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Title: What Predict Response to Acupuncture? A Secondary Analysis of Three Randomized Controlled Trials on Insomnia

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ABSTRACT

Objective: Few studies have investigated the predictors of specific and non-specific effects of acupuncture. The aim of this exploratory analysis was to determine the patient characteristics that could predict better response to acupuncture for insomnia.

Methods: We pooled the data of 3 randomized, double-blind, placebo-controlled trials of acupuncture for insomnia to examine sociodemographic variables, clinical characteristics, baseline sleep-wake variables, and treatment expectancy in relation to acupuncture response. Subjects with Insomnia Severity Index (ISI) scores improved by 8 points or more from baseline to 1-week posttreatment were classified as responders.

Results: A total of 116 subjects who received traditional needle acupuncture were included, of which 37 (31.9%) were classified as responders. Acupuncture responders had higher educational level ($P < 0.01$) and higher baseline ISI score ($P < 0.05$), compared to non-responders. By multivariate logistic regression analyses, only year of full-time education remained significant (OR: 1.21, 95% CI 1.06 to 1.38, $P < 0.01$).

Conclusion: Consistent with previous studies, our data suggested that the response to acupuncture was difficult to predict. Although the predictive power by educational level was not enormous, our findings provided valuable information for patient selection in the treatment of chronic insomnia using acupuncture.

Keywords: Acupuncture; RCT; insomnia; predictors; response

Trial registration number: ClinicalTrials.gov, #NCT00839592, #NCT00838994, and #NCT01707706

INTRODUCTION

Acupuncture is a commonly used complementary and alternative treatment for insomnia.[1] Previous systematic reviews have suggested that acupuncture is effective for insomnia, but with a small effect size and marked heterogeneity in treatment outcome,[2] [3] possibly due to variation in acupuncture protocols and sample characteristics. It is believed that acupuncture has a relatively small specific effect but a large non-specific effect;[4] however, the mechanisms underlying these effects are poorly understood. Several physiological mechanisms, such as the sympatho-inhibitory, opioid and melatonin system, may be involved in the specific effect,[5] [6] while a combination of treatment expectancy, diagnostic procedures, patient-practitioner interaction, conditioning, intensive monitoring, anxiety reduction, and reporting bias may account for the non-specific effect.[7] [8]

Only a few studies have investigated the predictors of specific and non-specific effects of acupuncture. The number and frequency of treatment sessions, number and site of acupuncture points, other variations in treatment protocol, and the sensations elicited by acupuncture, typically called *deqi*, are believed to predict treatment outcome.[9] Among the non-specific factors that can predict treatment outcome, patient's expectation is probably the most frequently studied factor. A randomized controlled trial (RCT) in patients with knee osteoarthritis found that treatment expectancy, but not race, gender, or age, predicted acupuncture response.[10] In a study of patients with low back pain, higher expectation predicted greater response to both real and placebo acupuncture, while psychiatric comorbidity was not a significant predictor.[11] In contrast, a secondary analysis of a RCT of acupuncture for chronic back pain did not find pretreatment expectation and preference significantly associated with treatment response.[12] Another non-specific factor that has been shown to predict treatment response is regression to the mean. Patients with more severe

illness usually show greater response to acupuncture.[12-14] Other baseline characteristics that have been found to predict acupuncture response include non-use of analgesics,[12 14] non-receipt of disability allowance,[14] no previous surgical treatment,[14] and no complaint of headache.[14]

All these studies focused on patients with musculoskeletal pain, and none of them have addressed subjects with mental health problem. The limited number of publications available on this topic indicates that it is a under-studied field. Therefore, we conducted a post-hoc analysis of 3 randomized, double-blind, placebo-controlled trials of acupuncture for primary insomnia and residual insomnia in depressed patients. This study aimed to determine the patient characteristics that could predict better response to acupuncture for insomnia.

METHOD

Subjects

We pooled the data of 3 RCTs which were conducted by our research team (ClinicalTrials.gov identifier: #NCT00839592, #NCT00838994, and #NCT01707706).[15-17] The rationales, designs, and results of the RCTs have been previously reported.[15-17] In short, subjects were randomized to receive traditional acupuncture, minimal acupuncture, or non-invasive placebo acupuncture in a 1:1:1 ratio; or traditional acupuncture versus placebo acupuncture in a 1:1 ratio. Two of the RCTs included subjects with residual insomnia associated with major depressive disorder,[16 17] and 1 RCT was on primary insomnia.[15] Subjects were recruited from the community and at psychiatric outpatient clinics. This secondary analysis involved 116 subjects who received traditional acupuncture. Details of the inclusion and the exclusion criteria are available on the ClinicalTrials.gov. The major inclusion criteria were ethnic Chinese aged 18-70 years, fulfilling the criteria of insomnia symptom and

functional impairment in the Diagnostic and Statistical Manual of Mental Disorders, Fourth edition, text revision (DSM-IV-TR) for primary insomnia,[18] having insomnia of at least 3 nights per week for ≥ 3 months, an Insomnia Severity Index (ISI) score ≥ 15, no specific sleep disorders including circadian rhythm sleep-wake disorder, parasomnia, sleep apnea, or periodic limb movement disorder as assessed by clinical interview or overnight polysomnography, and not receiving acupuncture in the past 12 months. For the RCTs of residual insomnia associated with major depressive disorder**,** subjects had to have a past history of major depression according to the DSM-IV-TR and were in partial or full remission.

Study design and intervention

All study procedures were reviewed and approved by the local institutional review board. Subjects were screened through telephone, face-to-face interview, and laboratory-based overnight polysomnography. Eligible subjects completed a 7-day sleep-diary and 3-day or 7-day actigraphy recording 1 week prior to baseline. The acupuncture points used were the same in 2 RCTs,[15 16] including Baihui (GV20) and Yintang (EX-HN3), bilateral Ear Shenmen, Sishencong (EX-HN1), and Anmian (EX). In the remaining RCT, bilateral Neiguan (PC6), Shenmen (HT7), and Sanyinjiao (SP6) were used in addition. These acupuncture points were selected based on our previous systematic reviews[2 3] and experts' opinions. *Deqi* was achieved if possible; afterwards, the needles were connected to an electric stimulator (ITO ES160, Japan) to deliver electric-stimulation in continuous wave, frequency of 4 Hz, 0.4 ms square wave pulse and constant current. The needles were left for 30 min and then removed. Acupuncture treatment was performed by acupuncturists with at least 3 years' clinical experience of providing acupuncture treatment. Subjects were treated 3 times per week for 3 consecutive weeks in a quiet treatment room.

Outcome measures

The ISI,[19] sleep diary and actigraphy, 17-item Hamilton Depression Rating Scale (HAMD),[20] Hospital Anxiety and Depression Scale (HADS),[21] and Credibility of Treatment Rating Scale (CTRS)[22] were the outcome measures to be examined in this study. The ISI was used to assess the perceived severity of insomnia and accompanying functional impairments and its score ranged from 0 to 28. The daily sleep diary[23] inquired bedtime and rising time, time in bed (TIB), sleep onset latency, wake after sleep onset, number of awakenings, terminal wakefulness, and total sleep time (TST). Sleep efficiency (SE) was calculated as (TST/TIB × 100%). Wrist actigraph, a watch-like device, was used to record individuals' physical movements. By means of an accelerometer-microprocessor link, wrist actigraph could provide a valid objective measure of sleep.[24] Subjects were told to wear an actigraph on the non-dominant wrist every day for 3 days or 1 week. The recording length of epoch was set at 1 minute and the data was analyzed using Action-W or Actiware software. HAMD is a clinician-administered scale for the assessment of depression and its associated symptoms. HADS, a self-rated 14-item scale, is designed to assess the severity of depressive and anxiety symptoms, with higher scores suggestive of greater severity.[21] CTRS is a 4-item scale for the assessment of subjects' confidence in the treatment to alleviate their complaints, confidence in recommending the treatment to their friends who have similar complaints, perceived logic of the treatment, and likelihood that the treatment would alleviate their other complaints.[22] The Chinese version of questionnaires and sleep diaries were used and they been shown to have adequate validity and reliability.[25]

Classification of responders/non-responders

Subjects with ISI scores improved by 8 points or more from baseline to 1-week posttreatment were classified as responders. The ISI score was selected because it assesses both severities of insomnia symptoms and related daytime impairments. The ISI cutoff as a definition of response has been used in a previous study of cognitive behavioral therapy for insomnia , which found a mean posttreatment reduction in ISI score of 8.3, equivalent to a within-group effect size of 2.0.[26] The ISI cutoff has a sensitivity of 60% and a specificity of 70% to detect an independent assessor-rated moderate improvement and was considered as the minimal significant difference.[27]

Statistical analysis

The factors examined were sociodemographic variables, clinical characteristics, current use of hypnotics, previous experience of acupuncture, CTRS score, and baseline sleep-wake variables, which included the ISI, sleep-diary-derived and actigraph-derived TST and SE. To avoid multiple comparisons, we only analyzed TST and SE among the sleep-diary and actigraph variables. Independent t test or chi square test was used to compare the baseline variables between acupuncture responders and non-responders. A univariate logistic regression analysis was conducted with response or non-response as binary variable, and the potential factors as explanatory variables. We did not include Bonferonni correction as it is overly conservative and would limit the number of variables to be entered into the regression model. Odds ratios (OR) and their 95% confidence interval (CI) were calculated. Finally, all significant variables were included in a multivariate logistic regression analysis.

RESULTS

Effect size and response rate

From baseline to 1-week posttreatment, the average reduction in ISI score for the 116

participants was 5.4 points (SD = 4.9; within group effect size = 1.34), while the average increase in sleep-diary-derived TST was 26.5 min (SD = 74.4; within group effect size = 0.32) and the increase in SE was 7.3% (SD = 13.0; within group effect size = 0.45). Thirty seven of the 116 subjects (31.9%) were classified as responders. The average reduction in ISI score in the responders were 10.9 points (SD = 3.1); for non-responders, it was 2.8 points (SD = 3.0). Univariate analyses showed that acupuncture responders had a higher educational level ($P< 0.01$) and higher baseline ISI score ($P< 0.05$), compared to non-responders (Table 1). Other sociodemographic and clinical variables were not related to acupuncture response.

Logistic regression

Table 2 summarizes the univariate and multivariate logistic regression analyses. Only educational level remained significant (OR: 1.21, 95% CI 1.06 to 1.38, $P< 0.01$) after controlling all significant factors. Acupuncture responders were 1.21-fold higher in educational level than non-responders.

DISCUSSION

Our secondary analysis on the pooled data of 3 RCTs showed that higher educational level and higher baseline ISI score were predictive of better acupuncture response for insomnia. However, when both variables were taken into account, only educational level remained a significant predictor. Consistent with the findings of acupuncture for painful conditions, our preliminary data suggested that the response to acupuncture among subjects with chronic insomnia was also difficult to predict.

One possible explanation for our findings is that higher education is associated with greater willingness to participate in acupuncture trials; hence their positive attitudes toward participation in an experiment, regardless of treatment expectancy, may

enhance treatment response. A previous survey in breast cancer patients showed that patients with higher education were more willing to participate in an acupuncture trial than those with lower education,[28] citing reasons for refusal to participate, including concern with experimentation, presence of placebo, and lack of interest in acupuncture. The skeptical attitudes toward experimentation may hamper treatment response. Another explanation is that subjects with higher educational level could more accurately report *deqi* sensation; hence the beneficial effect of acupuncture was enhanced.

Attempts have been made to explore the predictors of pharmacotherapy and psychotherapy in psychiatric conditions such as obsessive-compulsive disorder and panic disorder;[29] [30] however, no consistent predictors have been identified. This inability to predict treatment response may be particularly relevant for acupuncture, which is an intervention consisting of significant non-specific effects. Therefore, it is not surprising that only a few significant predictors for acupuncture response were found in this study.

Despite the availability of effective pharmacological[31] [32] and psycho-behavioral[33] [34] treatments for insomnia, it is common for people seeking complementary and alternative (CAM) therapies to help their sleep. [1] [35] Perhaps due to the unavailability of psycho-behavioral treatments and the potential adverse events associated with pharmacotherapy, CAM therapies, such as yoga, acupressure, herbal medicine, are often used.[35] [36] However, it is unclear which patients are more likely to respond to a particular CAM therapy. Patients may shift from one CAM treatment to another when the response is unsatisfying, which may cause delay in receiving effective treatment. There has been no studies examining the predictors to acupuncture in people with insomnia. Our study serves as a first step to identify those patients whose insomnia is more likely to be effectively treated by acupuncture.

A similar secondary analysis on the response to placebo acupuncture in subjects with chronic insomnia was completed recently.[37] We found that higher ISI score, longer sleep-diary-derived TST, less discrepancy between sleep-diary and actigraphy-derived TST, and higher expectation toward acupuncture were predictors to greater placebo response. As real acupuncture possesses specific and non-specific effects, while placebo acupuncture produces only non-specific effects, it is not surprising that the predictors are different.

We found that treatment expectancy was not a predictor of acupuncture effectiveness in subjects with insomnia. The finding is in contrast to the literature on chronic pain. Except one study,[12] all other studies[10 11 38 39] showed that treatment expectancy was relevant to acupuncture response. The difference in results suggests that the relationship between treatment expectancy and outcome may vary across conditions that have different pathophysiological mechanisms. Further research is needed to understand the effects of pretreatment expectations on acupuncture effectiveness.

In terms of TCM theory, *deqi* sensation is an essential part of acupuncture and is related to efficacy.[9] It has been postulated that the characteristics of *deqi* sensation, intensity and duration of *deqi*, and the propagated sensation along the meridian would impact on acupuncture response.[40] In our RCTs, although *deqi* sensation was elicited whenever possible, we did not assess the occurrence of *deqi.* There has been no standardized measure to assess the characteristics of *deqi* sensation. It would be helpful to develop an assessment tool to quantify *deqi* sensation in order to study its effects on treatment response.

There are several limitations in our study. First, the acupuncture protocol is standardized instead of individualized, which is different from usual clinical practice. However, the acupuncture points used in our RCTs are commonly used acupuncture

points for insomnia, suggesting that our protocol is probably similar to the clinical practice of most TCM practitioners. Second, despite pooling of 3 RCTs, the sample size is still small and may not have enough statistical power to reveal potential predictors. Third, although the ISI cutoff has been used to define treatment response in a previous study,[26] it has not been validated in the Chinese population. Finally, we have not assessed some potential predictors of acupuncture response, such as patient-practitioner interaction. In conclusion, year of full-time education was shown to be an independent predictor of the response to acupuncture in subjects with chronic insomnia. Although the predictive power is not enormous, our findings can still help suggest which patients with insomnia are more likely to be helped by acupuncture, and this is meaningful for pre-treatment patient selection. Future studies with larger sample size are required to gain a better understanding on this topic relevant to clinical determination.

License for Publication Statement

Contributors

Y-WF and C-KF contributed to the conception of the study. Y-WF and Y-YM contributed to the analysis and interpretation of data for the study. Y-YM contributed to the data acquisition. Y-WF and C-KF drafted the paper. L-LX revised it critically for important intellectual content.

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Competing interests

None.

Ethics approval

Ethics approval was obtained from the Institutional Review Board of the University of Hong Kong.

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Table 1. Sociodemographic, clinical and baseline characteristics of the sample

Variable [a]	All participants n = 116	Non-responders n = 79	Responders n = 37	*P* value t-test/ chi-square
Sociodemographic characteristics				
Age, y	48.7 ± 9.4	49.5 ± 9.1	46.0 ± 9.8	0.07
Female gender	88 (75.9)	59 (74.7)	29 (78.4)	0.67
Educational level, y	12.2 ± 3.5	11.7 ± 3.4	14.0 ± 3.1	0.001
Marital status				0.36
Never married	20 (17.2)	12 (15.2)	8 (21.6)	
Married/cohabiting	62 (53.4)	43 (54.4)	19 (51.4)	
Divorced/widowed	34 (29.4)	24 (30.4)	10 (27.0)	
Employment status				0.55
Employed	58 (50.0)	38 (48.1)	20 (54.1)	
Unemployed/retired/housework	58 (50.0)	41 (51.9)	17 (45.9)	
Clinical characteristics				
Chronic medical illnesses [b]	24 (20.7)	18 (22.8)	6 (16.2)	0.42
Insomnia duration, y	10.2 ± 9.2	9.0 ± 8.7	7.3 ± 6.4	0.26
Current hypnotics use	39 (33.6)	29 (36.7)	10 (27.0)	0.30
Current psychiatric medications	64 (55.2)	46 (58.2)	18 (48.6)	0.33
Past history of depression	86 (74.1)	62 (78.5)	24 (64.9)	0.12
Previous acupuncture experience [c]	35 (31.8)	24 (34.3)	10 (27.8)	0.50
Sleep parameters				
ISI total score	19.3 ± 3.1	19.0 ± 3.0	20.2 ± 3.0	0.04
Sleep diary variables				
TST	318.1 ± 83.6	312.9 ± 81.9	315.4 ± 98.7	0.89
SE	66.4 ± 16.6	67.0 ± 17.0	67.0 ± 17.2	1.00
Actigraph variables				
TST	402.4 ± 77.0	402.1 ± 69.2	386.3 ± 84.8	0.33
SE	82.6 ± 11.0	84.3 ± 7.6	81.7 ± 15.1	0.34
Anxiety and depression				
HAMD [d]	10.3 ± 4.1	10.5 ± 4.0	10.1 ± 4.5	0.71
HADS-anxiety [d]	8.6 ± 4.2	8.6 ± 4.4	8.7 ± 4.0	0.89
HADS-depression [d]	8.5 ± 4.3	8.1 ± 4.3	9.3 ± 4.3	0.22
Expectation to acupuncture				
CTRS				
Confidence in effectiveness	4.5 ± 1.1	4.5 ± 1.0	4.8 ± 1.1	0.31
Confidence in recommending to others	4.4 ± 1.1	4.3 ± 1.0	4.6 ± 1.0	0.10
Perceived logic	4.7 ± 1.1	4.6 ± 0.9	4.8 ± 1.1	0.32
Likelihood of relieving other complaints	4.4 ± 1.0	4.4 ± 0.9	4.4 ± 1.2	0.93

CTRS, credibility of treatment rating scale; HADS, hospital anxiety and depression scale; HAMD, Hamilton depression rating scale; ISI, insomnia severity index; SE, sleep efficiency; TST, total sleep time.

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

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

[c] Only 110 participants reported on the previous acupuncture experience due to missing.

[d] Only 86 and 90 participants completed HAMD and HADS, respectively, because these two questionnaires were not used by all three randomized controlled trials.

Table 2. Factors associated with acupuncture response by univariate and multivariate logistic analysis

Variable	Univariate OR (95% CI)	*P* value	Multivariate OR (95% CI)	*P* value
ISI score	1.15 (1.00, 1.31)	0.04	1.12 (0.97, 1.28)	0.12
Educational attainment	1.23 (1.08, 1.39)	0.002	1.21 (1.06, 1.38)	0.004

ISI, insomnia severity index.