Title:Traditional Chinese medicine diagnosis and response to
acupuncture for insomnia: an analysis of two randomized
placebo-controlled trials

Name of authors:Ka-Fai CHUNG, MBBS, MRCPsych*,1Wing-Fai YEUNG, BCM, PhD 2Feona Chung-Yin LEUNG, BCM 1Shi-Ping Zhang, PhD 3

Name of department:1 Department of Psychiatry, University of Hong Kong, Hong
Kong SAR, China;2 School of Nursing, Hong Kong
Polytechnic University, Hong Kong SAR, China;3 School of
Chinese Medicine, Hong Kong Baptist University, Hong Kong
SAR, China.

*Correspondence: Dr. K.F. Chung, Clinical Associate Professor, Department of Psychiatry, University of Hong Kong, Pokfulam Road, Hong Kong SAR, China. Telephone: 852-22554487, Fax: 852-28551345, E-mail: <u>kfchung@hkucc.hku.hk</u>

Word count:

2362 words (excluding title page, abstract, references, and tables)

Number of figures: 0

Number of tables: 3

ABSTRACT

Introduction: Acupuncture is a commonly used complementary and alternative medicine therapy for insomnia. Traditional Chinese medicine (TCM) diagnosis is sometimes used to guide treatment decisions. This study aimed to examine whether TCM diagnosis and symptom clusters were related to acupuncture response in subjects with insomnia.

Methods: The sample included 207 participants diagnosed with *deficiency of both the heart and spleen, heart-kidney non-interaction, liver-qi stagnation transforming into fire, and hyperactivity of fire due to yin deficiency* who were allocated to real acupuncture and had follow-up data. Standardized electroacupuncture was administered 3 times per week for 3 weeks. Primary outcome measure was Insomnia Severity Index (ISI). Both total ISI score and a dichotomous measure of response were analyzed. A 92-item symptom checklist was used to assist TCM diagnosis. A final agreed TCM diagnosis was made based on 2 Chinese medicine practitioners.

Results: Participants with *liver-qi stagnation transforming into fire* had the highest response rate of 36.6% from baseline to 1-week posttreatment, while the lowest response rate occurred in *hyperactivity of fire due to yin deficiency* at 13.0%; however, the difference was not statistically significant. There was a significant negative correlation between ISI change score and ratings on weary limbs, sore knees, or backache ($\rho = -0.17$, P <0.05), but no significant relationships with other symptom clusters, tongue and pulse features.

Conclusion: The response to acupuncture was unrelated to TCM diagnosis, possibly because the *zang fu* system was not sensitive to detect individual difference in acupuncture or the acupuncture points chosen were non-specific.

Keywords: Insomnia; acupuncture; diagnosis; TCM; response

Trial registration number: #NCT01707706 and #NCT01891097.

INTRODUCTION

Insomnia is the most common sleep complaint, with approximately 20% of the general population worldwide suffering from insomnia symptoms associated with distress or daytime impairment at least 3 times per week that have lasted for more than 1 month [1,2]. Pharmacological treatment may be effective, but its use is limited due to concerns about side effects and dependence. Psycho-behavioral treatment is another possible option, but it is under-utilized because of the time-intensive nature and the requirement of active participation and treatment adherence. Faced with the limitations of pharmacological and psychobehavioral treatments, complementary and alternative medicine has been commonly used for insomnia [3]. Among the different treatment modalities, acupuncture is one of the most popular and safest procedures. There are several systematic reviews [4-6] and randomized controlled trials [7-12] on the efficacy and safety of acupuncture for insomnia. The overall findings suggest that acupuncture has a robust and durable effect and it is safe.

The physiological mechanisms of acupuncture on insomnia remains unclear, but it may be related to the sympatho-inhibitory, opioid, and melatonin systems [13,14]; however, it remains difficult to predict who will respond to acupuncture. The traditional Chinese medicine (TCM) theories have been used to explain the onset and persistence of insomnia. A recent systematic review showed that there were variations between practitioners in their TCM diagnosis, but *deficiency of both the heart and spleen, heart-kidney non-interaction,*

liver-qi stagnation transforming into fire, and hyperactivity of fire due to yin deficiency were the 4 most common TCM diagnoses in subjects with insomnia, accounting for roughly 60% of all diagnoses [15]. We have developed a 92-item checklist to record the sleep-related and non-sleep-related symptoms and signs and tongue and pulse features that are associated with insomnia, which could be used for TCM diagnosis [16]. As there have been no studies examining the relationship between TCM diagnosis and acupuncture response, we conducted a post-hoc analysis of 2 randomized controlled trials. The study aimed to examine whether TCM diagnosis and TCM symptom cluster were related to acupuncture response in subjects with insomnia.

METHODS

Subjects

Details of the studies can be found at www.ClinicalTrials.gov (identifiers: NCT01707706 and NCT01891097). The major inclusion criteria were (1) ethnic Chinese; (2) aged \geq 18 years; (3) having insomnia at least 3 nights per week for at least 3 months; and (4) fulfilling criteria A and B of the DSM-IV diagnosis of primary insomnia [17] in Study NCT01707706 or criteria A to E of the DSM-5 diagnosis of insomnia disorder [18] in Study NCT01891097. Study NCT01707706 investigated insomnia disorder with past major depressive episodes and required an Insomnia Severity Index (ISI) [19] score \geq 15 at baseline, while Study NCT01891097 examined insomnia disorder with or without past history of psychiatric

disorder and required sleep onset latency or wake after sleep onset > 30 minutes and sleep efficiency < 85% for at least 3 nights based on 1-week sleep diary. The exclusion criteria were (1) 17-item Hamilton Rating Scale for Depression (HDRS₁₇) [20] score > 18; (2) significant suicidal risk according to the HDRS₁₇ item on suicide (score \geq 3); (3) previous diagnosis of schizophrenia or other psychotic disorders; (4) current alcohol or substance use disorder; (5) any unstable psychiatric conditions or serious physical illnesses; (6) any sleep disorders, including sleep phase disorders, parasomnia, obstructive sleep apnea, defined as apnea-hypopnea index \geq 10, or periodic limb movement disorder, defined as periodic limb movement disorder index \geq 15, detected during screening or in-laboratory overnight polysomnography; and (7) currently pregnant or breast-feeding. Participants could continue using psychotropic medications, but no dosage increase was allowed. Acupuncture was provided free of charge and a HK\$200 (approximately US\$25) travel allowance was paid after completion of all study procedures.

Study procedure

The studies were reviewed and approved by the institutional review board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (UW 07-304 and UW 12-340). Subjects showing an interest in participation were initially assessed via telephone. After given written consent, subjects participated in a comprehensive face-to-face interview and were arranged laboratory-based overnight polysomnography. An experienced clinician took the sleep history and administered the Structured Clinical Interview for DSM-IV [21,22] to derive the psychiatric diagnoses and administered the HDRS₁₇. Chinese medicine practitioners who had at least 3 years' clinical experience formulated the TCM diagnosis with the help of a standardized symptom checklist [16]. A final agreed TCM diagnosis was made after discussion with a senior Chinese medicine practitioner. Study NCT01707706 had 150 participants randomized to acupuncture, minimal acupuncture, and placebo acupuncture in a ratio of 2:2:1 [7]. Study NCT01891097 randomized 224 participants to acupuncture, combined acupuncture and auricular acupuncture, and waitlist in a ratio of 3:3:1. Of the 252 subjects who received real acupuncture, including acupuncture or combined treatment, 243 (96.4%) had TCM diagnoses available. Of the 11 different TCM diagnoses made, only the 4 most common TCM patterns: *deficiency of both the heart and spleen, heart-kidney non-interaction, liver-qi stagnation transforming into fire,* and *hyperactivity of fire due to yin deficiency* had adequate numbers for between-diagnosis comparison (n = 207).

Intervention

The acupuncture points used included bilateral Ear Shenmen, Sishencong (EX-HN1), Anmian (EX), Neiguan (PC6), Shenmen (HT7), Sanyinjiao (SP6) and unilateral Yintang (EX-HN3) and Baihui (GV20). The traditional Chinese medicine style of acupuncture was adopted. The acupuncture points on the head, hands, and legs and those on the ears were treated using 0.25×25 mm and 0.20×25 mm stainless steel disposable needles, respectively (Suzhou Shenlong Medical Apparatus, Tai Chi, China). The depth of insertion was between 2 mm and 25 mm, depending on the acupuncture points. Degi was achieved if possible. Surgical tapes or hair pins were used to secure the needles. An electric stimulator (ITO ES160, Japan) was connected to all needles and delivered a constant current, 0.4-ms, squarewave, brief-pulse stimulus of 4 Hz frequency. The needles were left for 30 minutes and then removed. For subjects who received combined acupuncture and auricular acupuncture, borneol crystals were placed at Ear Shenmen, Heart, Kidney, Liver, Spleen, Occiput, and Subcortex and secured using adhesive plaster. Subjects were asked to press the borneol crystals lightly for 5 minutes in the morning, afternoon, and evening everyday, and remove them after 48 hours. The acupuncture and auricular point selection was based on expert opinion, systematic reviews [4,15,23] and our previous studies [7-9]. 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.

Measures

Socio-demographic variables and medical and psychiatric history

Participants reported their age, gender, years of full-time education, marital status, occupation, insomnia duration, and medical and psychiatric history.

Insomnia Severity Index (ISI)

The ISI is a 7-item self-rating scale that was used to assess the perceived severity of insomnia symptoms and the associated functional impairment in the previous week [19]. The scale is a 5-point Likert scale with anchor points ranging from "none" to "very severe", "very satisfied" to "very dissatisfied" and "not at all noticeable, worried, or interfering" to "very much noticeable, worried, or interfering". The total score ranges from 0 to 28. We used the change scores from baseline to posttreatment as indexes of treatment response. A dichotomous measure of response, defined as an improvement by 8 points or more was used, which was similar to previous studies [24,25]. The Chinese version of ISI, known to be valid and reliable, was used in this study [26].

17-item Hamilton Rating Scale for Depression (HDRS17)

The HDRS₁₇ is one of the most common clinician-administered scales to assess the severity of depression and the associated symptoms [20]. Higher scores indicate more severe depression over the past week.

Insomnia symptom checklist for TCM diagnosis

The 92-item checklist consists of 13 sleep-related, 61 non-sleep-related, 11 tongue, and 7 pulse items. The development of the checklist was based on a systematic review of the 10 most common TCM patterns of insomnia [16]. The non-sleep-related items were further subdivided under symptom clusters: eating, taste and appetite (12 items), emotions (11

items), chest and abdominal function (8 items), bladder and bowel function (6 items), headache, dizziness and tinnitus (6 items), coldness, hotness and sweating (5 items), menstruation and sexual function (4 items), complexion (4 items), limbs and back (3 items), and energy (3 items). The items were rated as 0 or 1, denoting absence or presence. The score of each cluster was generated by summing the score of each item.

Statistical analysis

We used SPSS version 23 (IBM Corp) for statistical analysis. Non-parametric tests were used in view of the skewed distribution of the ISI change score and TCM symptom cluster scores. Kruskal-Wallis test was used to compare the ISI change scores between TCM patterns. Chisquare test was used to examine the proportion of responders in each TCM pattern. Correlation between ISI change score and TCM symptom scores was preformed using Spearman correlation. Comparison of ISI change scores between subjects with or without particular tongue and pulse features was made using Wilcoxon rank-sum test.

RESULTS

One-hundred and fifty subjects were randomized in Study NCT01707706 (Supplementary Figure 1) and 224 subjects in Study NCT01891097 (Supplementary Figure 2). Among the 374 subjects, 207 were included in the secondary analysis. Their mean age was 52.5 years

and 76.8% were female (Table 1). The mean ISI and HDRS₁₇ score was 19.3 and 7.4, respectively, indicating moderate to severe insomnia and roughly half of the participants were in remission of depression, defined as a HDRS₁₇ score \leq 7. There was no significant difference in sociodemographic and clinical variables between TCM diagnoses.

Table 2 presents the changes in ISI score by TCM diagnosis. The mean change score of the sample was 4.7 from baseline to 1-week posttreatment, with 54 of 205 participants (26.3%) met the remission criterion, defined as an improvement by at least 8 points on the ISI. From baseline to 4-week posttreatment, the mean change score was 4.5, while 41 of 156 participants (26.3%) satisfied the remission criterion. Participants with *liver-qi stagnation transforming into fire* had the highest response rate of 36.6% from baseline to 1-week posttreatment, while *hyperactivity of fire due to yin deficiency* had the lowest response rate of 13.0%. However, there was no significant difference in ISI change score and remission rate between TCM diagnoses.

The correlations between ISI change score and TCM symptom cluster scores are shown in Table 3. There was a significant negative correlation between ISI change score from baseline to 4-week posttreatment with the limbs and back symptom cluster score. The presence of weary limbs, sore knees, and backache, the 3 items in the limbs and back symptom cluster, was associated with lesser improvement after acupuncture. The common tongue features included pale tongue, red tongue, thin, white, and yellow coating, and their prevalence were 29.4%, 30.9%, 78.4%, 46.1%, and 44.6%, respectively, while the common pulse features were fine, slippery, string-like, and sunken pulse, with prevalence at 72.1%, 49.0%, 72.1%, and 44.1%, respectively. However, the presence or absence of the tongue and pulse features was not associated with improvement from baseline to 1-week posttreatment and 4-week posttreatment (data not shown).

DISCUSSION

The present study showed that the TCM diagnoses in patients with insomnia were unable to predict their response to acupuncture. There are 2 possible explanations: first, the classification used in the study relies heavily on the *zang fu* system. Although it is instrumental for Chinese herbal medicine therapies, the *zang fu* system may not be applicable to acupuncture, hence it lacks the sensitivity in demonstrating differences in response. Further studies should explore whether a better system is available. In fact, our finding was in line with a systematic review on pattern-based treatments for insomnia, which showed similar effective rates of acupuncture across TCM diagnoses, albeit the poor methodological quality of the studies included in the review [15]. Secondly, the acupuncture points used in our study have been empirically used for insomnia regardless of TCM diagnosis. A previous systematic review showed that variations in the selection of acupuncture points were common between

practitioners. Disagreement was the greatest for *heart-kidney non-interaction* and *liver-qi stagnation transforming into fire*, but several acupuncture points were commonly used, including Shenmen (HT7), Yintang (EX-HN3), Sanyinjiao (SP6), Baihui (GV20), Anmian (EX) and Sishencong (EX-HN1) [15]. These acupuncture points were all included in our study, which might be an explanation for the similar response rates across TCM diagnoses.

We found that the presence of certain symptoms, including weary limbs, sore knees, and backache, was associated with lesser improvement after a course of acupuncture in patients with insomnia. The musculoskeletal symptoms are recognized as *kidney deficiency* according to the TCM theory. It will be interesting to further examine the response to acupuncture in patients with insomnia and *kidney deficiency* as compared to other TCM diagnoses.

According to the results of previous studies, the response to acupuncture was indeed difficult to predict. Across different conditions, only treatment expectation and baseline severity were more consistently shown to be predictors of acupuncture response [27,28]. On the contrary, the response to placebo acupuncture might be easier to predict. In our secondary analyses of 3 randomized placebo-controlled trials, we found that greater baseline insomnia severity, longer total sleep time, lesser discrepancy between subjectively and objectively-derived total sleep time, and higher treatment expectation were predictors to placebo acupuncture, while greater baseline insomnia severity and higher educational level were predictors to real

acupuncture [24]. The notion is that when a combination of specific and non-specific factors is in place, as in real acupuncture, the situation may be more difficult to predict than treatments possessing predominately non-specific effects.

There are several limitations in our study. First, the acupuncture protocol was standardized, with no reference to TCM diagnosis and other clinical factors, which is different from the usual clinical practice; thereby limiting the power to detect differences in response. Secondly, despite pooling 2 RCTs, the sample size is still small and may not have enough statistical power to reveal potential differences. Finally, the use of multiple correlations may have produced chance association between ISI change score and the limbs and back symptom cluster score.

In conclusion, there was no difference in the response rate to acupuncture in subjects with chronic insomnia diagnosed with different TCM patterns. A possible association between *kidney deficiency* and lesser improvement was detected, but the finding should be considered as preliminary. Instead of relying on the *zang fu* system, future studies should explore using other TCM diagnostic systems as pre-treatment assessment in patients receiving acupuncture. The question whether pattern-based individualized acupuncture is better than standardized acupuncture remains unanswered in the treatment of insomnia.

Funding

#NCT01707706 and #NCT01891097 were funded by Health and Medical Research Fund, Food and Health Bureau, Hong Kong.

Competing interests

None

REFERENCES

- 1. Chung KF, Yeung WF, Ho FY, *et al.* Cross-cultural and comparative epidemiology of insomnia: the Diagnostic and statistical manual (DSM), International classification of diseases (ICD) and International classification of sleep disorders (ICSD). *Sleep Med* 2015;16(4):477-82.
- 2. Roth T, Coulouvrat C, Hajak G, *et al.* Prevalence and perceived health associated with insomnia based on DSM-IV-TR; International Statistical Classification of Diseases and Related Health Problems, Tenth Revision; and Research Diagnostic Criteria/International Classification of Sleep Disorders, Second Edition criteria: results from the America Insomnia Survey. *Biol Psychiatry* 2011;69(6):592-600.
- **3.** Yeung WF, Chung KF, Yung KP, *et al.* The use of conventional and complementary therapies for insomnia among Hong Kong Chinese: a telephone survey. *Complement Ther Med* 2014;22(5):894-902.
- **4.** Yeung WF, Chung KF, Leung YK, *et al.* Traditional needle acupuncture treatment for insomnia: a systematic review of randomized controlled trials. *Sleep Med* 2009;10(7):694-704.
- 5. Cheuk DK, Yeung WF, Chung KF, *et al.* Acupuncture for insomnia. *Cochrane Database Syst Rev* 2012;9:CD005472.
- 6. Huang W, Kutner N, Bliwise DL. A systematic review of the effects of acupuncture in treating insomnia. *Sleep Med Rev* 2009;13(1):73-104.
- 7. Chung KF, Yeung WF, Yu YM, *et al.* Acupuncture for residual insomnia associated with major depressive disorder: a placebo- and sham-controlled, subject- and assessor-blind, randomized trial. *J Clin Psychiatry* 2015;76(6):e752-60.
- 8. Yeung WF, Chung KF, Tso KC, *et al.* Electroacupuncture for residual insomnia associated with major depressive disorder: a randomized controlled trial. *Sleep* 2011;34(6):807-15.
- 9. Yeung WF, Chung KF, Zhang SP, *et al.* Electroacupuncture for primary insomnia: a randomized controlled trial. *Sleep* 2009;32(8):1039-47.
- **10.** Kim YS, Lee SH, Jung WS, *et al.* Intradermal acupuncture on shen-men and nei-kuan acupoints in patients with insomnia after stroke. *Am J Chin Med* 2004;32(5):771-8.
- **11.** Lee SY, Baek YH, Park SU, *et al.* Intradermal acupuncture on shen-men and nei-kuan acupoints improves insomnia in stroke patients by reducing the sympathetic nervous activity: a randomized clinical trial. *Am J Chin Med* 2009;37(6):1013-21.
- 12. Hughes CM, McCullough CA, Bradbury I, *et al.* Acupuncture and reflexology for insomnia: a feasibility study. *Acupunct Med* 2009;27(4):163-8.
- **13.** Huang W, Kutner N, Bliwise DL. Autonomic activation in insomnia: the case for acupuncture. *J Clin Sleep Med* 2011;7(1):95-102.
- **14.** Zhao K. Acupuncture for the treatment of insomnia. *Int Rev Neurobiol* 2013;111:217-34.
- **15.** Yeung WF, Chung KF, Poon MM, *et al.* Prescription of chinese herbal medicine and selection of acupoints in pattern-based traditional chinese medicine treatment for insomnia: a systematic review. *Evid Based Complement Alternat Med* 2012;2012:902578.
- 16. Poon MM, Chung KF, Yeung WF, *et al.* Classification of insomnia using the traditional chinese medicine system: a systematic review. *Evid Based Complement Alternat Med* 2012;2012:735078.

- 17. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders* (DSM-IV.). Washington, DC: American Psychiatric Publishing, 1994.
- **18.** American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5.). Arlington, VA: American Psychiatric Publishing, 2013.
- **19.** Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med* 2001;2(4):297-307.
- **20.** Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56-62.
- **21.** Spitzer RL, Williams JB, Gibbon M, *et al.* The Structured Clinical Interview for DSM-III-R (SCID). I: History, rationale, and description. *Arch Gen Psychiatry* 1992;49(8):624-9.
- **22.** So E, Leung C, Chung D, *et al.* The Chinese-bilin⁻gual SCID-I/P Project: Stage 1 reliability for mood disorders and schizophrenia. *Hong Kong J Psychiatry* 2003;13(1):7-18.
- **23.** Yeung WF, Chung KF, Poon MM, *et al.* Acupressure, reflexology, and auricular acupressure for insomnia: a systematic review of randomized controlled trials. *Sleep Med* 2012;13(8):971-84.
- 24. Yeung WF, Chung KF, Yu BY, *et al.* Response to placebo acupuncture in insomnia: a secondary analysis of three randomized controlled trials. *Sleep Med* 2015;16(11):1372-6.
- **25.** Morin CM, Vallieres A, Guay B, *et al.* Cognitive behavioral therapy, singly and combined with medication, for persistent insomnia: a randomized controlled trial. *JAMA* 2009;301(19):2005-15.
- 26. Chung KF, Kan KK, Yeung WF. Assessing insomnia in adolescents: comparison of Insomnia Severity Index, Athens Insomnia Scale and Sleep Quality Index. *Sleep Med* 2011;12(5):463-70.
- 27. Chen LX, Mao JJ, Fernandes S, *et al.* Integrating acupuncture with exercise-based physical therapy for knee osteoarthritis: a randomized controlled trial. *J Clin Rheumatol* 2013;19(6):308-16.
- **28.** Glazov G. The influence of baseline characteristics on response to a laser acupuncture intervention: an exploratory analysis. *Acupunct Med* 2010;28(1):6-11.

		Deficiency of	Liver-qi stagnation	Hyperactivity	
	Heart-kidney	both the heart and	transforming into	of fire due to	
	noninteraction	spleen	fire	yin deficiency	Total
Variables	(n = 80)	(n = 62)	(n = 41)	(n = 24)	(n = 207)
Age, y	54.2 ± 9.3	51.7 ± 9.6	50.7 ± 10.9	51.5 ± 9.4	52.5 ± 9.7
Sex, male/female	13/67	15/47	14/27	6/18	48/159
Education attainment, y	10.1 ± 3.9	11.0 ± 3.0	11.5 ± 3.7	12.1 ± 3.7	10.9 ± 3.6
Marital status					
Never married	8 (10.0)	9 (14.5)	5 (12.2)	4 (16.7)	26 (12.6)
Married/cohabiting	61 (76.3)	42 (67.7)	26 (63.4)	13 (54.2)	142 (68.6)
Divorced/widowed	11 (13.8)	11 (17.7)	10 (24.4)	7 (29.2)	39 (18.8)
Occupation					
Professional and					
associate professional	8 (10.0)	3 (4.8)	1 (2.4)	5 (20.8)	17 (8.2)
Skilled and semi-skilled					
worker	17 (21.3)	11 (17.7)	10 (24.4)	5 (20.8)	44 (20.8)
Unskilled worker	8 (10.0)	6 (9.7)	4 (9.8)	1 (4.2)	19 (9.2)
Retired	16 (20.0)	10 (16.1)	7 (17.1)	4 (16.7)	37 (17.9)
Unemployed/housework	31 (38.8)	32 (51.6)	19 (46.3)	9 (37.5)	92 (44.0)
Insomnia duration, y	11.4 ± 10.3	13.1 ± 9.9	10.4 ± 8.5	9.9 ± 8.3	11.5 ± 9.7
Lifetime psychiatric disorder					
Insomnia disorder	41 (51.3)	33 (53.2)	16 (39.0)	11 (45.8)	101 (48.8)
MDD/MADD	29 (36.3)	27 (43.5)	22 (53.7)	12 (50.0)	90 (43.5)
Anxiety disorders/other					
diagnoses	10 (12.5)	2 (3.2)	3 (7.3)	1 (4.2)	16 (7.7)
Chronic medical illnesses ^a	19 (23.8)	18 (29.0)	15 (36.6)	5 (20.8)	57 (27.5)
ISI total score	18.9 ± 4.3	19.3 ± 3.5	20.0 ± 3.8	19.0 ± 3.8	19.3 ± 3.9
HDRS ₁₇ total score	6.8 ± 2.8	7.6 ± 4.0	8.3 ± 4.5	7.7 ± 4.0	7.4 ± 3.7

Table 1. Sample characteristics

Abbreviations: HDRS₁₇, 17-item Hamilton depression rating scale; ISI, Insomnia severity index; MDD, major depressive disorder; MADD, mixed anxiety depressive disorder.

Data are expressed in mean \pm SD or n (%).

^a Participants were on regular medications for the medical illnesses.

	Heart-kidney non- interaction	Deficiency of both the heart and spleen	Liver-qi stagnation transforming into fire	Hyperactivity of fire due to yin deficiency	Chi-square	Р
T0-T1 (N = 205)	N = 80	N = 61	N = 41	N = 23		
ISI total change score	4.9 ± 5.1	3.7 ± 4.2	5.7 ± 5.3	4.8 ± 6.5		0.35
ISI change score ≥ 8	23 (28.8)	13 (21.3)	15 (36.6)	3 (13.0)	5.35	0.15
T0-T2 (N = 156)	N = 58	N = 50	N = 31	N = 17		
ISI total change score	4.1 ± 4.6	3.9 ± 4.7	5.4 ± 4.1	5.9 ± 5.8		0.30
ISI change score ≥ 8	14 (24.1)	11 (22.0)	11 (35.5)	5 (29.4)	2.05	0.56

Table 2. Insomnia severity index (ISI) change scores by traditional Chinese medicine diagnosis

Values are expressed in mean \pm SD or n (%). P values based on Kruskal-Wallis test or Chi-square test T0 = baseline; T1 = 1-week posttreatment; T2 = 4-week posttreatment.

	ISI change score (T0-T1)	ISI change score (T0-T2)
Sleep-related	0.06	-0.06
Eating, taste and appetite	0.09	0.01
Emotions	0.08	-0.04
Chest and abdominal function	-0.002	-0.06
Bladder and bowel function	0.13	-0.03
Headache, dizziness and tinnitus	0.07	0.01
Coldness, hotness and sweating	-0.001	0.05
Menstruation and sexual function	0.001	0.06
Complexion	0.10	0.03
Limbs and back	-0.10	-0.17*
Energy	-0.05	-0.01
Sleep and non-sleep-related	0.07	-0.03

Table 3. Spearman's rho between insomnia severity index (ISI) change score and traditional Chinese medicine symptom cluster scores

* p < 0.05. T0 = baseline; T1 = 1-week posttreatment; T2 = 4-week posttreatment.







Supplementary Figure 2. Participant flowchart for study NCT01891097