Title: Insomnia with objective short sleep duration is associated with a reduced response to acupuncture: a secondary analysis of three randomized controlled trials

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Abstract

Study objectives

Insomnia with polysomnography-derived short sleep duration has been shown to have multiple biological risks and is proposed as the most biologically severe phenotype of the disorder. Preliminary data has suggested that this phenotype has a reduced response to non-pharmacological treatments and actigraphy can be used as a substitute of polysomnography to predict treatment response. The aim of this secondary analysis was to determine whether objective sleep duration was related to the response to acupuncture and whether actigraphy-derived sleep variables could be used as predictors of treatment response.

Methods

We pooled data from 3 randomized, placebo-controlled trials of acupuncture for insomnia. A reduction of Insomnia Severity Index score ≥8 points from baseline to 1-week posttreatment was used to define treatment response.

Results

A total of 185 subjects who had laboratory-based polysomnography for at least 7 hours were included; 62 of which (33.5%) had objective sleep duration <6 hours, while 50 subjects (27.0%) were classified as responders. Non-responders were significantly more likely to have below tertiary level education (P = 0.04) and objective short sleep duration (P = 0.02), while baseline sleep-diary and actigraphy-derived total sleep time and sleep efficiency were not significant predictors. Multivariate logistic regression showed that objective sleep duration was the only significant predictor of treatment response (OR = 2.23, 95% CI 1.01 to 4.91, P = 0.048).

Conclusions

Despite the marginally significance level, our finding was in line with the literature that insomnia with objective short sleep duration was associated with a reduced treatment response.

Keywords: Insomnia; acupuncture; predictors; sleep study; electroencephalography; phenotype; morbidity; mortality.

1. Introduction

Population-based studies have consistently shown that disturbed sleep and short sleep duration are associated with increased risks of morbidity and all-cause mortality [1]. Using actigraphy and polysomnography as objective measures of sleep, Smagula et al. [2] found that short sleep duration and sleep fragmentation had both independent and indirect effects via inflammatory burden on mortality. Kripke et al. [3] found that actigraphy-derived short sleep and lower sleep efficiency were significantly associated with higher mortality in elderly women. The literature supports that insomnia and short sleep duration are independently correlated with increased health risks. The combination of insomnia and short sleep duration within the same individual appears especially detrimental.

Vgontzas et al. [4] postulated that insomnia with objectively measured short sleep duration may be a phenotype that is associated with stronger biological risk, while insomnia with objective longer sleep duration is characterized by sleep misperception, lack of physiological arousal, higher rate of remission, and lower risk of morbidity and mortality. Emerging evidence seems to agree that insomnia with objective but not subjective short sleep duration is associated with increased cardiometabolic risks [5,6]. Vgontzas et al. [4] further commented that the 2 phenotypes may differ in terms of treatment response. Insomnia with objective short sleep duration may respond better to treatments that primarily aim at decreasing physiological hyperarousal and increasing sleep duration (e.g., medications and other biological treatments), whereas the other phenotype may require treatments that primarily target at decreasing cognitive-emotional hyperarousal and altering sleep misperception (e.g., cognitive-behavioral therapy). Since the current guidelines do not recommend polysomnography for routine assessment of insomnia [7,8], the use of objective sleep duration for phenotyping may have significant impact on how we diagnose and treat insomnia. A recent study supported that insomnia with objective short sleep duration was associated with a blunted response to cognitive-behavioral therapy for insomnia (CBT-I) [9], but another study found no difference in treatment response between subjects with objective short or longer sleep duration [10]. The difference in findings may be due to CBT-I's variable effects on physiological arousal. Despite a strong efficacy in reducing anxiety symptoms [11] and self-report ratings of pre-sleep arousal [12], data on CBT-I's effects on physiological arousal during sleep is limited. The study by Bathgate et al. [9] added that actigraphy may be used if polysomnography is not available because the authors found that actigraphy-derived sleep time had a high sensitivity and specificity to predict remission at 6-month follow-up.

Acupuncture is one of the complementary and alternative medicine therapies for insomnia [13] and is performed by inserting needles at special points on the body, called acupoints, followed by manual or electrical stimulation. Previous systematic reviews have shown that acupuncture possesses mild hypnotic effect for the treatment of primary and comorbid insomnia [14,15]. The mechanism of action of acupuncture is unclear, but a large part of its effect may be due to non-specific factors, including the ambiance of the practice setting, the time and quality of attention provided by the practitioner, and the expectations of the patient [16]. These non-specific factors may help to reduce cognitive-emotional hyperarousal, which is proposed to be more common in insomnia with objective longer sleep duration, as compared to insomnia with objective short sleep duration [4]. In view of the limited literature on using objective sleep duration for insomnia phenotyping, we aimed to examine whether insomnia with objective short and longer sleep duration had a different response to acupuncture. We also tested whether actigraphy-derived sleep variables can be used as predictors of treatment response. Due to the limited physiological but strong non-specific effects of acupuncture, we hypothesized that there was a reduced efficacy of acupuncture in subjects with insomnia and objective short sleep duration.

2. Method

2.1. Subjects

We pooled the data of 3 randomized controlled trials (RCTs) (ClinicalTrials.gov identifier: #NCT00839592, #NCT00838994, #NCT01707706) [17-19]. A total of 288 participants were randomized to receive traditional acupuncture, minimal acupuncture, or non-invasive placebo acupuncture. This secondary analysis involved 185 participants who had overnight polysomnography to rule out specific sleep disorders and the recording lasted for at least 7 hours. Participants were recruited from the community and at psychiatric outpatient clinics in Hong Kong. Two of the RCTs included people with residual insomnia associated with major depressive disorder [17,18] and one RCT was on people with primary insomnia [19]. The complete list of inclusion and exclusion criteria is available from the clinicaltrials.gov registry. In brief, participants had to be ethnic Chinese, aged 18-70 years, who fulfilled the insomnia symptoms and impairment criteria of the DSM-IV-TR diagnosis of primary insomnia [20], had been suffering from insomnia ≥ 3 nights per week for at least 3 months, had an Insomnia Severity Index (ISI) [21] score of at least 15, had no specific sleep disorders, including parasomnia, circadian rhythm sleep-wake disorder, sleep apnea, or periodic limb movement disorder as assessed by interview or polysomnography, and had not received any acupuncture in the past 12 months. For the participants with past episodes of major depressive disorder, the episodes had to fulfill the diagnostic criteria of DSM-IV-TR.

2.2. Study design

All procedures used in the studies were reviewed and approved by the local institutional review board. Subjects underwent telephone screening, face-to-face interview, and laboratory-based polysomnography (Alice 4 Diagnostics System, Respironics, Atlanta, Georgia). A monitoring montage consisting of electroencephalography, chin electromyography, electro-oculography, electrocardiography, airflow, respiratory effort, pulse oximetry, anterior tibialis electromyography, snoring sound, and body position monitoring was used. Polysomnography was scored according to the standard Rechtschaffen and Kales criteria by a registered polysomnographic technologist.

2.3. Intervention

For traditional acupuncture, the acupuncture points used were the same in our 2 RCTs [17,18] and included Yintang (EX-HN3) and Baihui (GV20), bilateral Ear Shenmen, Sishencong (EX-HN1), and Anmian (EX). In the most recent RCT [19], additional points, including Neiguan (PC6), Shenmen (HT7), and Sanyinjiao (SP6) were used. Subjects receiving minimal acupuncture [18,19] were needled superficially at points that have no therapeutic effects according to the traditional Chinese medicine theory. 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); "lower leg", 0.5 inch dorsal to Xuanzhong (GB39); and "deltoideus" (in the middle of the line insertion of Binao LI14 and acromion). For points on 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. The points selected had been used in previous acupuncture studies as sham controls [e.g., 22]. Details of the electro-stimulation procedure can be found in our previous papers [17-19]. For placebo acupuncture, Streitberger placebo needles were placed [23] 1 inch beside the acupuncture points used in traditional acupuncture to avoid therapeutic effect. The placebo needle was connected to an electric stimulator but with zero frequency and amplitude as to mimic real acupuncture. Acupuncture was performed by the same acupuncturist with at least 3 years of clinical experience of providing acupuncture treatment 3 times per week for 3 consecutive weeks.

2.4. Sleep diary, ISI, Hospital Anxiety and Depression Scale (HADS), and actigraphy

Major assessments were conducted at baseline and 1-week posttreatment. Subjects completed 1-week sleep diary, ISI, Hospital Anxiety and Depression Scale (HADS) [24] and received 3 days' [17] or 7 days' [18,19] actigraphy. The daily sleep diary [25] inquired about bedtime and rising time, from which total time in bed (TIB) was calculated. Subjects were also advised to estimate sleep onset latency, wake after sleep onset, the number of wakening, early morning awakening, and TST. Sleep efficiency was calculated as (TST/TIB × 100%). The ISI is designed to assess the perceived severity of insomnia symptoms and the associated functional impairment, with scores ranging from 0 to 28. The HADS is a self-report scale used to assess the severity of anxiety and depression, with higher scores indicating greater severity. Chinese versions of the ISI and HADS were used [26,27]. The cut-off point for ISI to indicate severe insomnia was 21/22 [21]. For HADS, the cut-off point was 15/16 for psychiatric cases [27]. Actigraphs (Model Actiwatch-2; Respironics Inc; Murrysville, Pennsylvania; Octagonal Basic Motionlogger, Ambulatory Monitoring, Inc., Ardsley, NY) are watch-like devices that record individuals' physical movements by means of an accelerometer-microprocessor link. Wrist actigraphy is considered as a valid objective measure of sleep because movement is related to wakefulness and lack of movement with sleep [28]. In this study, the recording length of epoch was set at 1 minute and the data was analyzed with Actiware software (Version 5, Respironics Inc) or Action-W software (Version 2.0, Ambulatory Monitoring, Inc.).

2.5. Classification of objective short and longer sleep duration

Insomnia with short sleep duration was defined as polysomnography-derived sleep duration <6 hours. The cutoff has been used in previous studies [4-6] and proven optimal for predicting morbidity and mortality among subjects with insomnia.

2.6. Classification of responders and non-responders

In line with a previous study [29], participants with ISI scores improved by 8 points or more from baseline to 1-week posttreatment were classified as responders. The ISI score was used because it assesses both severities of insomnia and related daytime impairments.

2.7. Statistical analysis

Independent t test was used to determine if insomnia with objective short and longer sleep duration differed in regard to age, insomnia duration, baseline ratings on ISI and HADS, and baseline sleep diary and actigraphy variables. Chi-square test was used to examine whether there were differences in sex, marital status, and education level between the 2 groups. Differences in treatment response in regard to sociodemographic and clinical variables were tested by independent t or chi-square test. Univariate and multivariate logistic regression analyses were conducted with response or non-response as the binary variable, and the variables that had a significant bivariate relationship with response as potential predictors. As the study was exploratory, no adjustment for multiple comparisons was made for the univariate and multivariate analyses. Odds ratios (ORs) and their 95% confidence interval (CI) were calculated.

3. Result

3.1. Proportion with objective short sleep duration and response rate

Sixty-two of the 185 subjects (33.5%) had objective short sleep duration. Response at 1-week posttreatment was observed in 50 participants (27.0%). The decrease in ISI score in the 50 responders and the 135 non-responders was 10.3 (SD = 2.7) and 2.3 (SD = 3.0), respectively.

3.2. Relationship between objective short sleep duration and sociodemographic and clinical variables (Table 1)

Subjects with objective short sleep duration had significantly lower educational level (P = 0.003) and lower actigraphy-derived sleep efficiency (P = 0.002) compared to subjects with objective longer sleep duration. There were no other significant differences between the 2 groups.

3.3. Predictors of treatment response by sociodemographic variables, baseline severity and type of acupuncture treatment (Table 2)

Non-responders were significantly more likely to have below tertiary level education (P = 0.04) and objective short sleep duration (P = 0.02). Baseline actigraphy-derived total sleep time and sleep efficiency were not significant predictors.

3.4. Logistic regression (Table 3)

Multivariate logistic regression showed that objective sleep duration was the only significant predictor of treatment response (OR = 2.23, 95% CI = 1.01, 4.91, P = 0.048).

4. Discussion

We performed a secondary analysis on whether polysomnography-derived sleep duration was a predictor of response in subjects with insomnia treated with acupuncture. Our study showed that polysomnography-derived sleep duration and educational level were associated with treatment response; upon multivariate logistic regression, only sleep duration remained a significant predictor. Subjects with insomnia and objective sleep duration 6 hours or longer had

2.23 times higher chance of treatment response than insomnia with sleep duration less than 6 hours. Our findings support the growing literature on using polysomnography-derived sleep duration for subtyping insomnia [4]. We could not replicate the findings of a recent study which showed that actigraphy-derived sleep duration was able to predict treatment response in subjects with insomnia treated by cognitive-behavioral therapy [9].

The finding that insomnia with objective short sleep duration had a reduced response to acupuncture was in line with our current understanding on the efficacy of acupuncture for insomnia. Acupuncture possesses a mild hypnotic effect and its efficacy is largely related to non-specific therapeutic components. For a phenotype that is characterized by high level of physiological arousal, the effect of acupuncture may be less pronounced. We found that there was no difference in the response rate between different types of acupuncture treatment. This finding can be due to our stringent criteria of response, but it also suggests that acupuncture has a strong placebo component [30].

In our sample of insomnia patients, we found that educational level was related to objective sleep duration and the response to acupuncture. Low educational attainment has been shown to be a correlate of insomnia in population-based survey [31,32], but the finding has not been consistent. A study in Asian outpatients with major depressive disorder showed that low educational level was associated with severe insomnia [33]. One possible explanation to account for the relationship between low educational attainment and poor response to acupuncture may be related to subjects' attitudes toward acupuncture trials. A previous survey of breast cancer patients showed that those with a higher level of education were more willing to participate in an acupuncture trial than those with lower education [34]. Skeptical attitudes toward experimentation may hamper treatment response in our sample with lower educational level.

In this study, actigraphy-derived sleep efficiency was significantly lower in subjects with insomnia and objective short sleep duration compared to insomnia with objective longer sleep duration; however, actigraphy-derived parameters were not associated with treatment response. Contrary to a recent study [9], our findings did not support using actigraphy as a substitute to classify subjects into objective short or longer sleep duration. Previous studies have shown that actigraphy tends to overestimate sleep duration compared to polysomnography and the correlation between actigraphy- and polysomnography-derived sleep duration is low to moderate [35-37]. Another problem with actigraphy is a lack of control over extended period of time in bed, which can result in sleep fragmentation, but relatively normal sleep duration. Further studies are needed for testing the use of actigraphy to classify insomnia into different phenotypes.

Although current guidelines do not support polysomnography for routine assessment of insomnia [7,8], with growing evidence that objective sleep duration may be useful for the assessment and treatment of insomnia, more convenient and less costly methodology should be used for sleep studies. Preliminary data has shown that forehead electroencephalogram electrode set is reliable for sleep staging and suitable for patient's self-application during home polysomnography [38,39]. Further studies on the application of new technology in insomnia research are needed.

Our study has several limitations. First, polysomnography was conducted based on subjects' usual bedtime and rise time; hence our study did not fix the recording time. Previous studies on the biological risks and treatment response of insomnia with objective short sleep duration have used both fixed [5] and non-fixed [6,9,10] recording time. Also, current guidelines do not endorse whether to employ a fixed time in bed or to allow subjects to choose their time in bed during polysomnography [40]. Further studies are needed to determine whether it is worthwhile to standardize the methodology of polysomnography. There was no significant difference in the response rate across treatment groups; hence we pooled the 3 groups in statistical analysis. It may be preferable to analyze subjects receiving different treatments (traditional, minimal, or placebo acupuncture), but the statistical power will be reduced. We used the ISI cutoff of ≥8 to define treatment response; however, the cutoff has not been specifically validated in the Chinese population. Our response rate, at about 30%, was relatively low, compared to cognitive-behavioral therapy for insomnia, which was shown to have a response rate at around 60% [29]. The low response rate may be due to the fact that almost 70% of our subjects were patients in regional psychiatric clinics; hence our results may not be generalizable in other settings. Lastly, the significant association between objective sleep duration and treatment response was marginally significant.

In conclusion, polysomnography-derived objective sleep duration was shown to predict the response to acupuncture in subjects with insomnia, whereas subjective and actigraphy-derived sleep duration and questionnaire scores were not significant predictors. Our finding is in line with the postulation that insomnia with objective short sleep duration may require treatments that primarily aim at decreasing physiological hyperarousal. Further studies should be performed on the proposed insomnia phenotyping that employs objective sleep duration.

Conflict of interest

None.

Acknowledgments

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Table 1. Sociodemographic and baseline characteristics of the sample

Variable [a]	All participants n = 185	Insomnia with PSG-derived TST < 6 hours n = 62	Insomnia with PSG-derived TST ≥ 6 hours n = 123	*P* value t-test/chi-square
Age, y	48.7 ± 9.5	50.3 ± 9.1	47.9 ± 9.6	0.10
Female gender	145 (78.4)	48 (77.4)	97 (78.9)	0.82
Education level				0.003
Tertiary or above	63 (34.1)	12 (19.4)	51 (41.5)	
Marital status				0.47
Never married	38 (20.5)	10 (16.1)	28 (22.8)	
Married/cohabiting	106 (57.3)	37 (59.7)	69 (56.1)	
Divorced/widowed	41 (22.2)	15 (24.2)	26 (21.1)	
Occupation				0.17
Professional and associate professional	23 (12.4)	3 (4.8)	20 (16.3)	
Skilled and semi-skilled worker	37 (20.0)	11 (17.7)	26 (21.1)	
Unskilled worker	24 (13.0)	10 (16.1)	14 (11.4)	
Retired	22 (11.9)	7 (11.3)	15 (12.2)	
Unemployed/housework	79 (42.7)	31 (50.0)	48 (39.0)	
Chronic medical illnesses [b]	36 (19.5)	10 (16.1)	26 (21.1)	0.42
Insomnia duration, y	10.4 ± 9.7	10.8 ± 10.2	10.3 ± 9.4	0.72
Insomnia diagnosis				0.21
Primary insomnia	59 (31.9)	16 (25.8)	43 (35.0)	
Insomnia with past MDE	126 (68.1)	46 (74.2)	80 (65.0)	
Current hypnotics use	58 (31.4)	21 (33.9)	37 (30.1)	0.60
ISI total score	19.2 ± 3.1	18.9 ± 3.2	19.4 ± 3.1	0.27
Sleep diary variables				
TST	311.6 ± 78.9	306.0 ± 69.8	314.4 ± 83.2	0.50
SE	65.8 ± 16.2	64.3 ± 16.4	66.6 ± 16.1	0.37
Actigraph variables				
TST	402.0 ± 76.2	393.8 ± 83.7	406.1 ± 72.1	0.30
SE	82.8 ± 11.5	79.2 ± 13.3	84.6 ± 10.0	0.002
HADS total score [c]	18.4 ± 7.9	20.5 ± 9.2	17.7 ± 8.2	0.14
Acupuncture treatment				0.90
Traditional	76 (41.1)	25 (40.3)	51 (41.5)	
Minimal	47 (25.4)	17 (27.4)	30 (24.4)	
Placebo	62 (33.5)	20 (32.3)	42 (34.1)	

HADS, hospital anxiety and depression scale; ISI, insomnia severity index; MDE, major depressive episode; PSG, polysomnography; SE, sleep efficiency; TST, total sleep time.

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

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

[c] Only 94 participants had HADS data.

Table 2. Prediction of acupuncture response by sociodemographic characteristics and baseline severity

Variable [a]	Responders n = 50	Non-responders n = 135	*P* value t-test/chi-square
Age, y	48.5 ± 8.3	48.8 ± 9.9	0.88
Female gender	40 (78.4)	105 (77.8)	0.74
Education level			0.04
Tertiary or above	23 (46.0)	40 (29.6)	
Marital status			0.94
Never married	10 (20.0)	28 (20.7)	
Married/cohabiting	28 (56.0)	78 (57.8)	
Divorced/widowed	12 (24.0)	29 (21.5)	
Occupation			0.78
Professional and associate professional	7 (14.0)	16 (11.9)	
Skilled and semi-skilled worker	11 (22.0)	26 (19.3)	
Unskilled worker	5 (10.0)	19 (14.1)	
Retired	4 (8.0)	18 (13.3)	
Unemployed/housework	23 (46.0)	56 (41.5)	
Chronic medical illnesses [b]	9 (18.0)	27 (20.0)	0.76
Insomnia duration, y	9.1 ± 7.4	10.9 ± 10.3	0.24
Insomnia diagnosis			0.47
Primary insomnia	18 (36.0)	41 (30.3)	
Insomnia with past MDE	32 (64.0)	94 (69.6)	
Current hypnotics use	11 (22.0)	47 (34.8)	0.10
ISI total score ≥ 22 [c]	16 (32.0)	26 (19.3)	0.07
Sleep diary variables			
TST < 6 hours	14 (28.0)	37 (27.4)	0.94
SE < 75% [d]	21 (42.0)	37 (27.4)	0.06
Actigraph variables			
TST < 6 hours	16 (32.0)	33 (24.4)	0.30
SE < 75% [d]	15 (30.0)	26 (19.3)	0.12
PSG-derived TST < 6 hours	10 (20.0)	52 (38.5)	0.02
HADS total score ≥ 16 [e]	13 (52.0)	45 (68.2)	0.15
Acupuncture treatment			0.42
Traditional	23 (46.0)	53 (39.3)	
Minimal	14 (28.0)	33 (24.4)	
Placebo	13 (26.0)	49 (36.3)	

HADS, hospital anxiety and depression scale; ISI, insomnia severity index; MDD, major depressive episode; PSG, polysomnography; SE, sleep efficiency; TST, total sleep time.

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

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

[c] Cut-off point for severe insomnia.

[d] Equivalent to 6 hours' sleep for a fixed time in bed of 8 hours.

[e] Cut-off point for psychiatric cases. Only 94 participants had HADS data.

Table 3. Factors associated with a better response to acupuncture by univariate and multivariate adjustment.

Variables	Univariate OR (95% CI)	*P* value	Multivariate OR (95% CI)	*P* value
PSG-derived TST ≥ 6 hours	2.51 (1.16, 5.44)	0.02	2.23 (1.01, 4.91)	0.048
Tertiary or above in education	2.02 (1.04, 3.94)	0.04	1.74 (0.88, 3.46)	0.11

PSG, polysomnography; TST, total sleep time.