous studies (Rickels et al., 1990; Schweizer et al., 1990; Voshaar et al., 2003), advised a 25% reduction of daily benzodiazepine consumption in the first and second weeks and following with 25% reduction for the remaining 50% of benzodiazepine every 3–4 days. Subjects' withdrawal symptoms were evaluated by a research assistant every week during the treatment period. The research assistant also discussed any problems encountered during benzodiazepine tapering, counted the remaining tablets, and reviewed the withdrawal schedule for the following weeks. If it was too difficult for the subjects to cope, they felt unable to meet the reduction goal, or at least one item in the Benzodiazepine Withdrawal Symptom Questionnaire was rated as severe (Tyrer et al., 1990), we would suggest slowing down the tapering.

2.4.2. Placebo acupuncture combined with gradual tapering (placebo acupuncture group)

Subjects in this group would receive sham acupuncture using Streitberger placebo needles, a non-invasive sham device, after the same sterilization procedure as electroacupuncture group. The design of the Streitberger placebo needles ensures the appearance of skin penetration without creating real skin penetration when the needles are pressed (Streitberger and Kleinhenz, 1998). Needles were placed 1 inch away from the acupoints and connected with an electric-stimulator without any supply of electronic stimulation. The subjects followed the same gradual tapering as electroacupuncture group. The acupuncture in both groups was administered with the same, number of sessions, frequency and treatment duration. A standard operating procedure manual, which was developed to standardize the treatment procedure and dialogue between the acupuncturists and subjects, was adopted in both groups.

2.4.3. Fidelity of the intervention

The acupuncture intervention was performed by registered Chinese medicine practitioners with a bachelor's degree in Chinese medicine and at least 5 years' clinical experience in providing acupuncture treatment. The PI (WY) assessed and monitored the first 10 acupuncture treatments using a pre-designed standardized checklist and visited randomly to inspect the treatment adherence.

2.5. Outcome measures

2.5.1. Primary outcome

The primary outcome was the benzodiazepine cessation rate, which was the proportion of subjects who had successfully discontinued benzodiazepines at week 6 and week 16. Cessation rate of benzodiazepine was evaluated with 14-day prospective daily record which was suggested to have higher accuracy than retrospective recall of usage (Morin et al., 2004; Voshaar et al., 2003). The subjects were asked to fill in the 14-day daily drug record after the 4-week intervention period and they should had discontinued their benzodiazepine use if they had followed the tapering schedule. If they did not successfully discontinue, they were allowed to continue to decrease their benzodiazepine use after the intervention period, and they were asked to fill in the daily drug record again during the 2-week before week 16.

2.5.2. Secondary outcomes

The average equivalent benzodiazepine dose in diazepam and the percentage of reduction compared to the baseline were derived from the record of benzodiazepine consumption with a cross-checking of surplus medications at each visit. Benzodiazepine withdrawal symptoms encountered due to benzodiazepine tapering was assessed by the 20-item self-reported Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ) (Tyrer et al., 1990). The Chinese version of Insomnia Severity Index (ISI) was used to assess the perceived severity of insomnia, one of the most prevalent withdrawal symptoms (Chung et al., 2011). The Chinese version of Hospital Anxiety and Depression Scale (HADS) was a 14-item self-reported questionnaire evaluating subjects' anxiety and depression levels (Leung et al., 1999; Zigmond and Snaith, 1983). The Chinese version of the Substance Dependence Scale (SDS), replacing the term "substance" with "benzodiazepine", was adopted to indicate the severity of dependency on benzodiazepine in the previous 12 months (Gossop et al., 1995). The Credibility of Treatment Rating Scale (CTRS) was used to assess subjects' confidence and expectations of treatment (Vincent, 1990). Acupuncture-related safety outcomes were assessed with an adverse event form at each study visit (Chung et al., 2015).

2.6. Blinding assessment

All outcome measures were self-completed and collected by an independent research assistant who was blinded to treatment allocation. The acupuncturists who delivered the interventions were not involved in any assessment. The success of subject-blinding was assessed by, at the end of the last treatment session, asking the subject to guess which acupuncture (electroacupuncture or placebo acupuncture) they had received (Park et al., 2005).

2.7. Statistical analysis

The target sample size (72 per group) was enough to detect a 25% difference in the cessation rate between groups with a statistical power of 80% and Type I error of 0.05. Analysis was performed using intention-to-treat sample. Logistic or linear regression was used to assess the post-treatment difference week 6 (2 weeks post-treatment), and week 16 (12 weeks post-treatment) after imputation of missing values.

Missing values were handled by the multiple imputation technique, assuming data were missing at random (MAR). Ten sets of imputed values were generated to adjust for variability due to imputation. These completed datasets were analyzed separately with standard statistical methods and the results combined into a single multiple-imputation result (Little and Rubin, 2002).

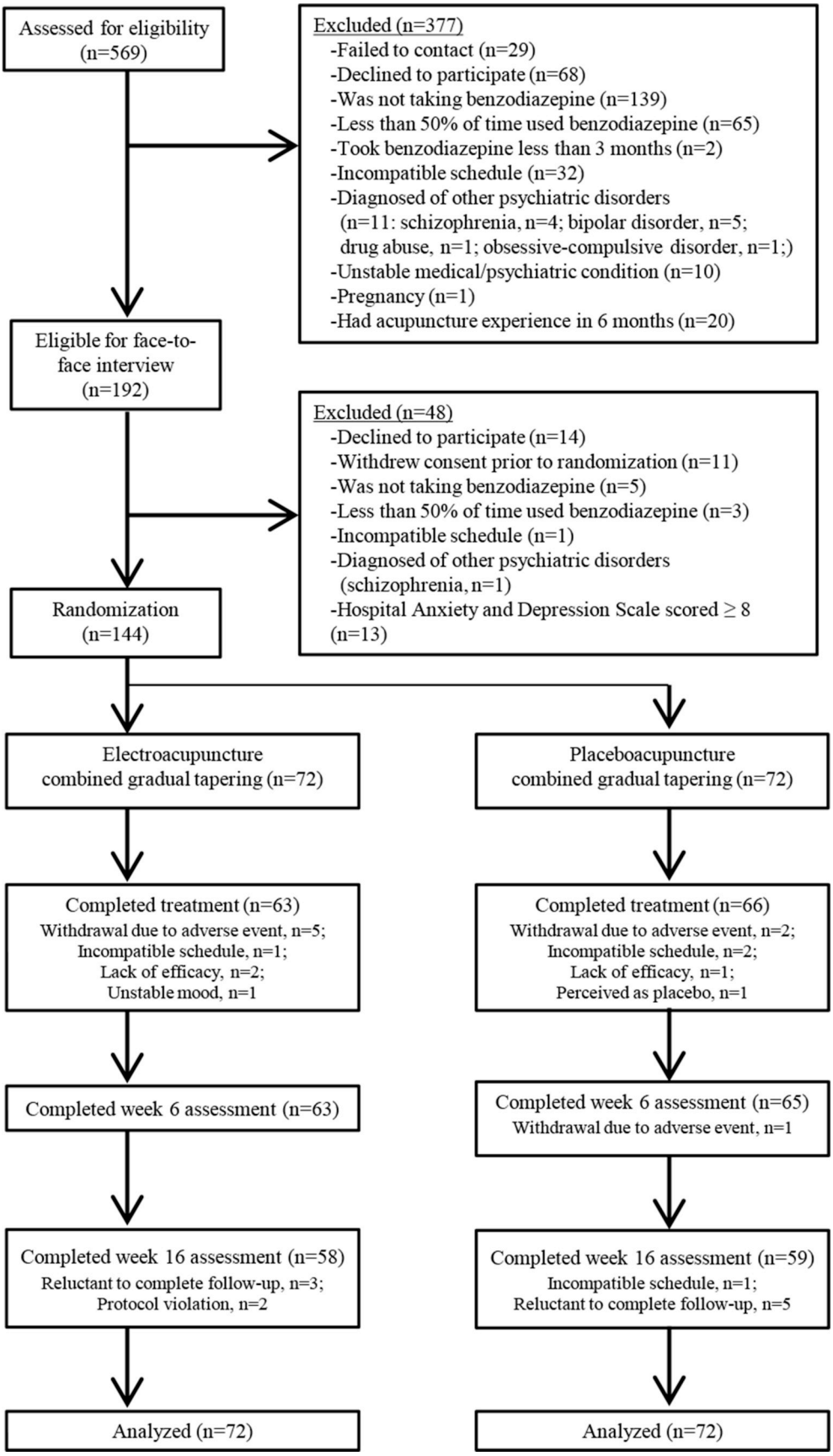

Fig. 1. Study recruitment flow chart.

To examine the effect of departures from the assumption of MAR on clinical outcomes, sensitivity analysis was performed by pattern mixture models using Stata RCTMISS (White, 2017) with various possible values of the informative missing parameters (Little and Rubin, 2002). The missing data due to dropout cases may have been associated with those who rebound in insomnia or anxiety levels, or those who fail to decrease consumption of benzodiazepine. For dichotomous outcomes, the informative missing parameter specified the odds ratio between the outcome and the missingness indicator. For continuous outcomes, it specified the mean difference between the unobserved outcome and the observed outcome. By varying the informative missing parameter, it was possible to examine the magnitude of departures from MAR assumptions on different outcomes.

3. Results

3.1. Participants

Between July 2015 and July 2017, a total of 644 patients were screened for eligibility and 192 agreed to a face-to-face screening and give written consent (Fig. 1). A total of 144 participants were randomized to the electroacupuncture or placebo acupuncture group. Subject characteristics are presented in Table 2. The mean age of participants was 57.5 years. Most of the subjects were female (72.9%). Their mean equivalent dose of benzodiazepine consumption was 8.6 mg for an average duration of 6.3 years. Subjects in the two groups did not differ in sociodemographic, clinical and baseline characteristics (all $P > .05$) except the use of antidepressants ($P = .02$). There were 15 subjects (10.4%) did not complete the treatment. Dropout rates at each follow-up time point did not significantly differ by intervention group (all $P > .05$).

3.2. Efficacy

3.2.1. Benzodiazepine usage

For the primary outcome measure, there was no significant difference between the electroacupuncture and placebo-acupuncture groups in the proportion of participants who successfully discontinued benzodiazepine consumption at weeks 6 (electroacupuncture and placebo acupuncture groups: 7.1% and 6.8%; $P = .96$) and 16 (electroacupuncture and placebo acupuncture groups: 10.4% and 11.7%, $P = .81$) (Table 3). No significant difference was found in dosage of benzodiazepine use, frequency of use, and reduction of benzodiazepine usage from baseline (all $P > .05$) (Table 3). Although at least 40% reduction of benzodiazepine usage from baseline was observed at week 6 (electroacupuncture and placebo acupuncture groups: 44.0% and −46.4%; $P = .67$) and week 16 (electroacupuncture and placebo acupuncture groups: 41.8% and −49.5%; $P = .30$), the reduction was similar in both groups.

3.2.2. Withdrawal symptoms, insomnia and mood

No significant differences in BWSQ, ISI or HADS anxiety and depression symptoms were observed between the two groups at week 6 and week 16 (Table 4, all $P > .05$).

3.3. Sensitivity analysis

The sensitivity analysis by imputing missing values with pattern mixture models did not show any significant differences in the outcomes between the subjects receiving electroacupuncture and placebo acupuncture, thus the same results were found when MAR was not assumed, indicating that the missingness did not alter our findings.

Table 2
Sociodemographic, clinical and baseline characteristics of participants.

Variable[a]	All participants n = 144	Range	Electro-acupuncture n = 72	Placebo acupuncture n = 72	*P* value *t*-test/chi-square
Age, y	57.5 ± 10.6	22–85	58.0 ± 9.4	57.0 ± 11.8	0.59
Female gender, %	105 (72.9)	/	49 (68.1)	56 (77.8)	0.19
Educational level, yr	10.9 ± 3.8	0–25	11.0 ± 4.1	10.8 ± 3.4	0.77
Marital status, %					0.40
Never married	21 (14.6)	/	8 (11.1)	13 (18.1)	
Married/cohabiting	95 (66.0)	/	51 (70.8)	44 (61.1)	
Divorced/widowed	28 (19.4)	/	13 (18.1)	15 (20.8)	
Employment status, %					0.85
Employed	39 (27.1)	/	19 (26.4)	20 (27.8)	
Unemployed/retired/housework	105 (72.9)	/	53 (73.6)	52 (72.2)	
BMI, kg/m^2	22.0 ± 3.0	15.0–31.6	22.1 ± 2.9	22.0 ± 3.1	0.90
Chronic medical illnesses, %[b]	73 (51.0)	/	33 (46.5)	37 (51.4)	0.56
Current anti-depressant user, %	93 (64.6)	/	40 (55.6)	53 (73.6)	0.02
Alcohol drinker, %	11 (7.6)	/	7 (9.7)	4 (5.6)	0.35
Benzodiazepine use					
Short benzodiazepine half-life, %	75 (52.1)	/	34 (47.2)	41 (56.9)	0.24
Equivalent dose in diazepam, mg/d	8.6 ± 9.0	0.8–44.3	8.5 ± 9.5	8.6 ± 8.6	0.94
Use of two or more benzodiazepines, %	40 (27.8)	/	17 (23.6)	23 (31.9)	0.26
Weekly frequency of use (d/wk)	6.6 ± 0.9	4–7	6.5 ± 0.9	6.7 ± 0.8	0.20
Duration of taking benzodiazepine, yr	6.3 ± 6.0	0.3–30.0	6.2 ± 6.9	6.3 ± 4.9	0.86
SDS	8.0 ± 2.9	1–15	7.8 ± 2.8	8.2 ± 3.0	0.44
BWSQ	8.0 ± 5.3	0–25	8.2 ± 6.1	7.7 ± 4.5	0.60
ISI	13.9 ± 5.2	0–26	14.4 ± 5.3	13.4 ± 5.0	0.25
HADS					
Anxiety	3.6 ± 2.3	0–7	3.5 ± 2.3	3.8 ± 2.4	0.39
Depression	3.5 ± 2.3	0–7	3.3 ± 2.4	3.6 ± 2.2	0.43
CTRS					
Confidence in effectiveness	4.1 ± 1.2	1–6	4.1 ± 1.3	4.1 ± 1.2	0.84
Confidence in recommending to others	4.1 ± 1.4	1–6	4.0 ± 1.4	4.1 ± 1.3	0.50
Perceived logic	4.7 ± 1.0	2–6	4.6 ± 1.0	4.9 ± 1.0	0.07
Likelihood of relieving other complaints	4.1 ± 1.3	1–6	4.1 ± 1.4	4.1 ± 1.1	0.90

Abbreviations: BMI, Body Mass Index; SDS, Severity of Dependence Scale; BWSQ, Benzodiazepine Withdrawal Symptom Questionnaire; ISI, Insomnia Severity Index; HADS, Hospital Anxiety and Depression Scale; CTRS, Credibility of Treatment Rating Scale.

[a] Data are presented as mean ± SD or number (%).

[b] Participants were on regular medications for their medical illnesses.

Table 3
Consumption of benzodiazepine across study time points.

	Electroacupuncture (n = 72)		Placebo acupuncture (n = 72)			
	Mean (SE)[a]	Within-group Effect size (95%CI)[b]	Mean (SE)[a]	Within-group Effect size (95%CI)[b]	Between-group Effect size (95%CI)[b]	*P*-value[c]
Cessation rate, %						
Week 6	7.1 (3.4)	/	6.8 (3.1)	/	1.03 (0.26, 4.08)[d]	0.96
Week 16	10.4 (4.3)	/	11.7 (4.2)	/	0.87 (0.29, 2.64)[d]	0.81
Equivalent dose of usage in diazepam, mg/d						
Baseline	8.5 (1.1)		8.6 (1.0)			
Week 6	5.3 (0.9)	0.38 (0.04, 0.70)	4.9 (0.8)	0.48 (0.15, 0.81)	−0.06 (−0.38, 0.27)	0.72
Week 16	5.8 (1.0)	0.30 (−0.03, 0.63)	5.0 (0.8)	0.47 (0.13, 0.80)	−0.10 (−0.43, 0.22)	0.51
Weekly frequency of use, d/wk						
Baseline	6.5 (0.1)		6.7 (0.1)			
Week 6	5.7 (0.3)	0.42 (0.09, 0.75)	5.8 (0.3)	0.47 (0.14, 0.80)	0.04 (−0.29, 0.37)	0.90
Week 16	5.6 (0.4)	0.36 (0.03, 0.69)	5.6 (0.4)	0.44 (0.11, 0.77)	0.00 (−0.33, 0.33)	0.99
Reduction of usage from baseline, %						
Week 6	−44.0 (3.8)	/	−46.4 (4.3)	/	−0.07 (−0.40, 0.26)	0.67
Week 16	−41.8 (5.7)	/	−49.5 (5.4)	/	−0.16 (−0.49, 0.16)	0.30

[a] Multiple imputation was used to handle missing values adjusted with covariates.
[b] Effect size was calculated with difference in means divided by pooled standard deviation for either comparing with baseline (within-group) or making group comparison at a particular time point (between-group).
[c] Data are compared using logistic regression for cessation rate or linear regression for remaining continuous outcomes.
[d] Data are presented as odds ratio (95% CI).

Table 4
Secondary outcome measures across study time points.

	Electro-acupuncture (n = 72)		Placebo acupuncture (n = 72)		Between-group Effect size (95%CI)[b]	*P*-value[c]
	Mean (SE)[a]	Within-group Effect size (95%CI)[b]	Mean (SE)[a]	Within-group Effect size (95%CI)[b]		
BWSQ						
Baseline	8.2 (0.7)		7.7 (0.5)			
Week 6	3.6 (0.5)	0.89 (0.54, 1.23)	4.5 (0.5)	0.75 (0.41, 1.09)	0.21 (−0.12, 0.54)	0.19
Week 16	5.2 (0.6)	0.54 (0.21, 0.87)	5.8 (0.7)	0.37 (0.04, 0.70)	0.11 (−0.22,0.43)	0.50
ISIrowhead						
Baseline	14.4 (0.6)		13.4 (0.6)			
Week 6	11.0 (0.7)	0.61 (0.28, 0.95)	11.2 (0.6)	0.43 (0.10, 0.76)	0.04 (−0.29, 0.36)	0.81
Week 16	10.9 (0.8)	0.58 (0.25, 0.91)	10.5 (0.7)	0.52 (0.19, 0.85)	−0.06 (−0.39, 0.26)	0.62
HADS-Anxiety						
Baseline	3.5 (0.3)		3.8 (0.3)			
Week 6	3.8 (0.5)	−0.09 (−0.41, 0.24)	3.7 (0.4)	0.03 (−0.29, 0.36)	−0.03 (−0.35, 0.30)	0.89
Week 16	3.9 (0.5)	−0.11 (−0.44, 0.21)	4.3 (0.5)	−0.14 (−0.47, 0.18)	0.09 (−0.23, 0.42)	0.63
HADS-Depression						
Baseline	3.3 (0.3)		3.6 (0.3)			
Week 6	3.5 (0.4)	−0.07 (−0.39, 0.26)	3.7 (0.4)	−0.03 (−0.36, 0.29)	0.06 (−0.27, 0.39)	0.68
Week 16	3.9 (0.5)	−0.17 (−0.50, 0.16)	4.5 (0.5)	−0.26 (−0.58, 0.07)	0.14 (−0.19, 0.47)	0.39
CTRS-Confidence in effectiveness [d]						
Baseline	4.1 (0.2)		4.1 (0.1)			
2nd Treatment	4.6 (0.1)	0.37 (0.04, 0.70)	4.6 (0.1)	0.59 (0.25, 0.92)	0.00 (−0.33, 0.33)	0.99
8th Treatment	4.5 (0.2)	0.24 (−0.09, 0.56)	4.8 (0.1)	0.82 (0.48, 1.16)	0.22 (−0.11, 0.55)	0.26
CTRS-Recommendation [d]						
Baseline	4.0 (0.2)		4.1 (0.2)			
2nd Treatment	4.6 (0.1)	0.45 (0.11, 0.78)	4.5 (0.2)	0.24 (−0.09, 0.56)	0.07 (−0.25, 0.40)	0.54
8th Treatment	4.8 (0.2)	0.47 (0.14, 0.80)	4.9 (0.1)	0.60 (0.26, 0.93)	−0.07 (−0.40, 0.25)	0.51
CTRS-Perceived logical [d]						
Baseline	4.0 (0.2)		4.1 (0.2)			
2nd Treatment	4.6 (0.1)	0.45 (0.11, 0.78)	4.5 (0.2)	0.24 (−0.09, 0.56)	0.07 (−0.25, 0.40)	0.89
8th Treatment	4.8 (0.2)	0.47 (0.14, 0.80)	4.9 (0.1)	0.60 (0.26, 0.93)	−0.07 (−0.40, 0.25)	0.07
CTRS-Relieve other complaints [d]						
Baseline	4.1 (0.2)		4.1 (0.1)			
2nd Treatment	4.2 (0.2)	0.06 (−0.27, 0.39)	4.3 (0.1)	0.24 (−0.09, 0.56)	−0.07 (−0.40, 0.25)	0.55
8th Treatment	4.2 (0.2)	0.06 (−0.27, 0.39)	4.6 (0.2)	0.37 (0.04, 0.70)	−0.24 (−0.56, 0.09)	0.16

Abbreviations: BWSQ, Benzodiazepine Withdrawal Symptom Questionnaire; ISI, Insomnia Severity Index; HADS, Hospital Anxiety and Depression Scale; CTRS, Credibility of Treatment Rating Scale.
[a] Multiple imputation was used to handle missing values adjusted with covariates.
[b] Effect size was calculated with difference in means divided by pooled standard deviation for either comparing with baseline (within-group) or making group comparison at a particular time point (between-group).
[c] Data were compared using linear regression.
[d] A higher score indicates a greater confidence/expectation.

Table 5
Group comparison of prevalence of adverse events.

Items[a]	All sample (n = 144)	Electroacupuncture (n = 72)	Placebo acupuncture (n = 72)	*P*-value[b]
Needle site pain	45 (31.3)	36 (50.0)	9 (12.5)	< 0.001
Itchiness/redness around the needle site	21 (14.6)	14 (19.4)	7 (9.7)	0.10
Fatigue	20 (13.9)	10 (13.9)	10 (13.9)	1.00
Headache/pain symptoms	18 (12.5)	13 (18.1)	5 (6.9)	0.04
Needle site bruises	16 (11.1)	14 (19.4)	2 (2.8)	0.002
Needle site bleeding	15 (10.4)	14 (19.4)	1 (1.4)	0.001
Paresthesia	14 (9.7)	8 (11.1)	6 (8.3)	0.57
Immediate dizziness	11 (7.6)	7 (9.7)	4 (5.6)	0.53
Dizziness after treatment	10 (6.9)	7 (9.7)	3 (4.2)	0.33
Unusual relaxation	7 (4.9)	4 (5.6)	3 (4.2)	1.00
Nausea	7 (4.9)	4 (5.6)	3 (4.2)	1.00
Other complaints	7 (4.9)	3 (4.2)	4 (5.6)	1.00
Dermatological problems	5 (3.5)	4 (5.6)	1 (1.4)	0.37
Symptom worsening	4 (2.8)	2 (2.8)	2 (2.8)	1.00
Needle site infection	2 (1.4)	2 (2.8)	0 (0.0)	0.50
Withdrawal due to adverse events	8 (5.6)	6 (8.3)	2 (2.8)	0.28

[a] Data presented as number (%).
[b] Chi-square/Fisher's exact test used for group comparison.

3.4. Treatment credibility and success of blinding

Subjects' confidence and expectations of the intervention that they had received did not significantly differ between the two groups (all $P > .05$). The subjects were asked to make a guess of their group allocations. There was no significant group difference in the proportion of subjects who guessed that they had received electroacupuncture acupuncture ($P = .40$) or had no idea which treatment they had received ($P = 1.00$).

3.5. Adverse events

The most commonly reported adverse events are described in Table 5. Most of the reported adverse events were mild and moderate in severity. However, pain at needle sites, needle site bruises, needle site bleeding and headache were more frequently reported in the electroacupuncture group (All $P < .05$). Withdrawal due to adverse events was 8.3% and 2.8% for the electroacupuncture and placebo acupuncture groups, respectively, which was not significantly different ($P = .28$). Two serious adverse events were reported. One participant in the electroacupuncture group was hospitalized due to photosensitivity; one in the placebo acupuncture group reported vomiting, diarrhea and fever, and was hospitalized. These two serious adverse events were considered unrelated to the acupuncture intervention.

4. Discussion

The present study is the first randomized, placebo-controlled trial to examine the benefits of electroacupuncture as an adjunct treatment of gradual benzodiazepine withdrawal in chronic benzodiazepine users. The findings show that offering an electroacupuncture treatment twice a week on a 4-week gradual tapering schedule did not enhance the cessation rate compared to non-invasive placebo acupuncture in chronic benzodiazepine users. Both groups showed that benzodiazepine usage decreased by approximately 40% from the baseline at 2 and 12 weeks after the intervention, together with a slight improvement in benzodiazepine withdrawal symptoms and insomnia symptoms; however, there was no significant difference between the groups. We found no evidence of an advantage of electroacupuncture over non-invasive placebo acupuncture on insomnia, anxiety, depression, or other withdrawal symptoms.

Based on our findings, the benzodiazepine cessation rates were 10.4% and 11.7% in the electroacupuncture and placebo-acupuncture groups respectively. A systematic review found that the cessation rate of gradual tapering alone varied across studies with a median of 48% (9 studies, ranging from 17 to 89%); the median cessation rates of the augmented psychological and pharmacological interventions were 72% (10 studies; ranging from 13 to 85%), and 56% (16 studies; ranging from 27 to 100%) respectively (Parr et al., 2009). The taper protocols in the previous studies usually allowed for flexible dose decreases over time, either by slowing the amount of reduction or by extending the duration. The relatively low cessation rate found in this study is probably due to the relatively short, fixed 4-week tapering schedule. A study by (Voshaar et al., 2003) used a 4- to 5-week tapering schedule, and half of the participants discontinued the use of benzodiazepine at 3 months. However, the attrition rate (10.4%) found in our study was lower than that of the study by Voshaar et al. (19.9%), which may be attributed to the fact that we did not aggressively request the participants to taper. We allowed them to slow down the tapering if they thought it was difficult to meet the reduction goal, or if any one withdrawal symptom item was rated as severe by them in the BWSQ. Thus, our study showed a moderate improvement in BWSQ (within-group effect size = 0.89) compared to the study by (Voshaar et al., 2003) (within-group effect size of BWSQ = 0.12). To facilitate the tapering, a longer tapering schedule can be considered in future studies (Lader and Russell, 1993).

While previous studies have usually focused on cessation rate, the reduction in benzodiazepine usage has been less reported. In this study, around a 40% reduction was found in benzodiazepine usage from the baseline after the intervention in both groups, and the reduction persisted at the week 16 follow-up. The percentage of benzodiazepine reduction found in this study was slightly higher than in those using minimal intervention, such as a letter, self-help information, or a short consultation with a GP (20–35%), and usual care (10–15%) (Cormack et al., 1994; Jørgensen, 2007; Mugunthan et al., 2011; Towie and Adams, 2006); and slightly lower than appointment with a GP to discuss (50%), found in previous RCTs (Towie and Adams, 2006).

The electroacupuncture treatment was well tolerated, as evidenced by having only 8.3% of the participants terminating acupuncture due to adverse events. Most of the adverse events were mild. Similar to our previous studies (Chung et al., 2015; Yeung et al., 2011), the common adverse events were needle site pain, needle site bruising, needle site bleeding and headache, which were more frequently reported in the electroacupuncture group than in the placebo acupuncture group. In terms of safety, non-invasive needling may be superior to deep needling, as both produce similar efficacy, and hence it can be considered for use in clinical practice. Although non-invasive placebo needles may not be commercially available for clinical practice, superficial needling can be adopted in clinical practice, as this is less invasive and may lead to fewer adverse events.

In the present study, we adopted a non-invasive sham device at preselected, fixed non-acupoint sites, which did not involve skin penetration or electrical stimulation, as a placebo control. Our results did not find any difference between verum and placebo acupuncture, indicating that the specific effects induced by skin penetration and electric-stimulation at specific acupoint sites were not significant. Thus, the improvement observed in this study can be attributed to the normal progression of the illness and non-specific effects associated with acupuncture, such as the ritual of the treatment, practitioner-patient interaction, and participants' expectations of the treatment. However, we cannot rule out that the preselected non-acupoint sites may produce therapeutic effects when tactile stimulation is given, although these non-acupoint sites are believed to have no specific effects in terms of TCM theory. Future studies may adopt using random non-acupoint sites to minimize the possible unknown effects of the preselected non-acupoint sites.

The use of placebo control in acupuncture trial is still controversial (Walach, 2001; Zheng et al., 2014). Placebo controls are typically developed for testing the specific efficacy of pharmacological treatment and, ideally, a placebo should be indistinguishable from the true intervention and physiologically inert (Paterson and Dieppe, 2005). However, it is challenging to design an adequate placebo for a complex non-pharm intervention such as acupuncture, in which the treatment characteristics may also contribute to the non-specific effects of the treatment (Paterson and Dieppe, 2005; Verhoef et al., 2005) Since placebo needling procedures could dramatically produce such robust non-specific therapeutic effects equal to those produced by verum acupuncture, there is little space left for the assumed specific effect of electroacupuncture (Zheng et al., 2014). However, patients can still benefit from the non-specific effect of a treatment, despite the fact that the specific effect is small. Further studies may compare the electroacupuncture treatment with other standard treatment or treatment as usual, which will provide more clinically relevant information to clinicians, practitioners, and patients.

The strengths of this study include a robust design and use of non-invasive sham needles for placebo control. The dialogue between the practitioners and participants was standardized to ensure that the interaction, which is a factor that would affect the effectiveness of acupuncture (Kaptchuk et al., 2008), was similar in both groups. We adopted a prospective daily record of benzodiazepine usage with weekly drug count to verify their self-report reduction. In addition, a relatively broad range of participants was included in this study, including those with anxiety or major depressive disorders, which enabled a higher generalizability of our findings.

This study has several limitations. First, the benzodiazepine usage was assessed by self-completed drug diary, but no urine drug testing or blood testing was conducted to verify the benzodiazepine cessation or reduction. Nevertheless, our research personnel checked the drug count during the assessment visits. Additional objective measures such as urine and blood tests are suggested in order to enhance the accuracy of the assessment of benzodiazepine consumption. Second, only a relatively short-term, 12-week post-treatment follow-up was included. Participants in this study followed a fixed schedule of benzodiazepine tapering over 4 weeks, which may be so rigid and some may need to take longer to adapt to the potential withdrawal symptoms caused by benzodiazepine dosage changes. A longer and flexible tapering schedule with longer follow-up assessment may reveal relapse rates or higher cessation rates. Third, the present study only assessed benzodiazepine usage by a 2-week drug diary prior to the post-intervention follow-up at 12 weeks, hence participants' benzodiazepine usage during the period without a drug diary record was uncertain and they might be more eager to taper or discontinue during the 2-week daily record period, as they needed to report their usage to the research personnel (Voshaar et al., 2006). Finally, we did not include a usual care or gradual tapering alone group. Future studies may include such a passive control group to elicit the usual benzodiazepine tapering behaviour in chronic users.

5. Conclusions

Electroacupuncture showed a similar cessation rate in benzodiazepine use to that of non-invasive placebo acupuncture in long-term users during a 4-week gradual tapering schedule. Despite a 40% decrease in the benzodiazepine usage in both groups, the effects may be attributed to the non-specific effects of acupuncture, rather than skin penetration at specific acupoint sites.

Author contributions

WF Yeung conceived and designed the trial. ZJ Zhang, SP Zhang and LX Lao provided experts' opinion to the acupuncture protocol. KF Chung and WC Chan provided advice on the tapering schedule of benzodiazepine. RMK Ng and CLW Chan provided assistance on subject recruitment. BYM Yu conducted the assessments. JCS Chau and NCL Lau delivered acupuncture treatment and recorded adverse events. LM Ho performed the data analyses. WF Yeung and BYM Yu drafted the manuscript. KF Chung, ZJ Zhang, SP Zhang, WC Chan, RMK Ng, CLW Chan, LM Ho and LX Lao revised the manuscript. All authors approved the final version accepted for publication.

Potential conflicts of interest

None.

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Appendix A. Supplementary data

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