See commentaries by Mischoulon and Kong

Acupuncture for Residual Insomnia Associated With Major Depressive Disorder: A Placebo- and Sham-Controlled, Subject- and Assessor-Blind, Randomized Trial

Ka-Fai Chung, MRCPsych; Wing-Fai Yeung, PhD; Yee-Man Yu, BSocSc; Kam-Ping Yung, MPhil; Shi-Ping Zhang, PhD; Zhang-Jin Zhang, PhD; Man-Tak Wong, MRCPsych; Wing-King Lee, MRCPsych; and Lai-Wah Chan, MRCPsych

ABSTRACT

Objective: To evaluate the efficacy and safety of acupuncture for residual insomnia and other residual symptoms associated with major depressive disorder (MDD).

Method: 150 participants having significant insomnia for more than 3 months and a history of MDD (both based on *DSM-IV-TR* criteria) were recruited from 4 psychiatric outpatient clinics in Hong Kong from May 2011 to August 2013 to receive 9 sessions of treatment over 3 weeks. They were randomized to receive acupuncture, minimal acupuncture, or placebo acupuncture. Primary outcome was sleep diary–derived sleep efficiency. Secondary outcomes included other sleep diary parameters, actigraphy, anxiety and depressive symptoms, daytime functioning, and adverse events.

Results: The mean difference in sleep diary–derived sleep efficiency at 1-week posttreatment was −1.40 (95% CI, −7.08 to 4.28) between the acupuncture and minimal acupuncture groups and was 3.10 (95% CI, −3.64 to 9.84) between the acupuncture and placebo acupuncture groups. A χ^2 test showed that acupuncture produced a significantly higher proportion of participants achieving sleep-onset latency ≤ 30 minutes than did minimal acupuncture at 1-week posttreatment ($P = .04$). However, there was no significant between-group difference in most of the other outcomes. Treatment blinding was successful, as a majority of participants did not know which treatment they had received.

Conclusions: Acupuncture was well tolerated, but the efficacy was only mild and similar to that of minimal acupuncture and placebo acupuncture. A high proportion of patients remained clinically significantly affected by insomnia after treatment. The finding raises certain doubts about the value of acupuncture and underscores the difficulties in the treatment of residual insomnia in MDD.

Trial Registration: ClinicalTrials.gov identifier: NCT01707706

J Clin Psychiatry 2015;76(6):e752–e760

Submitted: *March 10, 2014; accepted June 24, 2014 (doi:10.4088/JCP.14m09124).*

Corresponding author: *K. F. Chung, MRCPsych, Department of Psychiatry, The University of Hong Kong, Pokfulam Rd, Hong Kong SAR, China (kfchung@hkucc.hku.hk).*

Major depressive disorder (MDD) is a debilitating illness with lifetime prevalence at around 16% and a recurrence rate of 50%.[1] A sizable proportion of patients with MDD partially respond to antidepressants and are left with residual depressive symptoms.[2] Insomnia is one of the most common and clinically important residual symptoms associated with MDD. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study showed that the most common domain of residual depressive symptom was insomnia, which occurred in 94.6% of MDD patients who responded without remitting after up to 12 weeks of citalopram treatment.[3] There have been limited studies on the treatment of residual insomnia after full or partial remission of depression. On the basis of the available evidence, both pharmacologic and psychological treatments may help,[4–6] but the use of pharmacotherapy is limited by its adverse events and potential risks of abuse and dependence.[7] Psychological treatment has remained underutilized because of the time-intensive nature and requirement of active participation.[8]

Faced with the limitations of the currently available treatment, researchers have tested acupuncture as an adjunct therapy for residual insomnia associated with MDD.[9] Acupuncture is one of the most popular and safest complementary and alternative medicine therapies. To treat illnesses, the acupuncturist inserts fine needles at special points on the body. Stimulation of the acupuncture points can be performed manually or via electric currents. There have been multiple anecdotal reports and clinical studies,[10] including 2 randomized placebo-controlled trials[9,11] from our center on the efficacy of acupuncture for insomnia. In the study[9] on residual insomnia associated with MDD, we found that acupuncture was more efficacious than placebo control, but it had similar efficacy compared to minimal acupuncture. Placebo acupuncture uses placebo needles to mimic "real" acupuncture. A placebo needle has a blunt tip and retractable copper handle. When its tip touches the skin, a pricking sensation is felt, and the needle moves inside the handle and appears to be shortened, simulating the puncturing of the skin. A previous study[12] showed that the credibility of placebo needle is high, particularly in acupuncture-naive subjects. Minimal acupuncture is a sham intervention that avoids therapeutic needle points and *deqi*, a radiating feeling indicative of effective needling. There remain some unanswered questions from our study. First, it was a single-site randomized controlled trial (RCT). Second, the acupuncture regimen did not include needle points on the limbs such as Sanyinjiao (SP6) and Neiguan (PC6), which were also commonly used for insomnia.[13] The third unanswered question relates to the physiological mechanism of acupuncture. In our previous study,[9] participants in the minimal acupuncture group were needled superficially at points located on the limbs, while in the acupuncture

Clinical Points

- Treatment of residual insomnia associated with major depression is challenging. As pharmacotherapy and cognitive-behavioral therapy have limitations, acupuncture has been used for the treatment of insomnia.
- Our findings do not support traditional needle acupuncture being superior to minimal acupuncture and placebo acupuncture as adjunct therapy for residual insomnia associated with depression. A relatively mild hypnotic effect was produced, and it was most likely due to the nonspecific effects of acupuncture. Further studies using individualized acupuncture are needed.

group, points on the cranial region were needled. Since the somatosensory receptors and neural pathways mediating the acupuncture-evoked afferent impulses to subcortical and cortical areas are different for needling on the limbs with needling on the cranial region,[14] to test the specificity of acupuncture points, it is necessary to compare points that are similarly located but considered effective or ineffective based on the traditional Chinese medicine (TCM) theory.

Therefore, in the present study, we adopted an acupuncture regimen using specific acupuncture points on both the cranial region and the limbs, hoping to enhance the efficacy of acupuncture for insomnia. We compared "real" and "sham" acupuncture by needling at comparable sites, which aimed to provide more scientific data about the values of specific acupuncture points and *deqi* in acupuncture. The hypothesis was that acupuncture was more efficacious than minimal acupuncture and placebo acupuncture for the treatment of residual insomnia in MDD.

METHOD

Study Design

The study was a placebo- and sham-controlled, subject- and assessor-blinded randomized trial. Major assessments were at baseline, 1-week posttreatment, and 5-week posttreatment. We followed the CONSORT[15] and STRICTA[16] recommendations in designing and reporting of controlled trials and acupuncture studies. The study was registered at ClinicalTrials.gov (identifier: NCT01707706).

Participants

Patients were recruited from May 2011 to August 2013 at 4 regional psychiatric outpatient clinics in Hong Kong. The inclusion criteria were patients who (1) were ethnic Chinese; (2) were aged 18–70 years; (3) had a previous diagnosis of MDD based on *DSM-IV-TR* criteria, as assessed by a clinician using the Structured Clinical Interview for the *DSM-IV*; (4) fulfilled criteria A and B of the *DSM-IV* diagnosis of primary insomnia, meaning that participants had to have a predominant complaint of sleep difficulty associated with significant distress or functional impairment; (5) had insomnia ≥ 3 nights per week for at least 3 months; (6) had an Insomnia Severity Index (ISI) score ≥ 15 at screening and baseline; and (7) had been taking the same antidepressants at a fixed dose for at least 12 weeks prior to baseline and during the study.

Subjects were excluded if they: (1) had a 17-item Hamilton Depression Rating Scale ($HDRS_{17}$) score > 18 at screening and baseline; (2) had an apnea-hypopnea index ≥ 10 or a periodic limb movement disorder index ≥ 15 as assessed by in-laboratory overnight polysomnography; (3) had significant suicidal risk according to the $HDRS_{17}$ item on suicide (score ≥ 3); (4) had a previous diagnosis of schizophrenia, other psychotic disorders, or bipolar disorder; (5) had current alcohol or substance use disorder; (6) were pregnant, breast-feeding, or of childbearing potential but not using adequate contraception; (7) had infection or abscess close to the sites of selected acupuncture points; (8) had any serious illness; (9) had any acupuncture in the past 12 months; (10) took Chinese herbal medicine or over-the-counter drugs intended for insomnia within 2 weeks prior to baseline or during the study; or (11) took hypnotics at an increased dose within 4 weeks prior to baseline or during the study. Acupuncture was provided free of charge. A HK $200 (US $26) travel allowance was paid for participation after completion of all study procedures.

Study Procedure

All procedures used in the present study were reviewed and approved by the local institutional review board. Subjects showing an interest in participation were initially assessed via telephone. After giving written informed consent, potential subjects participated in a comprehensive face-to-face interview. Laboratory-based overnight polysomnography (Alice 4 Diagnostics System, Respironics, Atlanta, Georgia) was arranged to rule out specific sleep disorders. Participants refusing the test but who were considered unlikely to have any specific sleep disorders by the author (K.F.C.) based on clinical features could be exempted. Polysomnography-derived sleep variables were analyzed according to the standard Rechtschaffen and Kales criteria[17] by a registered polysomnographic technologist.

The subjects completed a 1-week sleep diary and actigraphy in the week prior to a scheduled baseline visit. Eligible subjects were randomly assigned to acupuncture, minimal acupuncture, or placebo acupuncture in a ratio of 2:2:1 by an independent administrator using a computer-generated list of numbers with a block size of 10, and they received their first treatment on the same day. The treatment allocation codes were kept in opaque envelopes and known only to the acupuncturists.

The subjects were told that, in this study, different types of acupuncture would be compared. They were told that "traditional acupuncture" was based on the TCM theory, "nontraditional acupuncture" did not follow the principles of TCM but was also associated with positive outcomes in clinical studies, and "placebo acupuncture" was a procedure that mimicked the real acupuncture procedure. Due to the nature of the intervention, it was not possible to blind the acupuncturists in this study. The assessment of depressive symptoms, past psychiatric history, and antidepressant

treatment history was conducted by an experienced clinician (K.F.C.) who was blind to the subjects' group allocation. The analyses of questionnaires, sleep diaries, and actigraphy results were conducted by independent investigators who were blind to group allocation.

Intervention

Subjects were treated 3 times per week for 3 consecutive weeks. All acupuncture treatments were performed in a quiet treatment room by the same acupuncturist, who was a registered Chinese medicine practitioner with at least 3 years of clinical experience of providing acupuncture treatment. There was a change in acupuncturist after the first quarter of the study period, as the first acupuncturist resigned from the post. To ensure quality of acupuncture treatment, the first 5 treatment sessions in each group (n = 15) were supervised by our senior acupuncturists (S.P.Z. and Z.J.Z.). The thrice-weekly treatment schedule, same as in our previous studies,[9,11] was selected to enhance treatment adherence, while the 3-week treatment duration was chosen to examine the short-term effect of acupuncture. The subjects had to receive a minimum of 4 treatments in 2 consecutive weeks; otherwise, they would be advised termination of study. In addition, they were advised to continue the same type and dosage of antidepressants throughout the study period. Sedatives, anxiolytics, and hypnotics could be continued during the study period. Dose escalation was disallowed, but dose reduction due to symptom improvement was allowed. Individual psychotherapy could be continued if it was ongoing prior to the study. Introduction of any new insomnia treatment during the study period was disallowed.

Acupuncture. Subjects were needled at bilateral Ear Shenmen, Sishencong (EX-HN1), Anmian (EX), Neiguan (PC6), Shenmen (HT7), Sanyinjiao (SP6), and unilateral Yintang (EX-HN3) and Baihui (GV20). The TCM style of acupuncture was adopted. The acupuncture points on the head, hands, and legs were treated using 0.25 × 25-mm needles, while those on ears were treated using 0.20 × 25-mm needles (Suzhou Shenlong Medical Apparatus Co, Ltd; Tai Chi, China); the depth of insertion was between 2 mm and 25 mm, depending on the points selected. The acupuncture point selection was based on expert opinion, systematic reviews,[10,13] and our previous studies[9,11] of acupuncture for insomnia. *Deqi* 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, square-wave, brief-pulse stimulus of 4-Hz frequency to the subjects. The needles were left for 30 minutes and then removed.

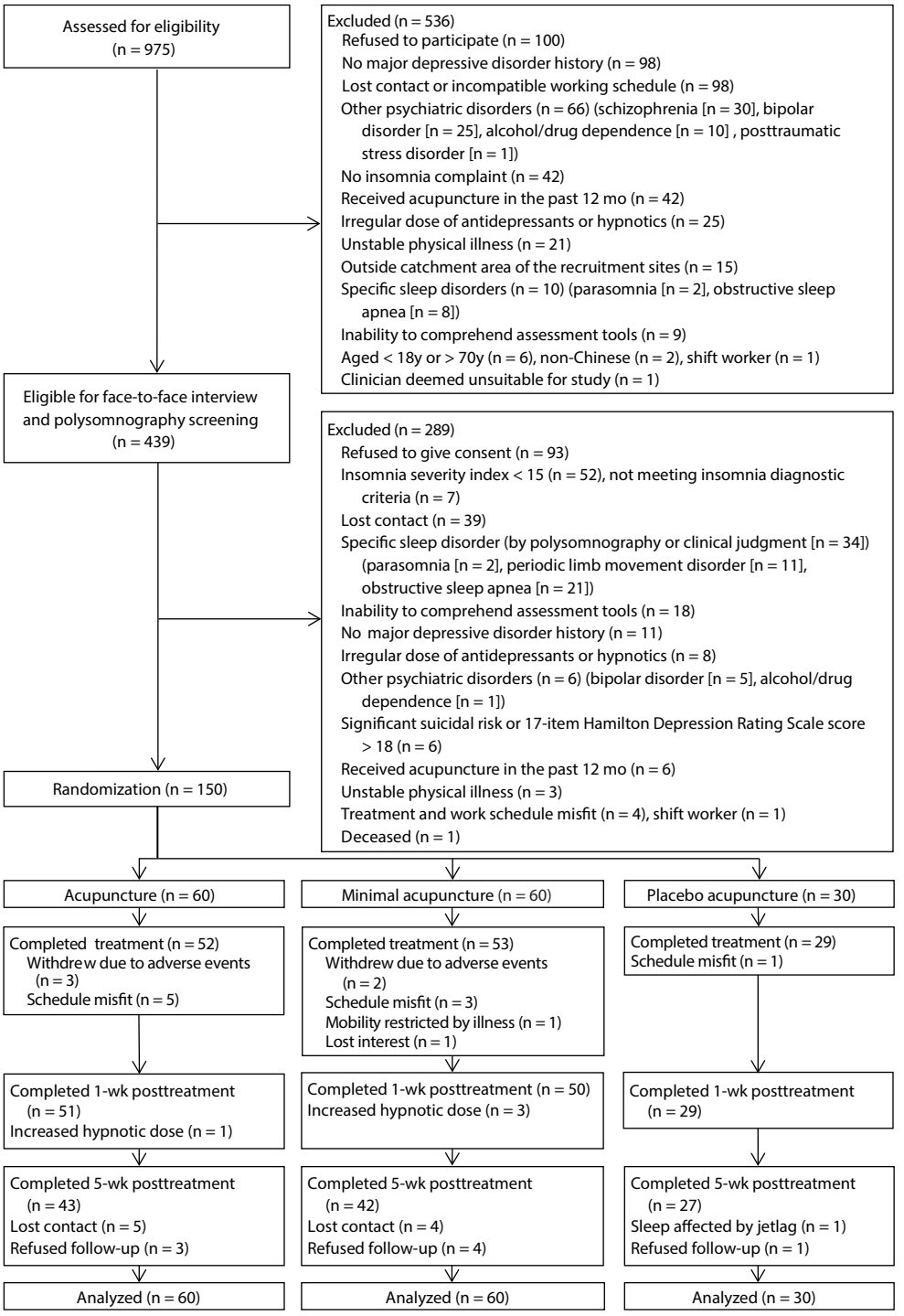
Minimal acupuncture. Subjects were needled at points that have no therapeutic effects according to the TCM theory and superficially to avoid *deqi*. The points on limbs included bilateral "forearm," 1 inch lateral to the middle point between Shaohai (HE3) and Shenmen (HE7); "upper arm," 1 inch lateral to Tianfu (LU 3); and "lower leg," 0.5 inch dorsal to Xuanzhong (GB39). For points on head, the points included bilateral "head," the middle point between Shuaigu (GB8) and Touwei (ST8); "forehead," the middle point between Touwei (ST8) and Yangbai (GB14); "neck," the middle point between Tianyou (TB16) and Tianrong (SI17); and "ear," a point on the helix, inferior to the apex. The points selected had been used in previous acupuncture studies as sham controls.[18,19] Other treatment conditions and electrostimulation were the same as in the acupuncture group.

Placebo acupuncture. Streitberger placebo needles[20] were placed at sites 1 inch beside the acupuncture points used in the acupuncture group, with the aim of avoiding acupressure effect. The needles were connected to an electric stimulator but with zero frequency and amplitude.

Measures

The primary outcome was the sleep diary–derived sleep efficiency, calculated as total sleep time divided by time in bed expressed in percentage. Sleep efficiency was chosen as the primary outcome because it is a recognized summary index of insomnia. Secondary outcomes included other sleep diary parameters, actigraphy measures, ISI,[21] Pittsburgh Sleep Quality Index (PSQI),[22] $HDRS_{17}$,[23] Hamilton Anxiety Rating Scale (HARS),[24] Hospital Anxiety and Depression Scale (HADS),[25] Somatic Symptom Inventory (SSI),[26] Sheehan Disability Scale (SDS),[27] Multidimensional Fatigue Inventory (MFI),[28] Epworth Sleepiness Scale (ESS),[29] and 36-item Short Form Health Survey (SF-36).[30] Sleep diary, ISI, and PSQI are standard self-report measures of sleep and insomnia symptoms.[31] Sleep quality was reported as very good, fairly good, fairly bad, or very bad on the sleep diary. Sleep diary–derived sleep efficiency of at least 85% or sleep-onset latency or wake time after sleep onset of 30 minutes or less are commonly used cutoff values for good sleep. The total score of ISI ranges from 0 to 28; a score above 14 indicates moderate insomnia. The PSQI score ranges from 0 to 21; a cutoff of 5 is most sensitive and specific to detect insomnia.[31] Actigraphs (Model Actiwatch-2; Respironics Inc; Murrysville, Pennsylvania) are watchlike devices that record physical movement by means of an accelerometer-microprocessor link. Because movement correlates with wakefulness and lack of movement with sleep, wrist actigraphy has been shown to be a valid objective measure of sleep.[32] In this study, actigraphs were worn 24 hours per day on the nondominant wrist for 1 week prior to each study visit. Epoch recording length was set at 1 minute, and data were analyzed with Actiware software (Version 5, Respironics Inc). The clinician-administered $HDRS_{17}$ and HARS and the self-report HADS were used to assess residual symptoms associated with MDD. The SSI, MFI, ESS, SDS, and SF-36 are self-report questionnaires used to assess the daytime consequences and functional impairment of insomnia. The SSI, MFI, and ESS were used to assess somatic complaints, fatigue, and daytime sleepiness, while the SDS and SF-36 covered functional impairment and quality of life. The success of blinding and the credibility of treatment were assessed using standardized measures.[33,34] Adverse events were monitored after the third, sixth, and ninth treatment sessions using a structured

Figure 1. Participant Flowchart



adverse events form. Pharmacologic treatment history was obtained for the 12 months preceding baseline visit using the Antidepressant Treatment History Form (ATHF).[35] A score of ≥ 3 on the ATHF scale of 0 to 4 is suggestive of an adequate antidepressant treatment trial. For example, 4 weeks or more of fluoxetine at 10–19 mg/d is scored as 2, 20–39 mg/d as 3, and ≥ 40 mg/d as 4. Apart from the Consensus Sleep Diary,[36] all Chinese-language questionnaires have been shown to have adequate validity and reliability.[37–42]

Data Analysis

Sample size estimation. Our sample size estimation was based on changes in sleep diary–derived sleep efficiency, the primary outcome. A clinically significant treatment effect was defined as a 10 percentage point difference in sleep diary–derived sleep efficiency between acupuncture and minimal acupuncture, equivalent to an effect size of 0.58. On the basis of our previous study,[9] a sample of 48 in the acupuncture and minimal acupuncture groups would have

Table 1. Demographic and Clinical Characteristics of the Participants

Variable[a]	Acupuncture (n = 60)	Minimal Acupuncture (n = 60)	Placebo Acupuncture (n = 30)	Total (n = 150)	χ^2/ *F* Value[b]	*P* Value
Age, y	48.8 ± 9.9	50.9 ± 9.5	47.4 ± 9.5	49.3 ± 9.7	1.45	.24
Sex, n					2.60	.27
Male	14	14	3	31		
Female	46	46	27	119		
Education attainment, y	10.7 ± 2.9	10.4 ± 3.4	11.6 ± 3.0	10.8 ± 3.2	1.55	.22
Marital status					5.31	.26
Never married	7 (11.7)	10 (16.7)	7 (23.3)	24 (16.0)		
Married/cohabiting	33 (55.0)	36 (60.0)	19 (63.3)	88 (58.7)		
Divorced/widowed	20 (33.3)	14 (23.3)	4 (13.3)	38 (25.3)		
Occupation					3.30	.91
Professional and associate professional	3 (5.0)	4 (6.7)	1 (3.3)	8 (5.3)		
Skilled and semiskilled worker	11 (18.3)	7 (11.7)	3 (10.0)	21 (14.0)		
Unskilled worker	8 (13.3)	5 (8.3)	3 (10.0)	16 (10.7)		
Retired	9 (15.0)	11 (18.3)	5 (16.7)	25 (16.7)		
Unemployed/housework	29 (48.3)	33 (55.0)	18 (60.0)	80 (53.3)		
Chronic medical illnesses[c]	16 (26.7)	13 (21.7)	8 (26.7)	37 (24.7)	0.48	.79
Insomnia duration, y	8.7 ± 7.1	12.0 ± 11.4	9.2 ± 8.4	10.1 ± 9.3	2.11	.13
ISI total score	19.6 ± 3.0	20.2 ± 3.6	19.6 ± 2.7	19.8 ± 3.2	0.63	.53
PSQI total score	14.1 ± 3.0	14.7 ± 2.5	15.0 ± 3.5	14.5 ± 2.9	1.14	.32
Age at onset of depression, y	39.9 ± 10.0	40.9 ± 10.5	38.6 ± 9.2	40.0 ± 10.0	0.52	.60
Depression duration, y	7.5 ± 6.1	8.9 ± 12.9	9.3 ± 15.9	8.4 ± 11.4	0.31	.74
$HDRS_{17}$ total score	10.4 ± 4.2	9.9 ± 4.1	11.5 ± 4.0	10.4 ± 4.2	1.49	.23
Current antidepressant	51 (85.0)	48 (80.0)	27 (90.0)	126 (84.0)	1.56	.46
Selective serotonin reuptake inhibitors	27 (45.0)	16 (26.7)	14 (46.7)	57 (38.0)	12.90	.12
Serotonin-norepinephrine reuptake inhibitors	8 (13.3)	5 (8.3)	1 (3.3)	14 (9.3)		
Tricyclic antidepressants and others	7 (11.7)	17 (28.3)	8 (26.7)	32 (21.3)		
Combination	9 (15.0)	10 (16.7)	4 (13.3)	23 (15.3)		
Current hypnotics	27 (45.0)	26 (43.3)	16 (53.3)	69 (46.0)	0.85	.66
Benzodiazepines	7 (11.7)	5 (8.3)	5 (16.7)	17 (11.3)	2.92	.82
Nonbenzodiazepine hypnotics	12 (20.0)	9 (15.0)	5 (16.7)	26 (17.3)		
Combination	7 (11.7)	9 (15.0)	4 (13.3)	20 (13.3)		
Antihistamine	1 (1.7)	3 (5.0)	2 (6.7)	6 (4.0)		
Equivalent dose of hypnotics in diazepam, mg/d	9.9 ± 11.7	8.3 ± 8.7	5.4 ± 3.7	8.4 ± 9.4	1.04	.36
Anxiolytics	11 (18.3)	13 (21.7)	6 (20.0)	30 (20)	0.21	.90
Antipsychotics, lithium, and anticonvulsants	12 (20.0)	6 (10.0)	5 (16.7)	23 (15.3)	2.36	.31

[a]Data are presented as mean ± SD or n (%), unless stated otherwise.
[b]Comparison between acupuncture, minimal acupuncture, and placebo acupuncture by the χ^2 test or analysis of variance.
[c]Participants were on regular medications for their medical illnesses.
Abbreviations: $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale, ISI = Insomnia Severity Index, PSQI = Pittsburgh Sleep Quality Index.

a power of 80% to detect the difference at an α level of .05. A 15 percentage point difference in posttreatment sleep diary–derived sleep efficiency or 0.87 in effect size was expected to occur between acupuncture and placebo acupuncture; hence, a sample size of 22 was needed in the placebo acupuncture group. Assuming a 10%–15% dropout, a sample size of 60, 60, and 30 for the acupuncture, minimal acupuncture and placebo acupuncture groups was used.

Data management and analysis. We used SPSS version 20.0 (IBM Corp) for all statistical analysis. Subjects who received at least 1 session of acupuncture were included in the analysis. Baseline group difference was examined using analysis of variance (ANOVA) or the χ^2 test. The effects of the intervention over time were assessed using the mixed-effects group (acupuncture, minimal acupuncture, and placebo acupuncture) by time (baseline, 1-week posttreatment and 5-week posttreatment) interaction. Missing data were handled by the mixed-effects model, which accounts for both random and fixed effects. Standardized effect size was computed by dividing the difference in means by the pooled standard deviation. Dichotomous outcome was assessed using χ^2 or Fisher exact test.

RESULTS

Subject Characteristics

Nine hundred seventy-five potential subjects were assessed for eligibility, of whom 439 were screened in person and 150 subjects were randomized (Figure 1). Participants had a mean age of 49.3 years; 79.3% were female, 58.7% married or cohabiting, and 30.0% were in paid employment (Table 1). Participants' mean duration of MDD diagnosis was 8.4 years, and the mean age at onset was 40 years. More than half of the participants (54.7%) had more than 1 episode of depression. The majority of participants (84.0%) were taking antidepressants; 38.0% were taking selective serotonin reuptake inhibitors, and 15.3% were using a combination of antidepressants. The mean ATHF score was 2.6; 56.0% of the sample scored ≥ 3, suggesting adequacy in antidepressant treatment. At baseline, the mean ISI and PSQI scores were 19.8 and 14.5, respectively, while the average sleep diary–derived sleep efficiency was 63.6%, indicating moderate to severe insomnia. Sixty-nine participants (46.0%) were taking hypnotics for their insomnia. There was no significant group difference in sociodemographics, clinical features, and pharmacotherapy. Sixteen subjects (10.7%) dropped out

Table 2. Major Subjective Sleep Measures Across Study Time Points

Sleep Diary Measure	Acupuncture (n = 60) Mean ± SE[a]	Acupuncture (n = 60) Within-Group Effect Size	Minimal Acupuncture (n = 60) Mean ± SE[a]	Minimal Acupuncture (n = 60) Within-Group Effect Size	Placebo Acupuncture (n = 30) Mean ± SE[a]	Placebo Acupuncture (n = 30) Within-Group Effect Size	Acupuncture vs Minimal Acupuncture, *P* Value[b]	Acupuncture vs Placebo Acupuncture, *P* Value[b]
Sleep onset latency, min								
Baseline	58.9 ± 5.5		69.0 ± 5.6		69.0 ± 7.8			
1-wk Posttreatment	47.5 ± 5.6	0.27	48.5 ± 5.8	0.46	54.9 ± 7.8	0.33	.16	.68
5-wk Posttreatment	46.4 ± 6.1	0.28	44.9 ± 6.3	0.52	50.4 ± 8.2	0.42	.25	.75
Wake after sleep onset, min								
Baseline	62.8 ± 6.7		62.2 ± 6.8		48.7 ± 9.5			
1-wk Posttreatment	46.3 ± 6.9	0.31	43.4 ± 7.1	0.35	48.2 ± 9.5	0.01	.69	.14
5-wk Posttreatment	48.5 ± 7.5	0.26	46.1 ± 7.7	0.29	41.6 ± 10.0	0.13	.96	.30
Sleep efficiency, %								
Baseline	64.6 ± 2.0		62.4 ± 2.0		64.0 ± 2.8			
1-wk Posttreatment	71.4 ± 2.0	0.44	72.8 ± 2.1	0.65	68.3 ± 2.8	0.20	.18	.40
5-wk Posttreatment	71.1 ± 2.3	0.39	72.3 ± 2.3	0.59	74.0 ± 3.0	0.44	.33	.13
Insomnia Severity Index score								
Baseline	19.6 ± 0.6		20.2 ± 0.6		19.6 ± 0.8			
1-wk Posttreatment	14.1 ± 0.6	1.20	15.5 ± 0.6	1.02	14.7 ± 0.8	1.11	.33	.60
5-wk Posttreatment	14.4 ± 0.7	1.04	13.6 ± 0.7	1.32	13.6 ± 0.9	1.29	.48	.43

[a]Estimated mean ± SE from linear mixed-effects models.
[b]*P* value for group-by-time interaction.
Abbreviation: SE = standard error.

during the treatment period, and 18 participants (12.0%) withdrew at 5-week posttreatment (Figure 1). There was no difference in attrition rate between the groups at 1-week and 5-week posttreatment (χ^2 test, $P > .05$).

Efficacy

Subjective sleep measures. Mixed-effects analysis showed that there was no significant group-by-time interaction in sleep diary–derived sleep efficiency, sleep-onset latency, total sleep time, wake time after sleep onset, and sleep quality at 1-week and 5-week posttreatment nor was there any difference in the ISI and PSQI scores (Table 2 and Supplementary eTable 1). The mean difference in sleep diary–derived sleep efficiency at 1-week posttreatment was −1.40 (95% CI, −7.08 to 4.28) between the acupuncture and minimal acupuncture groups and was 3.10 (95% CI, −3.64 to 9.84) between the acupuncture and placebo acupuncture groups. Although a significantly higher proportion of participants in the acupuncture group achieved a sleep-onset latency of ≤ 30 minutes compared to the minimal acupuncture group at 1-week posttreatment ($P = .04$), there was no significant difference between the acupuncture and placebo acupuncture groups, while at 5-week posttreatment, no significant group difference was observed (Supplementary eTable 2). In addition, there was no significant group difference in the proportion of participants attaining a sleep efficiency ≥ 85% or wake time after sleep onset ≤ 30 minutes at 1-week and 5-week posttreatment (Table 3).

Actigraphy measures. There was no significant group-by-time interaction in actigraphy-derived measures, except in wake time after sleep onset (Table 4). As there was a significant baseline difference in actigraphy-derived wake time after sleep onset (ANOVA, $P = .002$), the baseline wake time after sleep onset was applied as a covariate in the analysis.

Other clinical variables. There was no significant group-by-time interaction in $HDRS_{17}$ total score; $HDRS_{17}$ insomnia items score; HARS total score; HADS anxiety score; and SSI, SDS social and family, MFI, and ESS scores (Supplementary eTables 3 and 4). However, mixed-effects analysis showed that the acupuncture group had significantly greater improvement in SF-36 physical component summary score than the placebo acupuncture group at 1-week and 5-week posttreatment (group-by-time interaction, $P = .004$ and $P = .009$, respectively) (Supplementary eTable 4). At 5-week posttreatment, a significant improvement was observed in HADS depression score in the placebo group compared to the acupuncture group (group-by-time interaction, $P = .03$) and in SDS work score in the acupuncture group compared to the minimal acupuncture group (group-by-time interaction, $P = .03$), and a greater reduction in hypnotics dosage was observed in the placebo acupuncture group compared to the acupuncture group (group-by-time interaction, $P = .02$) (Supplementary eTable 1).

Credibility and Success of Blinding

There was no significant group difference in the Credibility of Treatment Rating Scale scores obtained after the second and ninth acupuncture sessions. In a finding consistent across the 3 groups, a majority of participants reported that they did not know which acupuncture group they were in (82.8% for acupuncture, 89.8% for minimal acupuncture, and 83.3% for placebo acupuncture). However, a significantly greater number of subjects made a correct guess in the acupuncture group compared to the minimal acupuncture group (13.8% for acupuncture, 1.7% for minimal acupuncture, and 6.7% for placebo acupuncture; Fisher exact test, $P = .03$) (Supplementary eTable 5).

Adverse Events

Overall, acupuncture and minimal acupuncture were well tolerated, with rates of discontinuation due to adverse events at 5.1% and 3.4%, respectively. None of the participant in the

Table 3. Proportions of Subjects Achieving Sleep Diary–Derived Sleep Efficiency ≥ 85%

Time Point	Acupuncture, n/n (%)[a]	Minimal Acupuncture, n/n (%)[a]	Placebo Acupuncture, n/n (%)[a]	Acupuncture vs Minimal Acupuncture, *P* Value[b]	Acupuncture vs Placebo Acupuncture, *P* Value[b]
Baseline	8/60 (13.3)	3/60 (5.0)	4/30 (13.3)	.20	1.00
1-wk Posttreatment	10/51 (19.6)	10/47 (21.3)	6/29 (20.7)	.84	.91
5-wk Posttreatment	9/41 (22.0)	8/37 (21.6)	7/25 (28.0)	.97	.58

[a]Number of participants meeting criterion from total number of participants analyzed.
[b]χ^2 or Fisher exact test.

Table 4. Actigraphy Measures Across Study Time Points

Actigraphy measure	Acupuncture (n = 60)		Minimal Acupuncture (n = 60)		Placebo Acupuncture (n = 30)		Acupuncture vs Minimal Acupuncture	Acupuncture vs Placebo Acupuncture
	Mean ± SE[a]	Within-Group Effect Size	Mean ± SE[a]	Within-Group Effect Size	Mean ± SE[a]	Within-Group Effect Size	*P* Value[b]	*P* Value[b]
Sleep onset latency, min								
Baseline	31.2 ± 4.1		30.1 ± 4.0		29.2 ± 5.7			
1-wk Posttreatment	33.9 ± 4.1	−0.08	29.8 ± 4.1	0.01	35.1 ± 5.8	−0.13	.56	.61
5-wk Posttreatment	33.4 ± 4.5	−0.07	27.4 ± 4.5	0.08	24.2 ± 6.0	0.11	.64	.26
Total sleep time, min								
Baseline	387.3 ± 13.5		390.7 ± 13.4		396.8 ± 18.9			
1-wk Posttreatment	395.1 ± 13.8	−0.07	415.0 ± 13.6	−0.23	391.2 ± 19.4	0.05	.76	.69
5-wk Posttreatment	392.9 ± 14.2	−0.05	389.1 ± 14.3	0.01	398.1 ± 19.4	−0.01	.74	.95
Wake after sleep onset, min[c]								
Baseline	53.4 ± 4.3		70.3 ± 4.2		76.4 ± 6.0			
1-wk Posttreatment	60.6 ± 4.3	−0.22	65.9 ± 4.3	0.13	74.5 ± 6.1	0.06	1.00	.55
5-wk Posttreatment	55.3 ± 4.6	−0.06	67.0 ± 4.7	0.10	81.9 ± 6.2	−0.16	.72	.39
Sleep efficiency, %								
Baseline	78.8 ± 1.4		76.0 ± 1.3		76.9 ± 1.9			
1-wk Posttreatment	78.3 ± 1.4	0.05	76.2 ± 1.4	−0.02	76.5 ± 1.9	0.04	.65	.98
5-wk Posttreatment	78.7 ± 1.4	0.01	77.7 ± 1.4	−0.16	77.3 ± 1.9	−0.04	.32	.92

[a]Estimated mean ± SE from linear mixed-effects models.
[b]*P* value for group by time interaction.
[c]*P* value for group-by-time interaction using linear mixed-effects models with baseline actigraphy-derived wake time after sleep onset between groups at baseline.
Abbreviation: SE = standard error.

placebo group dropped out due to adverse events (Figure 1). Two participants (3.3%) in the acupuncture group withdrew due to needle site pain, and 1 participant (1.7%) withdrew due to headache and nausea. In the minimal acupuncture group, 2 participants (3.3%) withdrew due to needle site pain. In both the acupuncture and minimal acupuncture groups, 42.4% of the participants reported adverse events; such proportion was significantly higher than that of the placebo acupuncture group (16.7%, χ^2 test, $P = .01$) (Supplementary eTable 6). No serious adverse events were reported during the study period.

DISCUSSION

The results of this RCT indicate that, although significant improvement over time was observed, there was no evidence to support better efficacy for traditional needle acupuncture as compared to minimal acupuncture and placebo acupuncture as an intervention for residual insomnia associated with MDD. Needling at specific acupuncture points and attaining *deqi* resulted in no better outcome than superficial needling at nontherapeutic points or treatment using placebo needles. Although a within-group effect size of greater than 1.0 was obtained in terms of the ISI score at posttreatment, the effect size in terms of sleep diary–derived sleep efficiency was quite small. Only a few participants could achieve a sleep efficiency ≥ 85% on completion of the 3-week acupuncture treatment, and there was almost no change in actigraphy-derived sleep parameters. Taken together, the results suggest that the TCM-style standardized acupuncture used in this study attained response mostly by its nonspecific effects. Further studies are needed to explore treatments for this debilitating and persistent problem.

There are strengths as well as methodological limitations of this study. We used a well-documented screening process, proper randomization, placebo acupuncture needles, validated subjective scales, objective measures, and comprehensive adverse event monitoring. Our sample size is the largest to date among published high-quality randomized studies of acupuncture for insomnia. Almost all of the participants were unable to tell the kind of acupuncture they received, and the credibility rating was similar across the 3 groups, so we believe we have achieved successful blinding and control for the nonspecific effects of acupuncture. We investigated the effects of acupuncture on relatively unselected real-world MDD patients with residual insomnia; hence, the results were more likely to be generalizable. In line with usual clinical practice, the subjects were allowed to reduce the use of hypnotics, and their dosage

of hypnotics was used as an outcome variable. We found that the dosage of hypnotics was significantly lower in the placebo acupuncture group, suggesting that the hypnotic dosage reduction and any associated withdrawal symptoms could not be a confounding factor resulting in the poor response to real acupuncture. Another limitation is that only 84.0% of the participants agreed to receive laboratory-based sleep study. To mimic real-world settings, we did not exclude those who refused polysomnography if they were unlikely to have any specific sleep disorders based on face-to-face interview.

We were unable to replicate the results of our previous RCT,[9] which showed that acupuncture and minimal acupuncture had better efficacy than placebo acupuncture. Despite an enhanced acupuncture regimen, the hypnotic efficacy of acupuncture did not much improve; moreover, there was greater placebo response in this study, which has narrowed down the group difference. One possible explanation for the greater response to placebo acupuncture in this study may be the patients' lower average baseline sleep efficiency (64.0%) compared to that (68.9%) in our previous RCT.[9] Possibly due to regression to the mean, lower baseline sleep efficiency may result in greater sleep efficiency change from baseline to posttreatment. Another possible explanation is the different ratios in group size in the 2 studies; hence, 33.3% of participants were randomized to placebo in our previous RCT, but only 20.0% were in this study, as acupuncture and minimal acupuncture were presented as efficacious in the informed consent. The reduced likelihood of receiving placebo acupuncture might have increased participants' expectation on receiving effective treatment, thus boosting the placebo effect. Some factors may have also reduced the potential effectiveness of the traditional needle acupuncture in this study. Apart from the acupuncture treatment not being designed and tailored according to TCM diagnoses and clinical response to acupuncture and that it was short in duration, the concomitant psychotropic medications most participants were taking might have played a role. It is uncertain whether the acupuncture-induced biophysiological effects failed to occur in most of our subjects who were using antidepressants, sedatives, or hypnotics. Secondary analyses will be needed to examine the effect of different concomitant medications and the use of caffeine on treatment response. A previous meta-analysis[43] on insomnia treatment showed that the mean within-group effect sizes for sleep diary variables was 0.85 for pharmacotherapy and 1.00 for cognitive-behavioral therapy, which were higher than the effect sizes obtained by acupuncture, minimal acupuncture, and placebo acupuncture in this study (0.35–0.45).

In conclusion, we found that the effectiveness of acupuncture provided in this study as an intervention for residual insomnia in MDD was mild at best, and it was mainly due to its nonspecific effects. After 3 weeks' thrice-weekly acupuncture treatment, a high proportion of patients remained significantly affected by insomnia. We are uncertain whether TCM pattern-based individualized acupuncture or treatment of longer duration could improve the effectiveness for insomnia. Further studies are needed to explore treatment for this debilitating and persistent problem that could affect the long-term outcome of MDD.

Drug names: citalopram (Celexa and others), diazepam (Diastat, Valium, and others), fluoxetine (Prozac and others), lithium (Lithobid and others).

Author affiliations: Department of Psychiatry (Dr Chung and Mss Yu and Yung) and School of Chinese Medicine (Drs Yeung and Z-J Zhang), University of Hong Kong; School of Chinese Medicine, Hong Kong Baptist University (Dr S-P Zhang); Department of Psychiatry, Kowloon Hospital (Dr Wong); Department of Psychiatry, Kwai Chung Hospital (Dr Lee); and Department of Psychiatry, United Christian Hospital (Dr Chan), Hong Kong Special Administrative Region.

Potential conflicts of interest: None reported.

Funding/support: This article was funded by the Health and Health Services Research Fund (HHSRF no. 08091101), Food and Health Bureau, Hong Kong Special Administrative Region.

Role of the sponsor: The sponsor had no role in the design of the present study, statistical analyses, interpretation of findings, writing the manuscript, or the decision to submit for publication.

Acknowledgments: The authors thank the doctors at Departments of Psychiatry, Kowloon Hospital, Kwai Chung Hospital, Queen Mary Hospital, and United Christian Hospital for their help in subject recruitment.

Supplementary material: See accompanying pages.

REFERENCES

1. Kessler RC, Berglund P, Demler O, et al; National Comorbidity Survey Replication. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA*. 2003;289(23):3095–3105.
2. Carney CE, Segal ZV, Edinger JD, et al. A comparison of rates of residual insomnia symptoms following pharmacotherapy or cognitive-behavioral therapy for major depressive disorder. *J Clin Psychiatry*. 2007;68(2):254–260.
3. McClintock SM, Husain MM, Wisniewski SR, et al. Residual symptoms in depressed outpatients who respond by 50% but do not remit to antidepressant medication. *J Clin Psychopharmacol*. 2011;31(2):180–186.
4. Fava M, McCall WV, Krystal A, et al. Eszopiclone co-administered with fluoxetine in patients with insomnia coexisting with major depressive disorder. *Biol Psychiatry*. 2006;59(11):1052–1060.
5. Nolen WA, Haffmans PM, Bouvy PF, et al. Hypnotics as concurrent medication in depression: a placebo-controlled, double-blind comparison of flunitrazepam and lormetazepam in patients with major depression, treated with a (tri)cyclic antidepressant. *J Affect Disord*. 1993;28(3):179–188.
6. Watanabe N, Furukawa TA, Shimodera S, et al. Brief behavioral therapy for refractory insomnia in residual depression: an assessor-blind, randomized controlled trial. *J Clin Psychiatry*. 2011;72(12):1651–1658.
7. National Institutes of Health. National Institutes of Health State of the Science Conference statement on Manifestations and Management of Chronic Insomnia in Adults, June 13–15, 2005. *Sleep*. 2005;28(9):1049–1057.
8. Krystal AD. The changing perspective on chronic insomnia management. *J Clin Psychiatry*. 2004;65(suppl 8):20–25.
9. 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):807–815.
10. 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.
11. Yeung WF, Chung KF, Zhang SP, et al. Electroacupuncture for primary insomnia: a randomized controlled trial. *Sleep*. 2009;32(8):1039–1047.
12. White P, Lewith G, Hopwood V, et al. The placebo needle, is it a valid and convincing placebo for use in acupuncture trials? a randomised, single-blind, cross-over pilot trial. *Pain*. 2003;106(3):401–409.
13. 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.
14. Zhang ZJ, Wang XM, McAlonan GM. Neural acupuncture unit: a new concept for interpreting effects and mechanisms of acupuncture. *Evid Based Complement Alternat Med*. 2012;2012:429412.
15. Boutron I, Moher D, Altman DG, et al; CONSORT Group. Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: explanation and elaboration. *Ann Intern Med*. 2008;148(4):295–309.
16. MacPherson H, White A, Cummings M, et al; STandards for Reporting Interventions in Controlled Trails of Acupuncture. Standards for reporting

interventions in controlled trials of acupuncture: the STRICTA recommendations. STandards for Reporting Interventions in Controlled Trails of Acupuncture. *Acupunct Med*. 2002;20(1):22–25.
17. Rechtschaffen A, Kales A. *A Manual of Standardized Terminology, Techniques and Scoring System of Sleep Stages in Human Subjects*. Los Angeles, CA: Brain Information Service/Brain Research Institute, University of California; 1968.
18. Melchart D, Streng A, Hoppe A, et al. Acupuncture in patients with tension-type headache: randomised controlled trial. *BMJ*. 2005;331(7513):376–382.
19. Sjöling M, Rolleri M, Englund E. Auricular acupuncture versus sham acupuncture in the treatment of women who have insomnia. *J Altern Complement Med*. 2008;14(1):39–46.
20. Streitberger K, Kleinhenz J. Introducing a placebo needle into acupuncture research. *Lancet*. 1998;352(9125):364–365.
21. Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med*. 2001;2(4):297–307.
22. Buysse DJ, Reynolds CF 3rd, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989;28(2):193–213.
23. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23(1):56–62.
24. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol*. 1959;32(1):50–55.
25. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand*. 1983;67(6):361–370.
26. Kroenke K, Spitzer RL, Williams JB, et al. Physical symptoms in primary care: predictors of psychiatric disorders and functional impairment. *Arch Fam Med*. 1994;3(9):774–779.
27. Leon AC, Olfson M, Portera L, et al. Assessing psychiatric impairment in primary care with the Sheehan Disability Scale. *Int J Psychiatry Med*. 1997;27(2):93–105.
28. Smets EM, Garssen B, Bonke B, et al. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res*. 1995;39(3):315–325.
29. Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep*. 1991;14(6):540–545.
30. Ware J, Snow K, Kosinski M, et al. *SF-36 Health Survey Manual and Interpretation Guide*. Boston, MA: The Health Institute, New England Medical Center; 1993.
31. Buysse DJ, Ancoli-Israel S, Edinger JD, et al. Recommendations for a standard research assessment of insomnia. *Sleep*. 2006;29(9):1155–1173.
32. Lichstein KL, Stone KC, Donaldson J, et al. Actigraphy validation with insomnia. *Sleep*. 2006;29(2):232–239.
33. Park J, White AR, James MA, et al. Acupuncture for subacute stroke rehabilitation: a sham-controlled, subject- and assessor-blind, randomized trial. *Arch Intern Med*. 2005;165(17):2026–2031.
34. Vincent C. Credibility assessment in trials of acupuncture. *Complement Med Res*. 1990;4(1):8–11.
35. Sackeim HA, Prudic J, Devanand DP, et al. The impact of medication resistance and continuation pharmacotherapy on relapse following response to electroconvulsive therapy in major depression. *J Clin Psychopharmacol*. 1990;10(2):96–104.
36. Carney CE, Buysse DJ, Ancoli-Israel S, et al. The consensus sleep diary: standardizing prospective sleep self-monitoring. *Sleep*. 2012;35(2):287–302.
37. 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):463–470.
38. Chung KF, Tang MK. Subjective sleep disturbance and its correlates in middle-aged Hong Kong Chinese women. *Maturitas*. 2006;53(4):396–404.
39. Leung CM, Wing YK, Kwong PK, et al. Validation of the Chinese-Cantonese version of the hospital anxiety and depression scale and comparison with the Hamilton Rating Scale of Depression. *Acta Psychiatr Scand*. 1999;100(6):456–461.
40. Lam CL, Gandek B, Ren XS, et al. Tests of scaling assumptions and construct validity of the Chinese (HK) version of the SF-36 Health Survey. *J Clin Epidemiol*. 1998;51(11):1139–1147.
41. Chung KF. Use of the Epworth Sleepiness Scale in Chinese patients with obstructive sleep apnea and normal hospital employees. *J Psychosom Res*. 2000;49(5):367–372.
42. Chung KF, Yu BY, Yung KP, et al. Assessment of fatigue using the Multidimensional Fatigue Inventory in patients with major depressive disorder. *Compr Psychiatry*. 2014;55(7):1671–1678.
43. Smith MT, Perlis ML, Park A, et al. Comparative meta-analysis of pharmacotherapy and behavior therapy for persistent insomnia. *Am J Psychiatry*. 2002;159(1):5–11.

Supplementary material follows this article.

THE JOURNAL OF
CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

Supplementary Material

Article Title: Acupuncture for Residual Insomnia Associated With Major Depressive Disorder: A Placebo- and Sham-Controlled, Subject- and Assessor-Blind, Randomized Trial

Author(s): Ka-Fai Chung, MRCPsych; Wing-Fai Yeung, PhD; Yee-Man Yu, BSocSc; Kam-Ping Yung, MPhil; Shi-Ping Zhang, PhD; Zhang-Jin Zhang, PhD; Man-Tak Wong, MRCPsych; Wing-King Lee, MRCPsych; and Lai-Wah Chan, MRCPsych

DOI Number: 10.4088/JCP.14m09124

List of Supplementary Material for the article

Disclaimer

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

Supplementary eTable 1 Other subjective sleep measures and hypnotics usage across study time points

	Acupuncture (n = 60)		Minimal acupuncture (n = 60)		Placebo acupuncture (n = 30)		A *v* MA	A *v* PA
Sleep diary	Mean ± SE[a]	Within-group effect size	Mean ± SE[a]	Within-group effect size	Mean ± SE[a]	Within-group effect size	P-value[b]	P-value[b]
TST, min								
Baseline	318.7 ± 10.3		314.6 ± 10.4		338.6 ± 14.5			
1-week Posttreatment	345.5 ± 10.5	-0.33	364.1 ± 10.8	-0.60	369.5 ± 14.5	-0.39	0.10	0.80
5-week Posttreatment	352.9 ± 11.6	-0.40	367.8 ± 12.0	-0.61	382.2 ± 15.3	-0.53	0.20	0.90
Sleep quality[c]								
Baseline	2.9 ± 0.1		2.9 ± 0.1		2.8 ± 0.1			
1-week Posttreatment	2.5 ± 0.1	0.50	2.6 ± 0.1	0.37	2.4 ± 0.1	0.80	0.31	0.82
5-week Posttreatment	2.6 ± 0.1	0.37	2.6 ± 0.1	0.37	2.5 ± 0.1	0.60	0.49	0.84
PSQI								
Baseline	14.1 ± 0.5		14.7 ± 0.5		15.0 ± 0.6			
1-week Posttreatment	11.7 ± 0.5	0.62	11.6 ± 0.5	0.79	12.1 ± 0.6	0.88	0.20	0.45
5-week Posttreatment	11.2 ± 0.5	0.74	10.5 ± 0.5	1.08	11.2 ± 0.7	1.07	0.22	0.54
Equivalent dose of hypnotics in diazepam, mg/d[d]								
Baseline	9.9 ± 1.7		8.3 ± 1.8		5.4 ± 2.4			
1-week Posttreatment	8.6 ± 1.7	0.10	5.3 ± 1.9	0.21	4.0 ± 2.4	0.11	0.51	0.89
5-week Posttreatment	9.5 ± 1.7	0.03	7.9 ± 1.9	0.03	2.6 ± 2.4	0.21	0.78	0.02

A = acupuncture; MA = minimal acupuncture; PA = placebo acupuncture; PSQI = Pittsburgh sleep quality index; TST = total sleep time.

[a] Estimated mean and standard error from linear mixed-effects models.

[b] P-value for group by time interaction.

[c] 1 = very good, 2 = fairly good, 3 = fairly bad, 4 = very bad.

[d] Only participants taking hypnotics and completed the study were analysed: acupuncture (n = 27), minimal acupuncture (n = 23), placebo acupuncture (n = 14).

Supplementary eTable 2 Proportions of subjects achieving sleep-diary-derived sleep onset latency (SOL) or wake after sleep onset (WASO) ≤ 30 min

	Acupuncture[a]	Minimal acupuncture[a]	Placebo acupuncture[a]	A *v* MA P-value[b]	A *v* PA P-value[b]
SOL ≤ 30 min					
Baseline	19/60 (31.7)	11/60 (18.3)	7/30 (23.3)	0.09	0.41
1-week Posttreatment	25/51 (49.0)	14/48 (29.2)	11/29 (37.9)	0.04	0.34
5-week Posttreatment	18/41 (43.9)	14/38 (36.8)	12/27 (48.0)	0.52	0.75
WASO ≤ 30 min					
Baseline	24/60 (40.0)	20/60 (33.3)	8/30 (26.7)	0.45	0.21
1-week Posttreatment	22/50 (44.0)	24/48 (50.0)	16/29 (55.2)	0.55	0.34
5-week Posttreatment	23/41 (56.1)	18/38 (47.4)	15/25 (60.0)	0.44	0.76

A = acupuncture; MA = minimal acupuncture; PA = placebo acupuncture.
[a] Number of participants meeting each criterion out of total number of participants analyzed.
[b] χ^2 test.

Supplementary eTable 3 17-item Hamilton Depression Rating Scale ($HDRS_{17}$), Hamilton Anxiety Rating Scale (HARS) and Hospital Anxiety and Depression Scale (HADS) scores across study time points

	Acupuncture (n = 60) Mean ± SE[a]	Minimal acupuncture (n = 60) Mean ± SE[a]	Placebo acupuncture (n = 30) Mean ± SE[a]	A *v* MA P-value[b]	A *v* PA P-value[b]
$HDRS_{17}$ total					
Baseline	10.4 ± 0.5	9.9 ± 0.5	11.5 ± 0.8		
1-week Posttreatment	8.6 ± 0.6	7.9 ± 0.6	8.2 ± 0.8	0.82	0.12
5-week Posttreatment	8.9 ± 0.6	7.6 ± 0.6	7.9 ± 0.8	0.67	0.10
$HDRS_{17}$ insomnia items					
Baseline	4.0 ± 0.2	3.9 ± 0.2	4.0 ± 0.3		
1-week Posttreatment	2.9 ± 0.2	3.0 ± 0.2	3.1 ± 0.3	0.52	0.59
5-week Posttreatment	3.0 ± 0.2	3.2 ± 0.2	2.8 ± 0.3	0.69	0.49
HARS					
Baseline	8.8 ± 0.6	7.7 ± 0.6	10.2 ± 0.9		
1-week Posttreatment	7.0 ± 0.7	6.1 ± 0.7	6.4 ± 0.9	0.77	0.07
5-week Posttreatment	7.6 ± 0.7	5.2 ± 0.8	6.4 ± 0.9	0.29	0.09
HADS-anxiety					
Baseline	9.8 ± 0.5	9.0 ± 0.5	9.9 ± 0.7		
1-week Posttreatment	8.9 ± 0.5	7.7 ± 0.5	8.2 ± 0.7	0.61	0.33
5-week Posttreatment	8.7 ± 0.6	6.7 ± 0.6	7.8 ± 0.8	0.30	0.42
HADS-depression					
Baseline	9.1 ± 0.6	8.6 ± 0.6	9.5 ± 0.8		
1-week Posttreatment	8.3 ± 0.6	7.4 ± 0.6	8.0 ± 0.8	0.45	0.28
5-week Posttreatment	8.5 ± 0.6	6.8 ± 0.6	6.9 ± 0.8	0.23	0.03

A = acupuncture; MA = minimal acupuncture; PA = placebo acupuncture.
[a] Estimated mean and standard error from linear mixed-effects models; higher scores represent greater severity.
[b] P-value for group by time interaction.

Supplementary eTable 4 Somatic Symptom Inventory (SSI), Sheehan Disability Scale (SDS), Multidimensional Fatigue Inventory (MFI), Epworth Sleepiness Scale (ESS) and Short form Health Survey-36 (SF-36) scores across study time points

	Acupuncture (n = 60) Mean ± SE[a]	Minimal acupuncture (n = 60) Mean ± SE[a]	Placebo acupuncture (n = 30) Mean ± SE[a]	A *v* MA P-value[b]	A *v* PA P-value[b]
SSI					
Baseline	2.5 ± 0.1	2.2 ± 0.1	2.3 ± 0.1		
1-week Posttreatment	2.4 ± 0.1	2.0 ± 0.1	2.2 ± 0.1	0.47	0.66
5-week Posttreatment	2.4 ± 0.1	1.9 ± 0.1	2.1 ± 0.1	0.22	0.84
SDS-work					
Baseline	5.4 ± 0.4	5.4 ± 0.4	5.3 ± 0.6		
1-week Posttreatment	5.0 ± 0.4	3.9 ± 0.4	4.9 ± 0.6	0.11	1.00
5-week Posttreatment	4.8 ± 0.4	2.8 ± 0.5	3.7 ± 0.6	0.03	0.29
SDS-social					
Baseline	5.5 ± 0.4	5.2 ± 0.4	5.6 ± 0.5		
1-week Posttreatment	4.7 ± 0.4	4.0 ± 0.4	4.1 ± 0.5	0.37	0.14
5-week Posttreatment	4.5 ± 0.4	3.5 ± 0.4	3.7 ± 0.5	0.32	0.17
SDS-family					
Baseline	5.6 ± 0.4	5.0 ± 0.4	5.4 ± 0.5		
1-week Posttreatment	4.8 ± 0.4	4.1 ± 0.4	4.3 ± 0.5	0.76	0.64
5-week Posttreatment	4.6 ± 0.4	3.4 ± 0.4	3.8 ± 0.5	0.47	0.64
MFI					
Baseline	72.1 ± 1.9	71.6 ± 1.9	73.1 ± 2.7		
1-week Posttreatment	70.8 ± 1.9	68.8 ± 2.0	70.5 ± 2.7	0.46	0.64
5-week Posttreatment	68.8 ± 2.1	66.4 ± 2.1	69.7 ± 2.8	0.73	0.83
ESS					
Baseline	9.4 ± 0.8	9.0 ± 0.8	8.2 ± 1.2		
1-week Posttreatment	8.1 ± 0.8	7.9 ± 0.8	6.3 ± 1.2	0.61	0.61
5-week Posttreatment	8.2 ± 0.9	8.1 ± 0.9	7.0 ± 1.2	0.90	0.77
SF-36-physical[c]					
Baseline	31.92 ± 1.58	34.75 ± 1.58	36.66 ± 2.23		
1-week Posttreatment	33.28 ± 1.60	35.90 ± 1.61	32.02 ± 2.23	0.90	0.004
5-week Posttreatment	32.03 ± 1.71	39.64 ± 1.73	34.26 ± 2.28	0.03	0.009
SF-36-mental[c]					
Baseline	34.00 ± 1.57	34.77 ± 1.57	34.70 ± 2.23		
1-week Posttreatment	36.21 ± 1.60	38.30 ± 1.62	38.02 ± 2.23	0.46	0.62
5-week Posttreatment	37.26 ± 1.74	39.81 ± 1.75	39.02 ± 2.29	0.72	0.87

A = acupuncture; MA = minimal acupuncture; PA = placebo acupuncture.

[a] Estimated mean and standard error from linear mixed-effects models. Except SF-36, higher scores suggestive of greater severity.

[b] P-value for group by time interaction.

[c] Higher scores represent better health.

Supplementary eTable 5 Creditability Treatment Rating Scale scores across groups and study time points and blinding success across groups

	Acupuncture (n = 60) Mean ± SE[a]	Minimal acupuncture (n = 60) Mean ± SE[a]	Placebo acupuncture (n = 30) Mean ± SE[a]	A *v* MA P-value[b]	A *v* PA P-value[b]
Creditability Treatment Rating Scale					
Perceived logic					
Baseline	2.63 ± 0.14	2.77 ± 0.14	3.10 ± 0.20		
2nd treatment	2.26 ± 0.14	2.33 ± 0.14	2.67 ± 0.20	0.79	0.80
9th treatment	2.10 ± 0.15	2.44 ± 0.15	2.65 ± 0.20	0.53	0.86
Confidence in alleviating the complaint					
Baseline	2.67 ± 0.14	2.82 ± 0.14	3.17 ± 0.20		
2nd treatment	2.42 ± 0.14	2.35 ± 0.14	2.67 ± 0.20	0.31	0.33
9th treatment	2.08 ± 0.15	2.29 ± 0.15	2.44 ± 0.20	0.36	0.63
Confidence in recommending to friends					
Baseline	2.27 ± 0.13	2.20 ± 0.13	2.87 ± 0.18		
2nd treatment	2.02 ± 0.13	1.95 ± 0.13	2.50 ± 0.18	0.98	0.52
9th treatment	1.74 ± 0.14	2.05 ± 0.14	2.41 ± 0.18	0.12	0.66
Likelihood that the treatment alleviates other complaints					
Baseline	2.47 ± 0.13	2.75 ± 0.13	3.03 ± 0.19		
2nd treatment	2.44 ± 0.14	2.45 ± 0.14	2.60 ± 0.19	0.17	0.11
9th treatment	2.16 ± 0.14	2.57 ± 0.14	2.61 ± 0.19	0.13	0.27
Blinding to treatment allocation[c]	n (%)	n (%)	n (%)		
Correct guess	8 (13.8)	1 (1.7)	2 (6.7)	0.03[d]	0.35[d]
Incorrect guess	2 (3.4)	5 (8.5)	3 (10.0)		
Don't know	48 (82.8)	53 (89.8)	25 (83.3)		

A = acupuncture; MA = minimal acupuncture; PA = placebo acupuncture.
[a] Estimated means and standard errors from linear mixed-effects model; lower scores represent greater confidence toward the received treatment.
[b] P-value for group by time interaction of the Creditability Treatment Rating Scale scores.
[c] Only participants remaining in the study were analyzed: acupuncture (n = 58), minimal acupuncture (n = 59), placebo acupuncture (n = 30).
[d] Fisher's exact test

Supplementary eTable 6 Number (percentages) of adverse events per patient as derived from a structured adverse events record form

	Acupuncture (n = 59)[a]	Minimal acupuncture (n = 59)[a]	Placebo acupuncture (n = 30)	A *v* MA P-value[a]	A *v* PA P-value[a]
Needle site pain	19 (32.2)	6 (10.2)	1 (3.3)	0.004	0.003
Needle site bruise	8 (13.6)	16 (27.1)	0 (0.0)	0.07	0.048
Headache/pain	8 (13.6)	7 (11.9)	3 (10.0)	0.78	0.74
Tiredness/fatigue	8 (13.6)	4 (6.8)	0 (0.0)	0.36	0.048
Paresthesia	7 (11.9)	1 (1.7)	0 (0.0)	0.06	0.09
Unusual relaxation	3 (5.1)	2 (3.4)	0 (0.0)	1.00	0.55
Nausea/GI symptom	3 (5.1)	1 (1.7)	1 (3.3)	0.62	1.00
Dizziness after treatment	3 (5.1)	0 (0.0)	1 (3.3)	0.24	1.00
Needle site reaction	2 (3.4)	1 (1.7)	0 (0.0)	1.00	0.55
Others	2 (3.4)	1 (1.7)	0 (0.0)	1.00	0.55
Dermatological problems	1 (1.7)	1 (1.7)	0 (0.0)	1.00	1.00
Needle site bleeding	1 (1.7)	0 (0.0)	0 (0.0)	1.00	1.00
Forgotten needle	0 (0.0)	1 (1.7)	0 (0.0)	1.00	1.00
Any adverse event	25 (42.4)	25 (42.4)	5 (16.7)	1.00	0.018
Dropped out due to adverse events	3 (5.1)	2 (3.4)	0 (0.0)	1.00	0.55

A = acupuncture; MA = minimal acupuncture; PA = placebo acupuncture.
[a] One participant in each group dropped out prior the first adverse event assessment.
[b] χ^2 or Fisher's exact test.