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Acupuncture Increases Nocturnal Melatonin Secretion And Reduces Insomnia And Anxiety

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by Spence, D Warren; Kayumov, Leonid; Chen, Adam; Lowe, Alan; Et al

The incidence of insomnia is estimated to be 35% to 40% of the adult population. It currently affects more than 60 million Americans, and this figure is expected to grow to 100 million by the middle of the 21st century.^{1,2} The defining characteristic of insomnia in the context of anxiety is a pattern of multiple arousals from sleep. Anxious subjects have difficulty maintaining sleep, spend less time in deep sleep, and their sleep is more fragmented than that of normal subjects.³⁻⁵ Conversely, sleep deprivation may produce symptoms that fall within the total complex of anxiety.⁴ Although current opinion suggests that insomnia and anxiety are separate entities, their symptoms overlap considerably. Individuals with insomnia and individuals with anxiety have elevated psychosomatic profiles on psychological tests,⁶⁻⁸ maintain chronically high states of arousal, and rely on an "internalizing" style of conflict resolution (DSM-IV, 4th Edition).⁹ These commonalities have prompted speculation¹⁰ that a common thread underlies the conditions, although their exact relationship, namely whether insomnia is the product of or simply a correlate of anxiety, is still inconsistently viewed in current diagnostic systems (i.e., the ICD-IO, DSM-IV and ICSD [International Classification of Sleep Disorders]).¹¹ It is nevertheless true that the dual diagnostic pattern of anxious insomnia is the most commonly seen problem in sleep disorder clinics today.¹² The high rate of comorbidity between anxiety and insomnia, coupled with the high population incidence of insomnia, undoubtedly account for this phenomenon. Although we are unaware of any epidemiological studies on the incidence of anxiety which does not fulfill the criteria for a defined anxiety disorder, it is reasonable to infer that a large segment of the population may have "subsyndromal" anxiety, symptoms that are not associated with debilitating psychopathology, but which nevertheless produce a significant degree of mental discomfort.

Traditional treatment strategies for anxious insomnia have emphasized benzodiazepines. The useful anxiolytic effects of these agents have made them the most widely prescribed of all pharmaceuticals.¹³ The risks of benzodiazepines, however, are well documented and involve physical as well as psychological effects. These include their potential to promote dependence or acute toxicity in overdose.^{14,15} Other adverse effects include sedation, psychomotor and cognitive impairment, memory loss, potentiation of other CNS

depressants, and treatment-emergent depression.¹⁶ Acupuncture, which relies on the release of neurally active agents from endogenous stores, has been shown to have a superior side effect profile compared to some psychoactive drugs^{17,18} and may thus represent a means for addressing the concerns about benzodiazepine therapy.

Evidence supporting acupuncture's utility as a treatment for insomnia has come from a variety of sources, including the non-western scientific literature. Among these, investigations by Nan and Qingming,¹⁹ Jiarong,²⁰ and Cangliang²¹ showed positive results. The shortcoming of these studies, however, is that their dependent measures have usually been inexact, relying mainly on subjective accounts of sleep experience or duration, and consequently, despite the consistency of their support for acupuncture, they are difficult to evaluate. Several European studies²²⁻²⁴ used polysomnography to measure acupuncture effects on sleep disorders, but all failed to monitor nocturnal neurochemical changes which would have strengthened their experimental design.

It is known that stress mediation is multifactorial and strongly influenced by GABAergic²⁵ and dopaminergic neurotransmission.²⁶⁻²⁷ The neurohormone melatonin may also be involved in these effects. Melatonin is a CNS depressant with anxiolytic,²⁸⁻²⁹ mild hypnotic³⁰ and anticonvulsant actions³¹ which may be related to its enhancements of GABAergic³²⁻³³ and striatal dopaminergic³⁴⁻³⁵ transmission. The effect of melatonin on mood and chronobiological functions has been established in a number of studies. The pattern of melatonin secretion over a 24-hour period is widely accepted as a measure of circadian activity in humans.^{36,37} This pattern is disrupted in insomnia. Compared to normal patients, those with insomnia have suppressed nocturnal outputs of melatonin³⁸⁻³⁹ and are more likely to have histories of depression.⁴⁰ As noted above, the anxiolytic effects of melatonin have been recently established in rodent models.⁴¹⁻⁴³ In humans, abnormalities in melatonin secretion have been confirmed in patients with bipolar I disorder.⁴⁴ Taken together these findings support the inference that melatonin deficiency may play a key role in anxiety-associated insomnia.

Some evidence has also been provided that melatonin interacts with the opioid peptides.⁴⁵⁻⁴⁶ Melatonin is both utilized and synthesized following acute pain episodes in humans,⁴⁷ the function of which may be to modulate fluctuations in opioid receptor expression and levels of beta-endorphin.⁴⁸ The relationship of melatonin with the opioidergic system is complex and not completely understood, although there is evidence that it has mixed opioid receptor agonist-antagonist activity.⁴⁹ In aggregate these findings lend support to the postulate of a "melatonin-opioid axis"⁴⁸ possibly serving a variety of protectant functions.

Evidence of the endogenous opioid basis of acupuncture analgesia has been supported both in human^{50,51} and animal studies.⁵²⁻⁵³ These have shown that acupuncture analgesia treatment increases CSF levels of met-enkephalin, beta-endorphin, and dynorphin and can be reversed by the opiate receptor blocker naloxone. These findings are relevant to the present study inasmuch as

the opioids not only mediate analgesia they also play a central role in subjectively experienced stress. In normal human subjects plasma beta endorphin levels are increased just before or after a stressful experience,⁵⁴⁻⁵⁵ and are associated with feelings of euphoria that is reported following, for example, bungee jumping.⁵⁶ In depressed patients elevated plasma beta endorphin levels are positively correlated with severe stress and phobia,⁵⁷ while anxious subjects show increases in beta endorphin immediately before and after cognitive and social Stressors.⁵⁸ There is thus a reasonable basis for the inference that acupuncture modulates anxious responses and that these effects are mediated by the endogenous opioid system.

At the present time there have been only a few studies of acupuncture's effects on melatonin. In one of these however⁵⁹ acupuncture was found to promote increases in melatonin in the pineal, the hippocampus, and in serum in rats.

The present study sought to use objective measures, including an analysis of 24-hour melatonin levels in urine, to evaluate acupuncture's effects on insomnia and anxiety. The hypotheses for this study were that a 5-week regimen of acupuncture would promote statistically significant improvements in polysomnographic markers of sleep quality, reduce anxiety (scores on the STAI), and enhance endogenous melatonin production in individuals scoring high on measures of anxiety and insomnia.

METHODS

Eighteen adult volunteers served as subjects in the study. To fulfill the inclusion criteria they had to report having symptoms of insomnia for at least two continuous years immediately prior to the study and to score above 50 (anxiety range) on the Zung Anxiety Self Rating Scale. The Zung is a validated self-administered rating scale⁶⁰ employing a 20-item list of symptoms in a Likert scale response format. The selected subjects had symptoms of anxiety but did not fulfill DSM-IV criteria for any particular anxiety disorder (i.e., their condition was subsyndromal). Of the 18 subjects 11 were women and 7 were men. all subjects were between the ages of 18 and 55. Their mean age was 39.0 ± 9.6 years. One was of Chinese descent, two were black, and 15 were Caucasian. Prior to participation in the study all had heard of acupuncture and three reported having had acupuncture treatment in the past for conditions unrelated to their sleep problems. In no instance did any of the subjects have acupuncture treatment in the two years prior to participation in the study. The subjects were recruited through several sources, including newspaper advertising, posters placed on hospital bulletin boards, announcements made through the local chapter of an independent sleep-wake disorders patient support group, and occasional notices on a public service program of a local television station.

An initial screening interview was carried out by a psychiatrist or by an associate qualified in psychological interviewing. A preliminary diagnosis for inclusion in the study was made on the basis of the International Classification of Sleep Disorders. The subjects had to report having at least two symptoms of

insomnia (fragmented sleep, frequent awakenings, early morning awakenings followed by an inability to fall back to sleep, feeling tired in the morning despite having spent a normal period of time in bed) for at least two years duration and that this experience was not related to an obvious environmental stressor. Potential participants with any concurrent medical, psychological, or psychiatric factors which might account for their sleep difficulties were excluded from the study. Other exclusion criteria were: a history of shift work within five years prior to the study, presence of other sleep disorders, age of less than 18 or greater than 55, a history of alcohol or drug abuse, current use of neurally active medications, or concurrently undergoing psychotherapy. The study protocol was approved by the Human Ethics Committee of the University of Toronto, and written informed consent was obtained from all participants after the procedures had been fully explained. All subjects were asked to sign a Committee-approved consent form confirming that they understood the goals, risks, and potential benefits of the study and their right to withdraw from the study at any time.

The study investigated the use of traditional (symptomatic) acupuncture without augmentation from herbs, pharmaceuticals or hormonal agents. Concentrations of a major melatonin metabolite 6-sulpha toxymelatonin (aMT6s) in urine were measured before and after the study (as described below). This was to evaluate changes in the neurohormone as released from endogenous sources (melatonin was not administered as an experimental treatment). For each subject the trial was conducted over a 7-week period during which the active phase of acupuncture therapy was 5 weeks (two sessions per week, 10 sessions in total). The acupuncture was administered by a master acupuncturist (AC) who was also the director of an acupuncture training program and clinic. The acupuncture needles were disposed of immediately after use and sterile technique was strictly observed. Each acupuncture session lasted approximately one hour. During the 1-week period preceding and following the active treatment phase, subjects were tested with polysomnography at an administratively convenient time in the Sleep Research Laboratory of the University Health Network, Toronto Western Hospital site. Figure 1 illustrates the design of the study.

Two consecutive overnight polysomnographic studies were performed at baseline (before treatment) and at the end of the 5 weeks of treatment with acupuncture. Polysomnographic results obtained on the first night during the before and after stages of the experiment were not included in the analysis to avoid a possible "first-night" effect.⁶¹ The sleep parameters included the sleep latency, sleep efficiency, the total sleep time, the arousal index, the percentage of REM sleep and REM latency, and the amount of time spent in stages 1 through 4. Additionally data were collected on the Alpha rating, an evaluative index of sleep quality⁶² which included an assessment of sleep fragmentation. For the baseline recordings, subjects chose their own retiring and wake up times as was consistent with their normal routine. Just before retiring on the second night of polysomnographic testing subjects were also asked to fill out several paper and pencil tests of mood and cognitive efficiency. These included the Toronto Alexithymia Scale,⁶³ a standard pre-sleep questionnaire; the Stanford Sleepiness Scale (SSS)⁶⁴; and a seven-item Fatigue Scale. Additionally they

were asked to fill out the State-Trait Anxiety Inventory⁶⁵ to gauge the effect of acupuncture on anxiety. The Center for Epidemiological Studies Depression Scale (CES-D)⁶⁶ was used to assess the presence of depressive symptoms.

On the following morning, immediately after awakening, each subject completed a standard post-sleep questionnaire, the SSS, and the Fatigue Scale. Approximately 20 minutes after awakening, subjects assessed their level of fatigue and sleepiness using the following scales: the Fatigue Severity Scale, the Epworth Sleepiness Scale,⁶⁷ the Toronto Western Hospital Fatigue Questionnaire, the Fatigue Scale, and the FaST Adjective Checklist. The results from testing were consolidated to form a composite fatigue score (comfatigue), which has been validated in studies on patients with multiple sclerosis.⁶⁸

After completing the fatigue questionnaires, the subjects were asked to complete a complex verbal reasoning task.⁶⁹ Accuracy and time to complete the test were assessed.

During both the pre- and posttest assessment phases urine samples were collected and the concentration changes of aMT6s (which reflects the changes in endogenous levels of melatonin) were subsequently measured with a commercially available competitive immunoassay ELISA kit (Buhlmann Laboratories AG, Allschwil, Switzerland). At aMT6s concentrations 2.0 and 12.5 ng/ml the intraassay coefficients of variation were 5.5% and 3.5%; at concentrations 5.0 and 40.0 ng/ml the interassay coefficients of variation were 0.7% and 9.7%. As discussed above, the pattern of melatonin secretion has been widely accepted as a measure of circadian activity in humans,^{36,37} and there is further evidence of decreases in melatonin output in patients suffering from insomnia. ^{39,40,70}

Statistical Analysis

The results of the polysomnographic recordings and psychometric testing were compared on a before and after basis for all subjects and are shown here as mean, scores. The matched pairs t test was used to assess the statistical significance of these changes. The melatonin analysis was treated as a "two within-subjects variables experiment," a type of multiple repeated measures test, where the two within-subject factors were (a) "time of day" and (b) "phase of the experiment" (i.e., before or after the experiment). These comparisons were carried out using the Statistical Package for the Social Sciences software (SPSS for Windows). The null hypothesis was rejected if the differences were significant at the 5% level.

RESULTS

The major objective and subjective measures obtained in the before and after stages of the experiment are displayed separately for convenience in Table 1 and Table 2. Objective measures (i.e., the polysomnographic recordings) are separated into three categories: sleep continuity, sleep architecture, and REM sleep, as shown in Table 1. The subjective variables, based on self-report

questionnaires and performance tests, are separately identified in Table 2. The means, their differences, standard deviations, and two-tailed significance levels are also shown for each sleep and test variable.

Sleep Duration and Sleep Quality Variables

The acupuncture treatment used in this study improved several polysomnographic parameters of sleep architecture. Among the sleep continuity variables, sleep onset latency (SOL) and the arousal index dropped significantly ($p = 0.003$ and $p = 0.001$, respectively), reflecting improvements in both sleep initiation and maintenance. The total sleep time (TST) and sleep efficiency similarly increased ($p = 0.001$ and $p = 0.002$, respectively). The Alpha index also improved significantly ($p = 0.017$). Some improvement in sleep quality was confirmed by the increase in the amount of time spent in stage three (slow wave) sleep ($p = 0.023$), but the amount of time spent in stage four sleep did not significantly change in the before-after comparison. The percentage of REM sleep and REM sleep latency, as well as the amount of time spent in stages one and two sleep remained unchanged following acupuncture.

Subjective Variables: Psychological Factors, Sleepiness, Fatigue, and Alertness

As shown in Table 2, both state and trait anxiety scores significantly improved ($p = 0.049$ and $p = 0.004$, respectively) following acupuncture. Additionally, scores on the CES-D showed significant improvements ($p = 0.001$). Scores on the Alexithymia Scale did not change significantly.

Scores on the Stanford Sleepiness Scale (SSS) indicated no significant differences (in the before and after comparison) when the test was administered just before the second night of sleep, but did show significant improvements ($p = 0.019$) when subjects were asked to report on their subjective sleepiness in the morning after the second night of sleep. The Fatigue Scale scores revealed a somewhat similar profile, with scores before sleep not showing any significant differences, but scores on the following morning indicated a significant improvement ($p = 0.045$) after 5 weeks of acupuncture. The improvement in fatigue scores were not paralleled by increases in alertness however: the ZOGIM-A, a test which measures alertness, indicated that the subjects felt significantly ($p = 0.004$) less alert following acupuncture. The composite fatigue scores (comfatigue) did not indicate any significant change. The timed test of cognitive skill indicated that subjects were able to perform the test more quickly ($p = 0.001$) following acupuncture, but the performance accuracy, while showing a small improvement, was not statistically significant.

6-Sulphatoxymelatonin Analysis

Urine analysis showed that nocturnal physiological levels of aMT6s increased following acupuncture and decreased during the morning and early afternoon (Figure 2).

Analysis of the main effects showed a significant ($p = 0.001$) interaction

between the two variables "time of day" (representing the four measurement periods 9 p.m. to midnight; midnight to 8 a.m.; 8 a.m. to 3 p.m. and 3 p.m. to 9 p.m.) and "phase of the experiment" (before versus after acupuncture), thus supporting the validity of individual time period comparisons on a pre- and post-treatment basis. No detectable changes (in urinary concentrations of aMT6s) were found for pairwise comparisons of periods 1 and 4 (9 p.m. to midnight, and 3 p.m. to 9 p.m.). Differences for periods 2 (midnight to 8 a.m.) and 3 (8 a.m. to 3 p.m.) however were significant ($p = 0.002$ and $p = 0.037$) reflecting postacupuncture increases in melatonin production at night and decreases during the morning and afternoon.

DISCUSSION

Our initial hypotheses were confirmed by the results of the present investigation. In an open clinical trial of 18 subjects, the administration of 5 weeks of acupuncture, totaling ten treatment sessions, was associated with normalization in a 24-hour profile of urinary aMT6s and a number of objectively measured improvements in sleep continuity and sleep architecture. Additionally, significant improvements in self-reported fatigue and sleepiness paralleled these changes. The exception to this trend was the reduction in alertness as measured by the ZOGIM-A test. As discussed below the apparent inconsistency of reduced alertness following improvements in sleep quality may possibly have been the result of a transition into a more adaptive and qualitatively different type of alertness. Self assessed feelings of anxiety and depression decreased following acupuncture. These findings are fairly consistent with the results of previous investigations showing that acupuncture has a generalized anxiolytic effect,⁷¹⁻⁷³ and with other polysomnographic studies of acupuncture effects in insomnia.²²⁻²⁴

The findings of nocturnal elevations in urinary aMT6s, indicating increased melatonin secretion, paralleled these changes. Melatonin regulates the rhythm of many functions and alterations in its secretory pattern have been found in a number of psychiatric disorders. These have included seasonal affective disorder, bipolar disorder, unipolar depression, bulimia, anorexia, schizophrenia, panic disorder, and obsessive-compulsive disorder,⁷⁴ but at present it has not been confirmed if these changes are causal to or simply a marker of other neurochemical dysfunctionalities. Further, it is not known if melatonin is equally involved in the development of the pathophysiology of each of these disorders. Due to practical limitations we were able to investigate changes in only one neurally active agent, but clearly it would have been desirable to study acupuncture's effects on a range of neurotransmitters which are known to be closely linked to the etiology of anxiety or insomnia. Dysregulation of catecholamine secretion for instance has circadian variations which correlate closely with pathological anxiety states⁷⁵ and moreover have been shown to be regulated by melatonin injections.⁷⁶ Our findings thus raise intriguing questions about the nature and course of acupuncture effects at the neurochemical level. Studies are needed to further elucidate the role of norepinephrine as well as that of serotonin, dopamine, GABA in the changes we observed in melatonin

secretion.

The results for the sleep architecture measurements showed no increases in the percentage of time spent in stages one or two, findings which have doubtful relevance for this clinical sample. Large improvements were seen however in the subjects' transition to stage three or slow wave sleep, reflective of significant gains in the quality of their sleep. A wide variability of responses in this observation reduced the significance level to $p = 0.023$. The percent of stage three sleep increased from a mean of 4.2% before treatment to a mean of 6.1% following treatment, closely approximating the normal mean of 7%. There was considerable variability in the amount of time spent in stage four sleep, with a number of subjects showing no improvement at all, thus accounting for the lack of statistical significance. The variability in responsiveness to acupuncture seen in, for instance, acupuncture analgesia treatment⁷⁷ has been known clinically and in scientific studies for some time. Although this variability has not been satisfactorily accounted for, one hypothesis is that psychological factors may be an impediment to treatment effectiveness. This is consistent with the findings of Widerstrom-Noga⁷⁸ and Creamer⁷⁹ showing that trait anxiety (measured by the STAI) can interfere with the effectiveness of acupuncture analgesia treatment. In this context our findings that, despite the variability of response, acupuncture improved overall sleep quality and had significant effects on anxiety are therefore noteworthy. The possibility that extreme scorers on trait anxiety are poor treatment candidates, or perhaps require additional treatment to show measurable changes, needs to be explored further with a sample that is larger than the one used in the present study.

In the present study subjects were screened to exclude those with clinical levels of psychopathology, including depression. Nevertheless a number of subjects showed elevated scores on the CES-D (depression) scale. This is in accordance with other findings showing that patients with insomnia may have symptoms of anxiety or depression which do not meet criteria for a specific mental disorder (DSM-IV, 4th Edition).⁹ In fact, symptom cooccurrence of anxiety and depression frequently exists in non-clinical samples which do not show serious sleep disturbance.⁸⁰ These symptoms were nevertheless reduced by acupuncture and are consistent with previous reports of acupuncture's effectiveness in treating mood disorders.^{81^82}

A finding that merits closer examination is the apparent lack of consistency implied in the failure of improvements in sleep quality to be accompanied by increasing alertness during the day. In our sample daytime alertness, as evaluated by self assessments or indirectly through measures of performance accuracy, either became worse or showed no improvement even though sleep quality was enhanced. Generally there is a positive correlation between tests of sleepiness (such as the Multiple Sleep Latency Test or MSLT) and daytime alertness (e.g., the Maintenance of Wakefulness Test, the MWT) (i.e., the better the nighttime sleep the greater the alertness during the day). In depressed patients however a negative relationship between the two tests is sometimes found.⁸³ Kayumov et al.⁸⁴ investigated this phenomenon in clinically

depressed patients who also scored high on anxiety measures. In the depressed group the sleep latency on the MWT showed paradoxical increases (i.e., was reflective of alertness) in concordance with the severity of sleep disturbance, whereas in the non-depressed group this did not occur. Our own findings are consistent with these previous studies and support the view⁸⁴ that in depressed or anxious subjects the underlying factors which cause sleep disturbance will also produce heightened alertness during the day. This view emphasizes that qualitative differences exist in the "adaptive" alertness of non-anxious subjects, which is mobilized by relevant environmental Stressors, and the accentuated or "vigilant" alertness of individuals suffering from excess emotional tension. In this group alertness is chronic and preferentially driven by internal rather than environmental demands, thus conferring to it a more invariant and non-discriminatory quality. Our finding therefore that alertness actually decreased following acupuncture may imply the substitution of one type of alertness for another rather than representing a decrement in cognitive efficiency. This possibility needs to be explored with testing instruments which are sensitive to these differences.

In this preliminary study acupuncture was shown to be of value as a therapeutic intervention for insomnia in anxious subjects and may therefore represent an alternative to pharmaceutical therapy for some categories of patients. Further, the central role attributed by classical and modern theories of personality to anxiety as the basis of most psychological defense mechanisms,^{85'86} as well as the evidence that abnormalities in melatonin secretion are involved in a number of psychiatric conditions,⁷⁴ suggest that acupuncture may have broad applicability to other types of psychopathology in which quality of sleep is impaired. An important shortcoming of this study however was its lack of a control group with a placebo acupuncture condition. The findings therefore need to be confirmed with a study employing a more rigorous design.

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