Acupuncture for persistent insomnia associated with major depressive disorder: a randomised controlled trial

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KEY MESSAGES

1. Standardised acupuncture has only a mild hypnotic effect for residual insomnia associated with major depressive disorder (MDD). Its efficacy does not differ to that of minimal acupuncture or placebo control.
2. The within-group effect size for the primary outcome measure—sleep-diary-derived sleep efficiency—was 0.4 at 1-week post-treatment, but there was almost no change in actigraphy-derived objective sleep parameters.
3. Standardised acupuncture and minimal acupuncture were well-tolerated, with rates of discontinuation (secondary to adverse events) of 5.0% and 3.3%, respectively.
4. Residual insomnia associated with MDD partially responds to non-specific factors of acupuncture, but it fails to attain full remission. Further studies exploring individualised acupuncture, a longer course of acupuncture and cognitive behavioural therapy for this persistent problem are needed.

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Introduction

Major depressive disorder (MDD) is a common psychiatric condition. A sizable proportion of patients with MDD partially respond to mainstream treatment and are left with residual symptoms, of which insomnia is the most common.[1] Although pharmacological and psychological treatments may help to alleviate residual insomnia, both have limitations. The use of complementary and alternative medicine therapies for insomnia has become more common. Acupuncture is one of the most popular procedures. In 2011, we published the first randomised trial of electroacupuncture for residual insomnia associated with MDD.[2] Electroacupuncture and minimal acupuncture were comparable and more efficacious than placebo control. In the present study, we aimed to enhance the efficacy of acupuncture for insomnia by augmenting essential acupoints. We hypothesised that electroacupuncture was significantly more efficacious than minimal acupuncture and placebo acupuncture for the treatment of residual insomnia in MDD.

Methods

The study was a placebo-controlled, subject- and assessor-blinded, randomised trial. The use of placebo needles was to control for the non-specific effects of acupuncture and the natural course of illness. Using superficial needling at non-therapeutic points could test the relevance of specific acupuncture points, deep needling, and *de qi*. Patients were assessed at baseline, 1-week and 5-week post-treatment. The study was registered at clinicaltrials.gov (identifier: NCT01707706).

Patients were recruited from May 2011 to August 2013 at four regional psychiatric outpatient clinics in Hong Kong. Inclusion criteria were: (1) age 18-70 years, (2) a diagnosis of MDD based on the DSM-IV criteria, (3) insomnia ≥3 nights per week for at least 3 months, (4) Insomnia Severity Index (ISI) score ≥15 at screening and baseline, and (5) taking the same antidepressants at a fixed dose for at least 12 weeks prior to baseline and during the study. Exclusion criteria were: (1) a 17-item Hamilton Rating Scale for Depression (HRSD-17) score >18 at screening and baseline, (2) an apnoea-hypopnoea index ≥10 or a periodic limb movement disorder index ≥15 as assessed by in-laboratory overnight polysomnography, (3) significant suicidal risk according to the HRSD-17 item on suicide (score ≥3). Eligible subjects were randomly assigned to electroacupuncture, minimal acupuncture, or placebo acupuncture in a ratio of 2:2:1.

Intervention was three times per week for three

consecutive weeks. All acupuncture treatments were performed by the same registered Chinese medicine practitioner who had at least 3 years of clinical experience.

For electroacupuncture, subjects were needled at bilateral Ear Shenmen, Sishencong (EX-HN1), Anmian (EX), Neiguan (PC6), Shenmen (HT7), Sanyinjiao (SP6), as well as unilateral Yintang (EX-HN3) and Baihui (GV20). *De qi* was achieved if possible. An electric-stimulator was connected to the 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.

For minimal acupuncture, subjects were needled superficially at non-acupoints on the head, ears, wrists, and legs that have no therapeutic effects according to the traditional Chinese medicine (TCM) theory. The points on the 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 the head, they 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. Other treatment conditions were the same as in the electroacupuncture group.

For placebo acupuncture, subjects were treated by placing placebo needles at sites 1 inch beside the acupoints used in the electroacupuncture group. The needles were connected to an electric-stimulator, but with zero frequency and amplitude.

The primary outcome measure was the sleep-diary-derived sleep efficiency. Secondary outcome measures included other sleep parameters derived from the sleep diary, actigraphy measures, ISI, Pittsburgh Sleep Quality Index (PSQI), HRSD-17, Hamilton Anxiety Rating Scale (HARS), Hospital Anxiety and Depression Scale (HADS), Somatic Symptom Inventory (SSI), Sheehan Disability Scale (SDS), Multidimensional Fatigue Inventory (MFI), Epworth Sleepiness Scale (ESS), 36-item Short Form Health Survey (SF-36), and Credibility of Treatment Rating Scale (CTRS). Dichotomous outcomes were the proportion of subjects who obtained a sleep-diary-derived sleep efficiency of at least 85% or a sleep-onset latency (SOL) or wake time after sleep onset (WASO) of ≤30 minutes. After the sixth treatment, the success of blinding was tested by asking the participants which kind of acupuncture treatment they thought they had received. Adverse events were assessed after the third, sixth, and ninth sessions, using a standardised adverse events form.

The effects of the intervention over time were assessed using the mixed-effects model of group-by-time interaction. Standardised effect size was computed by dividing the difference in means by the pooled standard deviation.

Results

A total of 150 subjects (mean age, 49.3 years) were randomised; 79.3% were female. They had been diagnosed with MDD for a mean of 8.4 years; 84.0% were taking antidepressants (Table 1). The electroacupuncture, minimal acupuncture, and placebo acupuncture groups were comparable in terms of sociodemographics, clinical features, and pharmacotherapy. Sixteen (10.7%) subjects dropped out, and 18 (12.0%) withdrew 5 weeks post-treatment (Fig). The attrition rate among the groups was comparable at 1-week and 5-week post-treatment (χ^2 test, P>0.05).

In mixed-effects model analysis, the between-group difference was not significant in sleep-diary-derived sleep efficiency, SOL, WASO, or sleep quality at 1-week or 5-week post-treatment (Table 2), nor in the ISI and PSQI scores. Nonetheless, a greater reduction in dosage of hypnotics was noted in the placebo acupuncture group compared with the electroacupuncture and minimal acupuncture groups at 5-week post-treatment (group-by-time interaction, P=0.02).

There was no significant group-by-time interaction in actigraphy-derived measures, HRSD-17, HARS, HADS anxiety and depression, SSI, SDS, MFI, or ESS scores. Nonetheless, mixed-effects model showed that electroacupunc¬ture and minimal acupuncture achieved greater improvement in SF-36 physical component summary score than placebo acupuncture at 1-week and 5-week post-treatment (group-by-time interaction, P<0.05).

A higher proportion of subjects in the electroacupuncture group achieved a SOL ≤30 minutes compared with those with minimal acupuncture at 1-week post-treatment (P=0.04), but not those with placebo acupuncture. At 5-week post-treatment, the between-group difference was not significant. There was no significant difference in the proportion of participants who attained a sleep efficiency ≥85% or WASO ≤30 minutes at 1-week and 5-week post-treatment (χ^2 test, all P>0.05).

There was no significant between-group difference in the CTRS score and the proportion of participants who correctly guessed, made a wrong guess, or had no idea which acupuncture treatment they had received (P=0.11).

Electroacupuncture and minimal acupuncture were well-tolerated, with rates of discontinuation (secondary to adverse events) of 5.0% and 3.3%, respectively. No serious adverse events were reported.

TABLE 1. Demographics and clinical characteristics of subjects

Variables	Mean±SD or No (%) of subjects			
	Electro-acupuncture (n=60)	Minimal acupuncture (n=60)	Placebo acupuncture (n=30)	Total (n=150)
Age (years)	48.8±9.9	50.9±9.5	47.4±9.5	49.3±9.7
No. of males:females	14:46	14:46	3:27	31:119
Education attainment (years)	10.7±2.9	10.4±3.4	11.6±3.0	10.8±3.2
Marital status				
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				
Professional and associate professional	3 (5.0)	4 (6.7)	1 (3.3)	8 (5.3)
Skilled and semi-skilled 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)
Insomnia duration (years)	8.7±7.1	12.0±11.4	9.2±8.4	10.1±9.3
Chronic medical illnesses	16 (26.7)	13 (21.7)	8 (26.7)	37 (24.7)
Insomnia Severity Index	19.6±3.0	20.2±3.6	19.6±2.7	19.8±3.2
Pittsburgh Sleep Quality Index	14.1±3.0	14.7±2.5	15.0±3.5	14.5±2.9
Age of onset of depression (years)	39.9±10.0	40.9±10.5	38.6±9.2	40.0±10.0
Depression duration (years)	7.5±6.1	8.9±12.9	9.3±15.9	8.4±11.4
17-item Hamilton Rating Scale for Depression	10.4±4.2	9.9±4.1	11.5±4.0	10.4±4.2
Current antidepressant use	51 (85.0)	48 (80.0)	27 (90.0)	126 (84.0)
Selective serotonin reuptake inhibitors	27 (45.0)	16 (26.7)	14 (46.7)	57 (38.0)
Serotonin and noradrenalin reuptake inhibitors	8 (13.3)	5 (8.3)	1 (3.3)	14 (9.3)
Tricyclic antidepressants and others	6 (10.0)	15 (25.0)	5 (16.7)	26 (17.3)
Others	1 (1.7)	2 (3.3)	3 (10.0)	6 (4.0)
Combination	9 (15.0)	10 (16.7)	4 (13.3)	23 (15.3)
Current hypnotics use	27 (45.0)	26 (43.3)	16 (53.3)	69 (46.0)
Benzodiazepines	7 (11.7)	5 (8.3)	5 (16.7)	17 (11.3)
Non-benzodiazepine hypnotics	12 (20.0)	9 (15.0)	5 (16.7)	26 (17.3)
Combination of benzodiazepines and non-benzodiazepine hypnotics	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)

Discussion

There was no evidence to support better efficacy of traditional needle acupuncture as an intervention for residual insomnia associated with MDD. Although a within-group effect size of >1.0 was noted in the ISI score, the effect size in sleep-diary-derived sleep efficiency was quite small. Only a few participants could achieve sleep efficiency ≥85% on completion of the 3-week acupuncture treatment, and there was almost no change in actigraphy-derived sleep parameters. These suggest that the TCM-style standardised acupuncture attained a response mostly by its non-specific effects; the mean sleep-diary-derived sleep efficiency post-treatment was 71.4%, indicating that acupuncture is not likely to be an adequate monotherapy for residual insomnia associated with MDD.

Our previous studies showed that electroacupuncture had slightly better efficacy than placebo acupuncture.[2,3] Despite an enhanced acupuncture regimen, the hypnotic efficacy of electroacupuncture did not improve much in the current study. In addition, there was a greater placebo response that narrowed down the group difference. Some factors may have reduced the effectiveness of the traditional acupuncture.

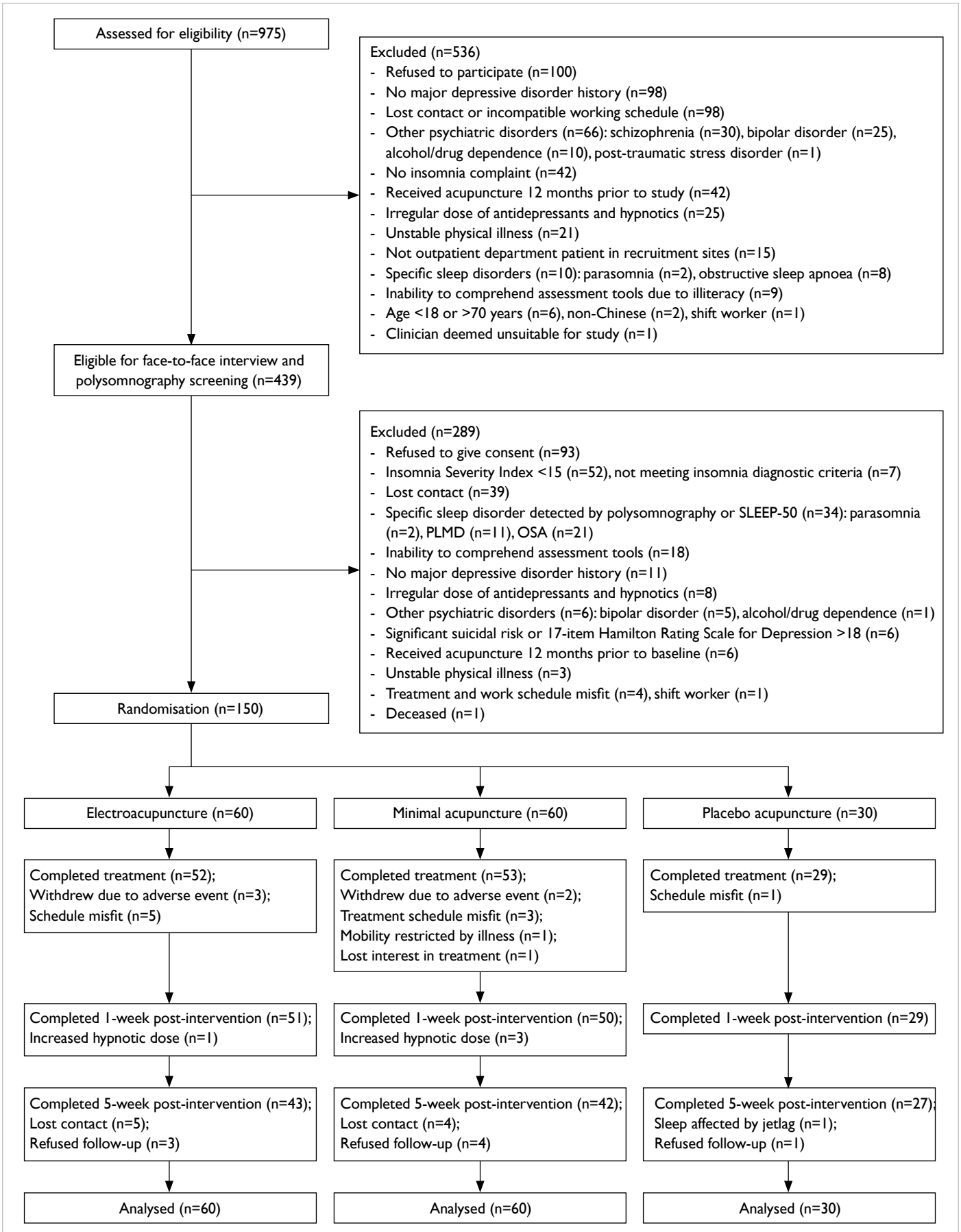

FIG. Flowchart of the subjects

TABLE 2. Sleep diary and actigraphy measures across study time points

Outcome measure	Electroacupuncture (n=60)		Minimal acupuncture (n=60)		Placebo acupuncture (n=30)		P value (group-by-time interaction)
	Mean±SE	Within-group effect size	Mean±SE	Within-group effect size	Mean±SE	Within-group effect size	
Sleep diary							
Sleep onset latency (mins)							
Baseline	58.9±5.5		69.0±5.6		69.0±7.8		
1-week post-treatment	47.5±5.6	0.27	48.5±5.8	0.46	54.9±7.8	0.33	0.33
5-week post-treatment	46.4±6.1	0.28	44.9±6.3	0.52	50.4±8.2	0.42	0.52
Total sleep time (mins)							
Baseline	318.7±10.3		314.6±10.4		338.6±14.5		
1-week post-treatment	345.5±10.5	-0.33	364.1±10.8	-0.60	369.5±14.5	-0.39	0.24
5-week post-treatment	352.9±11.6	-0.40	367.8±12.0	-0.61	382.2±15.3	-0.53	0.47
Wake time after sleep onset (mins)							
Baseline	62.8±6.7		62.2±6.8		48.7±9.5		
1-week post-treatment	46.3±6.9	0.31	43.4±7.1	0.35	48.2±9.5	0.01	0.16
5-week post-treatment	48.5±7.5	0.26	46.1±7.7	0.29	41.6±10.0	0.13	0.41
Sleep efficiency (%)							
Baseline	64.6±2.0		62.4±2.0		64.0±2.8		
1-week post-treatment	71.4±2.0	0.44	72.8±2.1	0.65	68.3±2.8	0.20	0.13
5-week post-treatment	71.1±2.3	0.39	72.3±2.3	0.59	74.0±3.0	0.44	0.09
Equivalent dose of hypnotics in diazepam (mg/d)*							
Baseline	9.9±1.7		8.3±1.8		5.4±2.4		
1-week post-treatment	8.6±1.7	0.10	5.3±1.9	0.21	4.0±2.4	0.11	0.60
5-week post-treatment	9.5±1.7	0.03	7.9±1.9	0.03	2.6±2.4	0.21	0.02†
Actigraphy							
Sleep onset latency (mins)							
Baseline	31.2±4.1		30.1±4.0		29.2±5.7		
1-week post-treatment	33.9±4.1	-0.08	29.8±4.1	0.01	35.1±5.8	-0.13	0.57
5-week post-treatment	33.4±4.5	-0.07	27.4±4.5	0.08	24.2±6.0	0.11	0.43
Total sleep time (mins)							
Baseline	387.3±13.5		390.7±13.4		396.8±18.9		
1-week post-treatment	395.1±13.8	-0.07	415.0±13.6	-0.23	391.2±19.4	0.05	0.47
5-week post-treatment	392.9±14.2	-0.05	389.1±14.3	0.01	398.1±19.4	-0.01	0.72
Wake time after sleep onset (mins)							
Baseline	53.4±4.3		70.3±4.2		76.4±6.0		
1-week post-treatment	60.6±4.3	-0.22	65.9±4.3	0.13	74.5±6.1	0.06	0.03‡
5-week post-treatment	55.3±4.6	-0.06	67.0±4.7	0.10	81.9±6.2	-0.16	0.05
Sleep efficiency (%)							
Baseline	78.8±1.4		76.0±1.3		76.9±1.9		
1-week post-treatment	78.3±1.4	0.05	76.2±1.4	-0.02	76.5±1.9	0.04	0.88
5-week post-treatment	78.7±1.4	0.01	77.7±1.4	-0.16	77.3±1.9	-0.04	0.65

* Only subjects taking hypnotics and completed the study were analysed: electroacupuncture (n=27), minimal acupuncture (n=23), and placebo acupuncture (n=14)

† Post hoc group-by-time interaction: electroacupuncture vs placebo acupuncture (P=0.01), minimal acupuncture vs placebo acupuncture (P=0.06), electroacupuncture vs minimal acupuncture (P=0.69)

‡ Post hoc group-by-time interaction: electroacupuncture vs placebo acupuncture (P=0.09), minimal acupuncture vs placebo acupuncture (P=0.76), electroacupuncture vs minimal acupuncture (P=0.02)

In terms of TCM theory, acupuncture should be customised according to TCM diagnoses and clinical response to acupuncture treatment. We are uncertain whether individualised acupuncture would achieve better efficacy. Another potential factor is the length of treatment. The 3-week treatment period may be too short, and a difference between 'real' and 'placebo' acupuncture might have emerged if the treatment had been longer. The other potential factor relates to the biophysiologic mechanism of acupuncture.[4] Previous studies have shown that acupuncture can enhance a sympatho-inhibitory effect, opioid-dependent analgesic effect, and nocturnal melatonin secretion. It is uncertain whether these acupuncture-induced biophysiologic effects failed to occur in most of our subjects who were using antidepressants, sedatives, or hypnotics.

Nonetheless, the current study included a well-documented screening process, proper randomisation, placebo acupuncture needles, validated subjective scales, objective measures, and comprehensive adverse event monitoring. In addition, the sample size is the largest to date among other published studies.[5] Almost all subjects were unable to tell the kind of acupuncture they had received, so the blinding was successful.

Conclusion

The effectiveness of acupuncture as an intervention for residual insomnia in MDD was mild at best, mainly owing to its non-specific effects. After 3 weeks of thrice-weekly acupuncture treatment, a high proportion of patients remained significantly affected by insomnia. It is uncertain whether TCM pattern-based individualised acupuncture or acupuncture treatment of longer duration can improve its effectiveness for insomnia. Further studies are needed to explore treatments for this debilitating and persistent problem, which could affect the long-term outcome of MDD. Cognitive-behavioural therapy is a promising treatment for insomnia and its applicability as an intervention for patients with residual insomnia associated with MDD should be explored.

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