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• Review

Hazards of insomnia and the effects of acupuncture treatment on insomnia

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ABSTRACT

Insomnia is a common disease in modern society; it is made worse by increasingly fierce competition in the workplace and elsewhere, along with rapid economic and social development. Sleep disorders can result in changes in serum biomarkers and decreased immunity, and may cause maladies such as depression and cardiac diseases, as well as many other somatic symptoms. Western medications for treating insomnia can easily lead to addiction and other adverse effects. Fortunately, acupuncture can ease the symptoms of insomnia. This review summarizes the hazards associated with insomnia and the use of acupuncture in its treatment. Furthermore, the authors introduce an effective and low-cost method of treating insomnia with acupuncture. This review indicates that insomnia poses a major threat to mental health through its effects on serum components, heart function and the immune system of patients, which may lead to other physiological disorders. Anxiety and depression are the two main negative emotions affected by insomnia. Acupuncture, which has showed effectiveness against insomnia and its complications, may be an effective and complementary method for the treatment of insomnia and associated maladies.

Keywords: insomnia; complications; acupuncture; depressive disorder; immunity; heart diseases; review

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1 Introduction

Insomnia is a common chronic disease, which can have important negative impacts on health and well-being. In England, the prevalence of insomnia has shown a modest but steady increase over a 15-year period[1]. Insomnia can occur at any age and in individuals of any occupation. A cross-sectional study showed that of 604 Portuguese schoolteachers, 40.6% suffered from symptoms of insomnia; symptoms were correlated with occupational and sociodemographic variables[2]. Another study found that one in five preadolescents and young children of the general population suffered from insomnia. Moreover, the group with the highest prevalence of insomnia symptoms was 11–12 year old girls (30.6%)[3]. At the other end of the age spectrum, insomnia was found in 29.2% of a sample of elderly individuals 65 years and older[4]. A patient suffering from insomnia often experiences daytime consequences such as sleepiness, fatigue, loss of concentration, changes in mood, as well as changes

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in their family relationships and social performance[5]. In Western medicine, there are three main methods for treating insomnia: nonpharmacological strategies, cognitive behavioral therapy and medication. The former two are chiefly used for the treatment of chronic insomnia. The use of sleeping pills is typically restricted to cases of acute insomnia; however, such pharmacological treatments may lead to addiction or substance abuse when used over an extended period. Furthermore, quality of life might be degraded as a result of the adverse effects of sleep medication[6]. Insomnia symptoms are also associated with subsequent psychotropic medication in a dose-dependent manner[7]. In addition, among older adults taking insomnia medication, there is a greater risk of accidental events[8]. Fortunately, acupuncture has been used in clinics for thousands of years, and has been proven to treat every single disease. It is reported that auricular-acupuncture and acupuncture are effective in relieving both chronic and acute insomnia symptoms with no side effects[9–11]. Whereas drug prescription for insomnia is fixed and treats very specific symptoms, the selection of acupoints can be adapted to the syndromes being treated. In addition, acupuncture has the characteristics of safety, less physiological interference, low price and simplicity for the operator; it is an accepted treatment by patients all over the world. This review summarizes the hazards of insomnia and the use of acupuncture for the treatment of insomnia.

2 Development of negative emotions and acupuncture treatment

2.1 Development of negative emotions

Anxiety and depression are the two main negative emotions caused by insomnia. Impaired sleep quality may result in reduction of pleasurable experiences among healthy and mood-disordered persons[12].

Studies have found a strong association between depression and insomnia[13–16], while insomnia has been found to be a significant predictor of change in depression[17,18]. Rates of depression and suicidal ideation are significantly increased in patients with persistent insomnia[19]. Apart from insomnia symptoms, non-refreshing sleep and difficulties of initiating or maintaining sleep are all associated with an increased risk of depression[20]. Moreover, all persons, from adolescents to seniors, may have suicidal ideations when suffering from severe insomnia and depression; the link between suicidal ideation and insomnia may be mediated by depressive symptoms[21,22].

Women, in particular, suffer greatly from insomnia and depression, and are significantly more vulnerable to depression than men (P<0.05) with symptoms of insomnia[23]. Women with diary-defined sleep deficiency reported more depressive symptoms (P=0.02) and perceived more stress (P<0.01) than those who were not sleep deficient[24]. In perinatal women with higher insomnia severity index (ISI) scores, the odds ratios for reporting depression symptoms and generalized anxiety were 7.70 and 2.55 respectively, which were significantly higher than in women with lower ISI scores[25]. Postpartum depression is also associated with insomnia during pregnancy, and treatment of insomnia during pregnancy may prevent postpartum depression[26]. Further complicating the situation, depression also contributes to nonrestorative sleep in pre- and postmenopausal women[27].

A study found that insomnia affected the balance of optimism and depression experienced by Chinese college students, suggesting that significant differences in depressive symptoms could be due to change of scores in their sleep status[28]. Another study, enrolling 819 participants, reported that insomnia symptoms influenced depressive symptoms by stimulating some of the negative aspects of perfectionism ("Concerns over Mistakes and Doubts about Actions")[29]. Despair associated with poor sleep also partly explained how insomnia was related to depression[30]. However, insomnia was not only associated with the overall index of negative emotions (combination of somatic anxious arousal, rumination and worry), but also with the interactive effects of negative emotions[31]. In general, insomnia can increase the subsequent risk of major depression by 2- to 3-fold. The relationship between insomnia and depression was more consistent for major depression than for minor depression[32]. Table 1 displays the characteristics of some studies examining insomnia and the risk of development of negative emotions.

Nevertheless, the biological processes underlying this causal relationship are unclear. One study showed the heritability (30.7%) of insomnia symptoms, with the remainder of the symtoms ascribed to unique environmental effects. The prevalence of insomnia symptoms was 32.4% in individuals with depression and/or anxiety disorders, which was higher than 16.5% in persons without[33]. It is insomnia-specific unique environmental effects that play an important role in the etiology of depression. Another study found that genetic and unique environmental factors accounted for 49% and 51%, respectively[34]. However, environmental factors played a more important role than genetic factors in each symptom. Examination of the nervous system has shown that patients with insomnia appear to have fragmented rapid eye movement (REM) sleep, which very likely disturbs the basal processes of emotion regulation. The interaction between the affective arousal system and persistent insomnia could gradually alter the cognitive

Table 1 Characteristics of studies examining the insomnia and the risk of negative emotion development

Country	Age (year)	Design	Sample size	Risk to emotion	Follow-up (year)	Emotion	Criteria for evaluation
China (2011)[14]	Adolescents	Cross-sectional analysis	719	$P<0.001$	—	Depression	PSQI, CIAS, GHQ-12
Japan (2012)[18]	20 or older	Longitudinal study	1 577	$P<0.01$	2	Depression	PSQI and Epidemiologic Studies Depression Scale
Korea (2013)[19]	43–73	Longitudinal study	1 282	$P=0.001$, $P=0.002$	6	Depression, suicidal ideation	Beck Depression Inventory, 4 questions about insomnia based on their symptoms during the past month
Finland (2012)[20]	43.9 (mean)	Cohort study	40 791	Hazard ratio increased	3.3	Depression	Self-reported sleep
USA (2012)[22]	18–36	Cross-sectional design	673	$P<0.01$	—	Suicide	DDNSI, ISI, CES-D, PCL-CL, SAS, SBQ-R
USA (2013)[24]	29.6±4.8	Part of a longitudinal study	160	$P=0.02$	2.2	Depression	Pittsburgh sleep diary, wrist actigraph, IDS, PSS, Revised Pregnancy Distress Questionnaire (NuPD*Q)*
USA (2013)[32]	11–17	Cohort study	3 134	$P<0.05$	1	Depression	DSM-IV criteria, DISC-IV

CES-D: Canter of Epidemiological Studies Depression Scale; CIAS: the Chinese Internet Addiction Scale; DDNSI: Disturbing Dreams and Nightmare Severity Index; DISC-IV: Diagnostic Interview Schedule for Children, Version 4; DSM-IV: diagnostic and statistical manual of mental disorder-IV; GHQ-12: the 12-item version of General Health Questionnaire; IDS: the Inventory for Depressive Symptoms; ISI: Insomnia Severity Index; PCL-CL: PTSD Checklist-Civilian Version; PSQI: Pittsburgh Sleep Quality Index; PSS: Perceived Stress Scale; SAS: the Zung Self-Rating Anxiety Scale; SBQ-R: the Suicidal Behaviors Questionnaire-Revised.

system, which could, in turn, develop into depression[35]. Furthermore, a study of depression in older women found low leukocyte mtDNA content[36]. Insomnia can produce oxidative damage and result in mitochondrial dysfunction; thus the impaired mitochondrial function found in this study could be the result of depression, caused by insomnia, in women.

2.2 Acupuncture treatment in insomnia with depression and anxiety

Treatment of insomnia is very important for the management of negative emotions; conversely, the treatment of negative emotions can also help in the prevention of insomnia. Acupuncture is a good choice for treating these symptoms, as the effect of acupuncture on depression, anxiety and the psychological state of patients can be significant[37–40]. Anmian acupoints, behind the ears, are used to treat insomnia. Acupuncture at meridian acupoints, combined with three Anmian acupoints could improve depression, anxiety and sleep quality of patients with insomnia[41]. Acupuncture therapy could also facilitate hypnotic induction by reducing anxiety[42]. For insomnia accompanied by depressive disorders, acupuncture treatment is superior to Western medication, with milder adverse reactions[43]. Acupuncture has helped to regulate the secretion of melatonin in day and night, improved symptoms of insomnia and decreased anxiety scores[44]. The degree of anxiety and depression also influences the therapeutic effect of acupuncture in treating patients with insomnia[45]. After review of the articles published in China, Yang *et al*[46] found that eight extraordinary meridians and all of the twelve regular meridians could be involved in the treatment of the negative emotions of insomnia. The depression was considered a yin disease that could be treated mainly by regulating yang meridians, of which the Governor Vessel was used in the highest frequency[46]. Shenmen (HT7), Baihui (DU20), Hegu (LI4) and Taichong (LR3) were the most commonly used acupoints in treating the negative emotions associated with insomnia[43]. These points improved insomnia and depression symptoms by calming the mind and regulating qi. Brain wave activity was improved significantly after acupuncture treatment[47]. The potential mechanism of

acupuncture in improving negative emotions may be associated with improvements of brain waves in patients.

3 Decreased immunity and acupuncture treatment

3.1 Decreased immunity

Patients with insomnia also frequently suffer from reduced immunity and increased inflammatory mediators. Fundamental research found that serum levels of inflammatory cytokines and leukocytes were increased in a lipopolysaccharide (LPS) + sleep deprivation (SD) group. Interleukin-6 (IL-6), lymphocytes, interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α) levels were also increased in bronchoalveolar lavage fluid (BALF) in the LPS + SD group, while the macrophage levels in BALF were decreased, which indicated a reduction in immune response after sleep deprivation. However, melatonin, which was mainly produced at night, significantly inhibited the recruitment of lymphocytes in serum and BALF (P<0.05) and reduced the serum levels and BALF levels of IL-1β, IL-6, TNF-α and IFN-γ[48]. After sleep restriction, myeloperoxidase levels, leukocyte and, among leukocyte subsets, neutrophil counts were all increased[49]. Meanwhile, a clinical investigation showed that nonrestorative sleep and difficulties initiating sleep were associated with increasing high-sensitivity C-reactive protein (hsCRP) levels among men. However, there was no evidence of this response in women[50]. Hemodialysis patients showed a CRP level ≥3.8 mg/L, which was significantly associated with sleep disorders[51]. In addition, the serum IL-6 level of kidney transplant patients with insomnia was remarkably higher than in patients without insomnia[52]. What's more, paradoxical sleep deprivation (PSD) could lead to a significant decrease in circulating lymphocytes and a general reduction in all cellular subsets of the spleen, mainly B and T cells[53]. However, no change in PSD response was found in the peritoneum or lymph nodes. In another sleep deprivation experiment[54], CD4, CD8, CD14, CD16, mitogen proliferation and human leukocyte antigen (locus)-DR all presented significant time-dependent changes after sleep deprivation; CD3 did not. Sleep loss can lead to an induction of inflammatory responses, the perturbation of cellular immunity and a homeostatic imbalance. Over 500 genes were expressed differentially in subjects after the second night of prolonged wakefulness and one night after sleep recovery[55]. Of these, some genes were related to diverse immune system responses, such as natural killer (NK) pathways, including granzymes, T-cell receptors, and killer cell lectin-like receptor family, which are very important for host defense. In another study, except for the significantly higher monocyte and NK cytotoxicity counts in males, no other effects were significant in any of the endocrine or immunological indices, after participants experienced 30 h of sleep deprivation, during which social, physiological, and cognitive tasks were conducted[56]. These marked contradictions in different studies might reflect differences in the methodology used for immunological assessments or in study design, including the duration of sleep deprivation and timing of sample collection. Table 2 gives a description of some immune markers present after sleep disorders.

3.2 Acupuncture treatment for increasing immunity

Decreased immunity could be one explanation for the increase in susceptibility to infections reported after sleep reduction[54]. Acupuncture has a good effect on the immune system and has the ability to protect

Table 2 A description of some immune markers after sleep disorder

Increased	Decreased
Monocytes	Macrophage levels
Myeloperoxidase	Circulating lymphocytes
Interleukin-6	All cellular subsets of spleen, mainly T and B cells
Lymphocytes	CD4, CD8, CD14 and CD16
Interferon-γ	The mitogen proliferation values
Tumor necrosis factor-α	Human leukocyte antigen (locus) DR
Leukocytes	Expression of over 500 genes related to diverse immune system responses, stress response, and DNA damage and repair
hsCRP/CRP	
Natural killer cytotoxicity	

CRP: C-reactive protein; hsCRP: high-sensitivity C-reactive protein.

immunology from damage caused by chemotherapy[57,58]. An experiment in 1975 reported the effects of acupuncture on immune responses in sensitized rabbits and guinea pigs[59]; counts of CD3, CD4 and CD8, and the percentage of NK cells and monocyte phagocytosis were all increased after acupuncture treatment[60]; the local mucosal immunological system can also be affected by acupuncture[61]. Electro-acupuncture (EA) can regulate serum cytokine levels in healthy conditions[62]. EA stimulation at Ququan (H8) was shown to modulate humoral immune response of rats injected with sheep-red-blood cells antigen[63]. Some studies have investigated how acupuncture affects immunology during the time after treatment. Acupuncture showed the best effects on the immune system 72 h after a single session and the effect could persist one month after a complete treatment, which consisted of 10 sessions[64]. Another study found that leukocyte count of cholera mice increased and reached its highest quantities 2 h after acupuncture treatment, and decreased to normal levels after 24 h[65].

Acupuncture can promote T-lymphocyte transformation function through the regulation of central catecholaminergic neurons; the mechanism may be mainly attributed to speeding up the anabolism of the DNA and promoting the anabolism of T-lymphocytes[66]. Another report[67] found EA promoted T-lymphocyte transformation by boosting the release of endogenous opioids produced in the brain. These endogenous opioids promoted an immune response. Furthermore, it can be inferred that the serotonergic system plays a main role in EA regulation of humoral immunity, while the catecholaminergic system plays an important role in EA regulation of cellular immunity[68]. In addition, Cx43 plays an important role in the transmission of acupuncture signals in the regulation of the immune system. Research found that acupuncture could notably increase the spleen index, thymus index and leukocyte number in Cx43+/+ mice. In Cx43 knockout mice, these effects of acupuncture were not observed[69]. Therefore, acupuncture can be an effective method for strengthening the immunity of patients with insomnia.

4 Increased oxyradicals and acupuncture treatment

4.1 Increased oxyradicals

Insomnia may result in increased oxyradicals. A study showed that insomnia patients had significantly lower glutathione peroxidase (GSH-Px) activity and higher malondialdehyde (MDA) levels compared with healthy individuals, which signals increase of oxyradicals[70]. Lipoperoxides are produced in the reaction between polyunsaturated fatty acids and oxygen. A cross-sectional study with 187 perimenopausal women found that there was a positive correlation between insomnia score, menopause rating score and lipoperoxides in postmenopausal women[71]. This predicted an indirect relationship between oxygen and insomnia. IL-18, hs CRP and oxidized low-density lipoprotein levels declined remarkably with cognitive-behavioral therapy in sleep-disturbed hemodialysis patients[72]. Patients with insomnia had lower serum paraoxonase and arylesterase activities, lower serum total antioxidant status, lower oxidative stress index and lower total oxidant status relative to the healthy controls[73]. Patients with insomnia had reduced levels of serum antioxidant enzymes and increased systemic oxidative stress. Another study showed that sleep deprivation enhanced antioxidant responses in rat brains[74]. Acute (6 h) sleep deprivation under sustained hypoxia increased total glutathione (GSHt) production in the brainstem, cerebellum and neocortex and increased nitric oxide (NO) levels in the hippocampus while decreasing hippocampal lipid oxidation. Elevated glucose metabolism may play an important role in producing enhanced free radicals in the brain, while oxidative stress seems to be an underlying condition related to insomnia.

4.2 Acupuncture treatment for decreasing oxyradicals

Numerous studies have shown that acupuncture can reduce the production of free radicals. Sanyinjiao (SP6) and ZusanLi (ST36) belong to the channels of spleen and stomach, respectively and function in regulating blood and qi, invigorating qi, and eliminating pathogenic factors. Acupuncture stimulation at SP6 and ST36 has antioxidative effects[75]. Acupuncture can adjust the metabolism of serum oxygen free radicals by down-regulating the production of serum MDA and hydrogen peroxide, and up-regulating serum superoxide dismutase (SOD), GSHt, GSH-Px activity and carnitine production[75–79]. In addition to increasing the levels of SOD and GSH-Px, acupuncture treatment can also significantly increase the expression of CuZnSOD mRNA and protein to ameliorate oxidative injuries[80]. Moreover, acupuncture can improve the antioxidant status of erythrocytes and stabilize disordered lipid peroxidation (LPO) processes[81]. Acupuncture also prevented formation and accumulation of LPO products in the main regions of the brain[82]. In addition, EA treatment increased the activity of SOD in the liver, hypothalamus and red blood cells[83]. Furthermore, acupuncture at different Shichen (traditional twelve 2-hour periods) has different effects on serum SOD and MDA, which can decrease MDA content and increase SOD activity. The decreasing amplitude of MDA was smallest in the Hai period and largest in the Wu period, while the increasing amplitude of SOD activity was smallest in the Wu period and largest in the Mao period[84]. Two studies concerned with the improvement of oxidative stress through the use of acupuncture are shown in Table 3.

Table 3 Characteristics of two studies about improving oxidative stress by using acupuncture

Items	China (2012)[77]	Japan (2011)[79]
Acupoint	Zusanli (ST36) and Sanyinjiao (SP6)	Right ST36 and Jiexi (ST41)
Manipulating	Manipulating the acupuncture needles intermittently for 20 min, once daily, and with 7 days being a treatment course, conducted for three courses with an interval of 3 days between two courses	Uniform reinforcing and reducing method by twirling the acupuncture needle for 15 min, and then connected to an electric stimulator with dense-sparse waves
Effect	(1) Up-regulating serum GSH-Px and SOD activityies (2) Down-regulating serum MDA level	(1) Carnitine and glutathione in muscle are increased
Analysis	(1) The status of oxidative stress is a disharmony of qi and blood, which would lead to extravasated blood and damp toxin. (2) SP6 is the convergent acupoint of spleen meridian, kidney meridian, and liver meridian, having the functions of clearing and activating the channels and collaterals, and promoting circulation. (3) ST36 and ST41 both belong to Five Shu acupoints of Stomach Channel of Foot-Yang Ming. These points have the functions of dredging the channel, regulating blood and qi, invigorating qi and eliminating pathogenic factors.	

GSH-Px: glutathione peroxidase; SOD: superoxide dismutase; MDA: malondialdehyde.

5 Causes of cardiac disease and acupuncture treatment

5.1 Causes of cardiac disease

Research shows that various diseases have a certain relationship with insomnia, especially cardiovascular disease (CVD). The relationship between delta power and changes in cardiac autonomic activity is altered in patients with chronic primary insomnia[85]. Insomnia often leads to a state of sympathetic inhibition and vagus nerve stimulation, which impacts physiological functions, such as heart rate (HR), blood pressure (BP) and blood supply to the cardiac muscles. Insomnia and sleep duration may interact to almost double the risk of CVD and coronary heart disease (CHD). Women with high insomnia scores had an elevated risk of CHD (38%) and CVD (27%), while shorter (≤5 h) and longer (≥10 h) sleep duration demonstrated a significantly higher incidence of CHD (25%) and CVD (19%)[86]. Laugsand *et al*[87] found that there was a dose-dependent relationship between the risk of heart failure and the number of insomnia symptoms. The multi-adjusted hazard ratios for people with one, two and three insomnia symptoms were 0.96, 1.35 and 4.53 respectively, compared with people without insomnia symptoms. In addition, insomnia was associated with hypertension and HR[88–91]. A combination of three sleep complaints [waking up repeatedly (sleep continuity disturbance, SCD), difficulty falling asleep (DFA), awakening tired and fatigued (nonrestorative sleep, NRS)] was related to a slightly increased risk of CVD (*OR* 1.5, 1.1–2.0), but not hypertension. Either DFA or SCD was associated with an increased risk of hypertension[92]. Heart disease may be related to certain insomnia symptoms. A study discovered that patients with chronic primary insomnia have an irregular HR and heart rate variability (HRV), consistent with increased sympathetic activity[93]. This significant difference between insomniacs and controls was only detected when awake before sleep and during stage-2 non-REM sleep, but not during REM sleep, slow-wave sleep, or post-sleep wake. It is hypothesized that autonomic hyperarousal may be a major pathogenic mechanism in primary insomnia, and confirmed that insomnia is associated with an increased risk of CVD disease. Table 4 displays the characteristics of studies that addressed the risk of cardiac disease induced by insomnia.

Another study also found alterations in HRV variables and a lower wake-to-sleep HR reduction might increase cardiovascular mortality and morbidity observed in patients with insomnia[94]. Moreover, the primary insomnia patients showed marked reduction in parasympathetic-related HRV indices and physiologic complexity relative to healthy controls. Alterations in HRV indices were related to perceived-sleep questionnaire scores, which suggested a pivotal role of sleep disturbance in adjusting cardiovascular variability in patients with primary insomnia[95]. Sympathetic predominance, associated with a vagal withdrawal, is the potential pathogenic mechanism for heart diseases, while melatonin, with its high nocturnal concentrations, is a potential therapeutic target in diseases ranging from insomnia and depression to cardiovascular diseases. It was hypothesized that a reduction in melatonin caused by insomnia is also a vital risk factor of CVD[96]. In summary, insomnia is a potential cause of CVD.

5.2 Acupuncture treatment for cardiac diseases

Once insomnia induces or aggravates cardiac diseases, the treatment of cardiac disease is also very necessary for the treatment of insomnia. There is a long history

Table 4 Characteristics of studies concerning the risk for cardiac disease induced by insomnia

Study/year	Cases/follow-up	Risk for cardiac disease
A large Norwegian cohort study (2014)[87]	1 412 cases of heart failure occurred during a mean follow-up of 11.3 years	The hazard ratios for people with one, two, and three insomnia symptoms were 0.96, 1.35 and 4.53 respectively
The Penn State Cohort (2012)[90]	1 741 adults of the Cohort; 1 395 were followed up after 7.5 years	Odds ratios of the risk for incident hypertension in poor sleepers and chronic insomniacs were 1.6 and 3.8 respectively
The 2005-2008 United States National Health and Nutrition Examination Surveys (2013)[91]	*N*=12 643/3 years of follow-up	Odds ratio of current antihypertensive medications 1.33, 1.04–1.70; odds ratio of doctor-diagnosed hypertension 1.49, 1.19–1.88
Atherosclerosis Risk in Communities (ARIC) Study (2007)[92]	8 757 ARIC participants without hypertension and 11 863 ARIC participants without cardiovascular disease at baseline and with 6 years of follow-up	A combination of three sleep complaints (SCD, DFA, NRS) was associated with a slightly increased risk of cardiovascular disease (odds ratio 1.5, 1.1–2.0) but not hypertension. Either DFA or SCD was associated with increased risk of hypertension

SCD: sleep continuity disturbance; DFA: difficulty falling asleep; NRS: nonrestorative sleep.

of acupuncture treatment for heart disease. The main treatment principles of acupuncture in treating heart disease include promoting blood circulation for removing blood stasis, regulating the function of liver and spleen, soothing the liver and suppressing yang.

The effective rate of the combined treatment with ginger-partition moxibustion and acupuncture for patients with cardiac arrhythmia was higher than that of Western medicine[97]. Litscher *et al*[98] found that HR of insomnia patients decreased remarkably ($P<0.01$) during and after acupuncture stimulation of the Shenmen (HT7) acupoint. Total HRV was also increased ($P<0.05$) immediately after acupuncture stimulation, but the effect was not long-lasting[98,99]. Meanwhile, acupuncture can lead to an increase of cardiovagal modulation of HR combined with a trend towards a decrease of low frequency (LF) and an increase of high frequency (HF) spectral power[100]. However, another study found the opposite effect: acupuncture substantially reduced HRV, causing a 41% decrease in the standard deviation; variances of LF and HF ranges were both markedly reduced, but the LF/HF ratio and the HR were not altered[101]. These inconsistent results require further study. Nevertheless, the results suggest that acupuncture can regulate function of the cardiac autonomic nervous system (ANS)[100]. Acupuncture may attenuate the imbalance between parasympathetic and sympathetic activities, decreasing the LF/HF ratio power[102]. Furthermore, acupuncture effects on HRV rely on both the ANS and the complete central nervous system[103]. The modulation of cardiac autonomic function has the characteristic of point specificity. A study showed that the stimulation of Danzhong (CV17), but not of Zhongting (CV16), increased the power of the HF component of HRV ($P=0.01$) and reduced HR ($P=0.01$)[104].

As for hypertension, acupuncture was significantly superior to medication in relieving casual blood pressure and ambulatory blood pressure[105]. Acupuncture was also shown to have immediate and long-term effects in lowering BP[106]. Stimulating at Yanglingquan (GB34) can reduce not only femoral arterial pressure, but also the size of cardiac muscle cells, preventing heart hypertrophy[107]. However, another study found acupuncture at Sishencong (EX-HN1) and Baihui (GV20), with needle-retention for 8 h, had a shorter duration and was relatively slower in reducing BP compared to the administration of Nifedipine tablets (20 mg/d)[108]. But needle stimulation for 8 h was still as effectively as medication at lowering systolic pressure at the time-points of 2, 4 and 6 h and lowering diastolic pressure at the time-points of 2, 4, 6 and 8 h after treatment[108]. It is suggested that acupuncture may adjust the cardiovascular system through a complicated brain network at the cortical level, the hypothalamus and the brainstem[109]. Another study found that ear acupuncture could improve HR and hypertension by increasing the level of response of cardiac-related neurons in the nucleus tractus solitarius, which can be attenuated by atropine and local anesthetics[110]. Acupoints selected to improve cardiac disease comprise the twelve regular meridians, eight extra channels and even the extra nerve points. Therapeutic principles differ from different acupoints; a summary of the characteristics of some acupoints for itreating cardiac disease is given in Table 5. These points can improve both heart function and insomnia symptoms.

6 Summary

This review summarized the hazards of insomnia and the relationship between insomnia and other diseases.

Table 5 Characteristics of points selected for treating cardiac disease

Meridian	Point	Efficacy
Urinary bladder meridian	Xinshu (BL15), Ganshu (BL18), Pishu (BL20), Shenshu (BL23), Shenmai (BL62)	Regulating viscera function, nourishing yin and suppressing hyperactive yang, and invigorating qi
Spleen meridian	Gongsun (SP4), Sanyinjiao (SP6)	Strengthening spleen and eliminating dampness
Concepion meridian	Guanyuan (CV4), Zhongting (CV16), Danzhong (CV17)	Relaxing the chest, and invigorating primordial qi
Gallbladder meridian	Fengchi (GB20), Yanglingquan (GB34), Xiaxi (GB43)	Calming the liver to stop the wind
Liver meridian	Xingjian (LR2), Taichong (LR3)	Dispersing and rectifying the depressed liver-energy, and calming the liver to stop the wind
Lung meridian	Hegu (LI4), Quchi (LI11)	Regulating qi and blood, strengthening spleen and eliminating dampness
Stomach meridian	Renying (ST9), Zusanli (ST36)	Regulating qi and blood, strengthening spleen and eliminating dampness
Governor meridian	Baihui (GV20)	Tranquilizing mind
Pericardium meridian	Neiguan (PC6)	Tranquilizing mind
Kidney meridian	Fuliu (KI7)	Clearing damp
Heart meridian	Shenmen (HT7)	Tranquilizing mind

Furthermore, the authors introduced an effective and cost-efficient method of acupuncture for insomnia treatment. Our review indicates that insomnia poses a major threat to mental health, and that anxiety and depression are the two main negative emotions involved. Moreover, insomnia has a direct effect on serum components, heart function and the immune system of patients, which may result in physiological disorders.

Sleep helps individuals recover from the physical and mental exhaustion of daily work. Insomnia is one of the most important factors contributing to health. According to the theory of traditional Chinese medicine, insomnia is a state of yang excess and yin deficiency that will result in a variety of symptoms, such as headaches, distress, heart palpitations, nausea, anxiety, depression, suicidal ideation, as well as other psychological disorders and symptoms. Other modern research has shown that insomnia is also a risk factor for the development of depression, decreased immunity, increased oxyradicals, cardiac disease and more.

In the theory of traditional Chinese medicine, five kinds of spirits inhabit the five zang-organs (heart, liver, lung, spleen and kidney). Each kind of spirit has a corresponding physiological function. The five zang-organs are unable to perform this function during insomnia, which could manifest in symptoms such as deficiency of vital energy, fatigue, confusion, abnormal psychology and heart state disturbance. In addition, the state of qi and blood will be changed in these patients. Further, emotional distress associated with insomnia would impair the function of the viscera. In the Western medical context, it is also expected that a change in the immune system and inflammatory biomarkers would also take place in the same patients. Modern research could help us to understand traditional Chinese medicine theory in this context.

Insomnia is a potential risk factor in many diseases. Proper treatment of insomnia would largely reduce the occurrence or severity of other diseases and benefit the treatment of other symptoms. Acupuncture produces notable advantages in the treatment of insomnia and its complications. For example, treatment with acupuncture can balance the emotions and increase feelings of vitality[111]. Immune function, serum oxygen-free radicals and heart disease all respond well to acupuncture. Shenmai (BL62) and Zhaohai (KI6), which are two of the eight confluence points in meridian theory, have a special function in treating insomnia. Additionally, the points of Baihui (DU20), Sishencong (EX6), Anmian (Extra), Shenmen (HT7), Zusanli (ST36) and Sanyinjiao (SP6) are often used for treatment of insomnia. The acupuncture prescription of regulating yin-yang and the five viscera are more effective for intractable insomnia; therefore, acupuncture can be a constructive and complementary method for insomnia and its complications.

With the rapid development of medical and molecular technology, more and more research is taking place at the molecular level. Based on the reviewed literature, all of

the harmful effects of insomnia can be effectively treated by acupuncture. Yet, there are limitations to the literature reviewed in this paper. Insomnia patients in some studies were self-diagnosed, and there were no uniform standard criteria for insomnia diagnosis. Few studies investigated the pathogenesis of insomnia and its relationship to other diseases. Studies on the therapeutic mechanisms of acupuncture were also limited. Further research can focus on formulating standard diagnostic criteria and using advanced technology, such as molecular tools, to study the mechanisms of insomnia. Since traditional Chinese medicine is effective in treating insomnia, utilizing the theory and guidance of this practice may bring hope to insomnia patients.

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8 Conflict of interests

No potential conflicts of interests relevant to this article exist.

REFERENCES

1 Calem M, Bisla J, Begum A, Dewey M, Bebbington PE, Brugha T, Cooper C, Jenkins R, Lindesay J, McManus S, Meltzer H, Spiers N, Weich S, Stewart R. Increased prevalence of insomnia and changes in hypnotics use in England over 15 years: analysis of the 1993, 2000, and 2007 National Psychiatric Morbidity Surveys. *Sleep*. 2012; 35(3): 377–384.

2 Pereira C, Almeida C, Veiga N, Amaral O. Prevalence and determinants of insomnia symptoms among schoolteachers. *Aten Primaria*. 2014; 46(Suppl 5): 118–122.

3 Calhoun SL, Fernandez-Mendoza J, Vgontzas AN, Liao D, Bixler EO. Prevalence of insomnia symptoms in a general population sample of young children and preadolescents: gender effects. *Sleep Med*. 2014; 15(1): 91–95.

4 Kim WH, Kim BS, Kim SK, Chang SM, Lee DW, Cho MJ, Bae JN. Prevalence of insomnia and associated factors in a community sample of elderly individuals in South Korea. *Int Psychogeriatr*. 2013; 25(10): 1729–1737.

5 Medina-Chávez JH, Fuentes-Alexandro SA, Gil-Palafox IB, Adame-Galván L, Solís-Lam F, Sánchez-Herrera LY, Sánchez-Narváez F; Instituto Mexicano del Seguro Social. Clinical practice guideline. Diagnosis and treatment of insomnia in the elderly. *Rev Med Inst Mex Seguro Soc*. 2014; 52(1): 108–119. Spanish with abstract in English.

6 Sasai T, Inoue Y, Komada Y, Nomura T, Matsuura M, Matsushima E. Effects of insomnia and sleep medication on health-related quality of life. *Sleep Med*. 2010; 11(5): 452–457.

7 Haaramo P, Lallukka T, Lahelma E, Hublin C, Rahkonen O. Insomnia symptoms and subsequent psychotropic medication: a register-linked study with 5-year follow-up. *Soc Psychiatry Psychiatr Epidemiol*. 2014; 49(12): 1993–2002.

8 Avidan AY, Palmer LA, Doan JF, Baran RW. Insomnia medication use and the probability of an accidental event in an older adult population. *Drug Healthc Patient Saf*. 2010; 2: 225–232.

9 Jiang B, Ma ZH, Zuo F. Auricular acupuncture for insomnia: a randomized controlled trial. *Zhonghua Liu Xing Bing Xue Za Zhi*. 2010; 31(12): 1400–1402. Chinese with abstract in English.

10 Ling L, Jiang XM, Xue JW, Wang M, Ke R. Clinical study on the visceral differentiation-based acupuncture therapy for insomnia. *J Tradit Chin Med*. 2008; 28(4): 270–273.

11 Zhou YL, Gao XY, Wang PY, Ren S. Effect of acupuncture at different acupoints on expression of hypothalamic GABA and $GABA_A$ receptor proteins in insomnia rats. *Zhen Ci Yan Jiu*. 2012; 37(4): 302–307. Chinese with abstract in English.

12 Bower B, Bylsma LM, Morris BH, Rottenberg J. Poor reported sleep quality predicts low positive affect in daily life among healthy and mood-disordered persons. *J Sleep Res*. 2010; 19(2): 323–332.

13 Sivertsen B, Salo P, Mykletun A, Hysing M, Pallesen S, Krokstad S, Nordhus IH, Øverland S. The bidirectional association between depression and insomnia: the HUNT study. *Psychosom Med*. 2012; 74(7): 758–765.

14 Cheung LM, Wong WS. The effects of insomnia and internet addiction on depression in Hong Kong Chinese adolescents: an exploratory cross-sectional analysis. *J Sleep Res*. 2011; 20(2): 311–317.

15 Coryell VT, Ziegelstein RC, Hirt K, Quain A, Marine JE, Smith MT. Clinical correlates of insomnia in patients with acute coronary syndrome. *Int Heart J*. 2013; 54(5): 258–265.

16 Kato T. Insomnia symptoms, depressive symptoms, and suicide ideation in Japanese white-collar employees. *Int J Behav Med*. 2014; 21(3): 506–510.

17 Wright KM, Britt TW, Bliese PD, Adler AB, Picchioni D, Moore D. Insomnia as predictor versus outcome of PTSD and depression among Iraq combat veterans. *J Clin Psychol*. 2011; 67(12): 1240–1258.

18 Okajima I, Komada Y, Nomura T, Nakashima K, Inoue Y. Insomnia as a risk for depression: a longitudinal epidemiologic study on a Japanese rural cohort. *J Clin Psychiatry*. 2012; 73(3): 377–383.

19 Suh S, Kim H, Yang HC, Cho ER, Lee SK, Shin C. Longitudinal course of depression scores with and without insomnia in non-depressed individuals: a 6-year follow-up longitudinal study in a Korean cohort. *Sleep*. 2013; 36(3): 369–376.

20 Salo P, Sivertsen B, Oksanen T, Sjösten N, Pentti J, Virtanen M, Kivimäki M, Vahtera J. Insomnia symptoms as a predictor of incident treatment for depression: prospective cohort study of 40,791 men and women. *Sleep Med*. 2012;

13(3): 278–284.
21 Lapierre S, Boyer R, Desjardins S, Dubé M, Lorrain D, Préville M, Brassard J. Daily hassles, physical illness, and sleep problems in older adults with wishes to die. *Int Psychogeriatr.* 2012; 24(2): 243–252.
22 Nadorff MR, Fiske A, Sperry JA, Petts R, Gregg JJ. Insomnia symptoms, nightmares, and suicidal ideation in older adults. *J Gerontol B Psychol Sci Soc Sci.* 2013; 68(2): 145–152.
23 Lee MH, Lee SA, Lee GH, Ryu HS, Chung S, Chung YS, Kim WS. Gender differences in the effect of comorbid insomnia symptom on depression, anxiety, fatigue, and daytime sleepiness in patients with obstructive sleep apnea. *Sleep Breath*. 2014; 18(1): 111–117.
24 Okun ML, Kline CE, Roberts JM, Wettlaufer B, Glover K, Hall M. Prevalence of sleep deficiency in early gestation and its associations with stress and depressive symptoms. *J Womens Health (Larchmt)*. 2013; 22(12): 1028–1037.
25 Swanson LM, Pickett SM, Flynn H, Armitage R. Relationships among depression, anxiety, and insomnia symptoms in perinatal women seeking mental health treatment. *J Womens Health (Larchmt)*. 2011; 20(4): 553–558.
26 Khazaie H, Ghadami MR, Knight DC, Emamian F, Tahmasian M. Insomnia treatment in the third trimester of pregnancy reduces postpartum depression symptoms: a randomized clinical trial. *Psychiatry Res*. 2013; 210(3): 901–905.
27 Terauchi M, Hiramitsu S, Akiyoshi M, Owa Y, Kato K, Obayashi S, Matsushima E, Kubota T. Associations between anxiety, depression and insomnia in peri- and post-menopausal women. *Maturitas*. 2012; 72(1): 61–65.
28 Cheuk Yan Sing, Wong WS. The effect of optimism on depression: the mediating and moderating role of insomnia. *J Health Psychol*. 2011; 16(8): 1251–1258.
29 Lombardo C, Mallia L, Battagliese G, Grano C, Violani C. Perfectionism mediates the relationship between insomnia and depressive symptoms. *Sleep Biol Rhythms*. 2013; 11(2): 90–98.
30 Sadler P, McLaren S, Jenkins M. A psychological pathway from insomnia to depression among older adults. *Int Psychogeriatr*. 2013; 25(8): 1375–1383.
31 Mitchell L, Mogg K, Bradley BP. Relationships between insomnia, negative emotionality and attention control. *Sleep Biol Rhythms*. 2012; 10(3): 237–243.
32 Roberts RE, Duong HT. Depression and insomnia among adolescents: a prospective perspective. *J Affect Disord*. 2013; 148(1): 66–71.
33 Gehrman PR, Meltzer LJ, Moore M, Pack AI, Perlis ML, Eaves LJ, Silberg JL. Heritability of insomnia symptoms in youth and their relationship to depression and anxiety. *Sleep*. 2011; 34(12): 1641–1646.
34 Hur YM, Burri A, Spector TD. The genetic and environmental structure of the covariation among the symptoms of insomnia, fatigue, and depression in adult females. *Twin Res Hum Genet*. 2012; 15(6): 720–726.
35 Baglioni C, Riemann D. Is chronic insomnia a precursor to major depression? Epidemiological and biological findings. *Curr Psychiatry Rep*. 2012; 14(5): 511–518.
36 Kim MY, Lee JW, Kang HC, Kim E, Lee DC. Leukocyte mitochondrial DNA (mtDNA) content is associated with depression in old women. *Arch Gerontol Geriatr*. 2011; 53(2): e218–e221.
37 Lyons Z, van der Watt G, Shen Z, Janca A. Acupuncture and Chinese herbs as treatments for depression: an Australian pilot study. *Complement Ther Clin Pract*. 2012; 18(4): 216–220.
38 Wang WD, Lu XY, Ng SM, Hong L, Zhao Y, Lin YN, Wang F. Effects of electro-acupuncture on personality traits in depression: a randomized controlled study. *Chin J Integr Med*. 2013; 19(10): 777–782.
39 Quah-Smith I, Smith C, Crawford JD, Russell J. Laser acupuncture for depression: a randomised double blind controlled trial using low intensity laser intervention. *J Affect Disord*. 2013; 148(2–3): 179–187.
40 Bussell J. The effect of acupuncture on working memory and anxiety. *J Acupunct Meridian Stud*. 2013; 6(5): 241–246.
41 Huo ZJ, Guo J, Li D. Effects of acupuncture with meridian acupoints and three Anmian acupoints on insomnia and related depression and anxiety state. *Chin J Integr Med*. 2013; 19(3): 187–191.
42 Lu DP, Lu GP. A comparison of the clinical effectiveness of various acupuncture points in reducing anxiety to facilitate hypnotic induction. *Int J Clin Exp Hypn*. 2013; 61(3): 271–281.
43 Luo WZ, Zhang QZ, Lai XS. Effect of acupuncture treatment of relieving depression and regulating mind on insomnia accompanied with depressive disorders. *Zhongguo Zhen Jiu*. 2010; 30(11): 899–903. Chinese with abstract in English.
44 Spence DW, Kayumov L, Chen A, Lowe A, Jain U, Katzman MA, Shen J, Perelman B, Shapiro CM. Acupuncture increases nocturnal melatonin secretion and reduces insomnia and anxiety: a preliminary report. *J Neuropsychiatry Clin Neurosci*. 2004; 16(1): 19–28.
45 Ruan JW, Hu YH, Rao ZD, Wen M, Zeng XX. Effects of the degrees of anxiety and depression on the therapeutic effect of acupuncture in the patient of insomnia. *Zhongguo Zhen Jiu*. 2006; 26(3): 186–188. Chinese with abstract in English.
46 Yang D, Zhai SQ. The relationship between meridians and mental state discussed from the treatment of depression with acupuncture and moxibustion. *Zhongguo Zhen Jiu*. 2013; 33(4): 317–320. Chinese with abstract in English.
47 Zhou XF, Li Y, Zhu H, Chen LL. Impacts of acupuncture at twelve meridians acupoints on brain waves of patients with general anxiety disorder. *Zhongguo Zhen Jiu*. 2013; 33(5): 395–398. Chinese with abstract in English.
48 Kim JY, Lee YD, Kim BJ, Kim SP, Kim DH, Jo KJ, Lee SK, Lee KH, Baik HW. Melatonin improves inflammatory cytokine profiles in lung inflammation associated with sleep deprivation. *Mol Med Rep*. 2012; 5(5): 1281–1284.
49 Faraut B, Boudjeltia KZ, Dyzma M, Rousseau A, David E, Stenuit P, Franck T, Van Antwerpen P, Vanhaeverbeek M, Kerkhofs M. Benefits of napping and an extended duration of recovery sleep on alertness and immune cells after acute sleep restriction. *Brain Behav Immun*. 2011; 25(1): 16–24.

50 Laugsand LE, Vatten LJ, Bjorngaard JH, Hveem K, Janszky I. Insomnia and high-sensitivity C-reactive protein: the HUNT study, Norway. *Psychosom Med*. 2012; 74(5): 543–553.

51 Razeghi E, Sahraian MA, Heidari R, Bagherzadeh M. Association of inflammatory biomarkers with sleep disorders in hemodialysis patients. *Acta Neurol Belg*. 2012; 112(1): 45–49.

52 Fornadi K, Lindner A, Czira ME, Szentkiralyi A, Lazar AS, Zoller R, Turanyi CZ, Veber O, Novak M, Mucsi I, Molnar MZ. Lack of association between objectively assessed sleep disorders and inflammatory markers among kidney transplant recipients. *Int Urol Nephrol*. 2012; 44(2): 607–617.

53 Zager A, Ruiz FS, Tufik S, Andersen ML. Immune outcomes of paradoxical sleep deprivation on cellular distribution in naive and lipopolysaccharide-stimulated mice. *Neuroimmunomodulation*. 2012; 19(2): 79–87.

54 Wilder-Smith A, Mustafa FB, Earnest A, Gen L, Macary PA. Impact of partial sleep deprivation on immune markers. *Sleep Med*. 2013; 14(10): 1031–1034.

55 Pellegrino R, Sunaga DY, Guindalini C, Martins RC, Mazzotti DR, Wei Z, Daye ZJ, Andersen ML, Tufik S. Whole blood genome-wide gene expression profile in males after prolonged wakefulness and sleep recovery. *Physiol Genomics*. 2012; 44(21): 1003–1012.

56 Matzner P, Hazut O, Naim R, Shaashua L, Sorski L, Levi B, Sadeh A, Wald I, Bar-Haim Y, Ben-Eliyahu S. Resilience of the immune system in healthy young students to 30-hour sleep deprivation with psychological stress. *Neuroimmunomodulation*. 2013; 20(4): 194–204.

57 Bianchi M, Jotti E, Sacerdote P, Panerai AE. Traditional acupuncture increases the content of β-endorphin in immune cells and influences mitogen induced proliferation. *Am J Chin Med*. 1991; 19(2): 101–104.

58 Ye F, Liu D, Wang S, Xu L. Effects of electro-acupuncture on T cell subpopulations, NK activity, humoral immunity and leukocyte count in patients undergoing chemotherapy. *J Tradit Chin Med*. 2007; 27(1): 19–21.

59 Chu YM, Affronti LF. Preliminary observations on the effect of acupuncture on immune responses in sensitized rabbits and guinea pigs. *Am J Chin Med (Gard City N Y)*. 1975; 3(2): 151–163.

60 Petti F, Bangrazi A, Liguori A, Reale G, Ippoliti F. Effects of acupuncture on immune response related to opioid-like peptides. *J Tradit Chin Med*. 1998; 18(1): 55–63.

61 Du Y, Meng S, Lei Y, Zhu Y. Regulative action of acupuncture and moxibustion on mucosal immunity. *Zhongguo Zhen Jiu*. 2005; 25(8): 594–596. Chinese with abstract in English.

62 Jong MS, Hwang SJ, Chen FP. Effects of electro-acupuncture on serum cytokine level and peripheral blood lymphocyte subpopulation at immune-related and non-immune-related points. *Acupunct Electrother Res*. 2006; 31(1–2): 45–59.

63 Sakic B, Kojic L, Jankovic BD, Skokljev A. Electro-acupuncture modifies humoral immune response in the rat. *Acupunct Electrother Res*. 1989; 14(2): 115–120.

64 Arranz L, Guayerbas N, Siboni L, De la Fuente M. Effect of acupuncture treatment on the immune function impairment found in anxious women. *Am J Chin Med*. 2007; 35(1): 35–51.

65 Kuan TK, Lee SP, Lin JG, Shen M. The effect of needle stimulation of acupuncture loci Tienshu (ST-25) Chung-Wan (CV-12) on the immune response in sensitized mice against experimental cholera. *Am J Chin Med*. 1986; 14(1–2): 73–83.

66 Zhao JC, Liu WG. Relationship between acupuncture-induced immunity and the regulation of central neurotransmitters in the rabbit: I. Effect of central catecholaminergic neurons in regulating acupuncture-induced immune function. *Acupunct Electrother Res*. 1988; 13(2–3): 79–85.

67 Zhao JC, Liu WQ. Relationship between acupuncture-induced immunity and the regulation of central neurotransmitter system in rabbits—II. Effect of the endogenous opioid peptides on the regulation of acupuncture-induced immune reaction. *Acupunct Electrother Res*. 1989; 14(1): 1–7.

68 Liu WG, Zhao JC. Relationship between acupuncture-induced immunity and the regulation of central neurotransmitters in the rabbit: VI. The influence of NDR stimulation on acupuncture regulation of immune function in rabbit. *Acupunct Electrother Res*. 1989; 14(3–4): 197–203.

69 Wu XH, Huang GY, Yang YQ, Xiong W. Influence of acupuncture on the immune function of immunosuppressive Cx43 knockout mice. *Zhen Ci Yan Jiu*. 2007; 32(5): 291–295. Chinese with abstract in English.

70 Gulec M, Ozkol H, Selvi Y, Tuluce Y, Aydin A, Besiroglu L, Ozdemir PG. Oxidative stress in patients with primary insomnia. *Prog Neuropsychopharmacol Biol Psychiatry*. 2012; 37(2): 247–251.

71 Sánchez-Rodríguez MA, Zacarías-Flores M, Arronte-Rosales A, Correa-Muñoz E, Mendoza-Núñez VM. Menopause as risk factor for oxidative stress. *Menopause*. 2012; 19(3): 361–367.

72 Chen HY, Cheng IC, Pan YJ, Chiu YL, Hsu SP, Pai MF, Yang JY, Peng YS, Tsai TJ, Wu KD. Cognitive-behavioral therapy for sleep disturbance decreases inflammatory cytokines and oxidative stress in hemodialysis patients. *Kidney Int*. 2011; 80(4): 415–422.

73 Liang B, Li YH, Kong H. Serum paraoxonase, arylesterase activities and oxidative status in patients with insomnia. *Eur Rev Med Pharmacol Sci*. 2013; 17(18): 2517–2522.

74 Ramanathan L, Siegel JM. Sleep deprivation under sustained hypoxia protects against oxidative stress. *Free Radic Biol Med*. 2011; 51(10): 1842–1848.

75 Wang H, Pan Y, Xue B, Wang X, Zhao F, Jia J, Liang X, Wang X. The antioxidative effect of electro-acupuncture in a mouse model of Parkinson's disease. *PLoS One*. 2011; 6(5): e19790.

76 Yu YP, Ju WP, Li ZG, Wang DZ, Wang YC, Xie AM. Acupuncture inhibits oxidative stress and rotational behavior in 6-hydroxydopamine lesioned rat. *Brain Res*. 2010; 1336: 58–65.

77 Liu CZ, Lei B. Effect of acupuncture on serum malonaldehyde content, superoxide dismutase and

glutathione peroxidase activity in chronic fatigue syndrome rats. *Zhen Ci Yan Jiu*. 2012; 37(1): 38–40, 58. Chinese with abstract in English.
78 He BM, Li WY, Li WS, Zhao WX. Effects of scalp acupuncture on regulative ability of oxidative stress reaction at operation stage. *Zhongguo Zhen Jiu*. 2006; 26(4): 291–394. Chinese with abstract in English.
79 Toda S. Investigation of electro-acupuncture and manual acupuncture on carnitine and glutathione in muscle. *Evid Based Complement Alternat Med*. 2011; 2011: 297130.
80 Liu CZ, Yu JC, Zhang XZ, Fu WW, Wang T, Han JX. Acupuncture prevents cognitive deficits and oxidative stress in cerebral multiinfarction rats. *Neurosci Lett*. 2006; 393(1): 45–50.
81 Pogosyan AS, Venediktova NI, Kosenko EA, Kaminskii YG. Antioxidant status of erythrocytes after acupuncture treatment. *Bull Exp Biol Med*. 2004; 138(1): 26–29.
82 Popova SP. Effect of acupuncture on dynamics of changes in lipid peroxidation and activity of antioxidant system in rats with gastroduodenal ulcer. *Fiziol Zh*. 2002; 48(6): 54–59. Ukrainian with abstract in English.
83 Rho SW, Choi GS, Ko EJ, Kim SK, Lee YS, Lee HJ, Hong MC, Shin MK, Min BI, Kee HJ, Lee CK, Bae HS. Molecular changes in remote tissues induced by electro-acupuncture stimulation at acupoint ST36. *Mol Cells*. 2008; 25(2): 178–183.
84 Xie GG, Zhao CJ, Lu XQ, Fan YS, Wu JW, Wen S. Effects of acupuncture at different Shichen (traditional twelve two-hour periods) on serum SOD and MDA in guinea pigs. *Zhongguo Zhen Jiu*. 2007; 27(10); 757–760. Chinese with abstract in English.
85 Jurysta F, Lanquart JP, Sputaels V, Dumont M, Migeotte PF, Leistedt S, Linkowski P, van de Borne P. The impact of chronic primary insomnia on the heart rate—EEG variability link. *Clin Neurophysiol*. 2009; 120(6): 1054–1060.
86 Sands-Lincoln M, Loucks EB, Lu B, Carskadon MA, Sharkey K, Stefanick ML, Ockene J, Shah N, Hairston KG, Robinson JG, Limacher M, Hale L, Eaton CB. Sleep duration, insomnia, and coronary heart disease among postmenopausal women in the Women's Health Initiative. *J Womens Health (Larchmt)*. 2013; 22(6): 477–486.
87 Laugsand LE, Strand LB, Platou C, Vatten LJ, Janszky I. Insomnia and the risk of incident heart failure: a population study. *Eur Heart J*. 2014; 35(21): 1382–1393.
88 Bruno RM, Palagini L, Gemignani A, Virdis A, Di Giulio A, Ghiadoni L, Riemann D, Taddei S. Poor sleep quality and resistant hypertension. *Sleep Med*. 2013; 14(11): 1157–1163.
89 Johansson JK, Kronholm E, Jula AM. Variability in home-measured blood pressure and heart rate: associations with self-reported insomnia and sleep duration. *J Hypertens*. 2011; 29(10): 1897–905.
90 Fernandez-Mendoza J, Vgontzas AN, Liao D, Shaffer ML, Vela-Bueno A, Basta M, Bixler EO. Insomnia with objective short sleep duration and incident hypertension: the Penn State Cohort. *Hypertension*. 2012; 60(4): 929–935.
91 Vozoris NT. The relationship between insomnia symptoms and hypertension using United States population-level data. *J Hypertens*. 2013; 31(4): 663–671.
92 Phillips B, Mannino DM. Do insomnia complaints cause hypertension or cardiovascular disease? *J Clin Sleep Med*. 2007; 3(5): 489–494.
93 Farina B, Dittoni S, Colicchio S, Testani E, Losurdo A, Gnoni V, Di Blasi C, Brunetti R, Contardi A, Mazza S, Della Marca G. Heart rate and heart rate variability modification in chronic insomnia patients. *Behav Sleep Med*. 2014; 12(4): 290–306.
94 Spiegelhalder K, Fuchs L, Ladwig J, Kyle SD, Nissen C, Voderholzer U, Feige B, Riemann D. Heart rate and heart rate variability in subjectively reported insomnia. *J Sleep Res*. 2011; 20(1 Pt 2): 137–145.
95 Yang AC, Tsai SJ, Yang CH, Kuo CH, Chen TJ, Hong CJ. Reduced physiologic complexity is associated with poor sleep in patients with major depression and primary insomnia. *J Affect Disord*. 2011; 131(1–3): 179–185.
96 Dominguez-Rodriguez A. Melatonin in cardiovascular disease. *Expert Opin Inv Drug*. 2012; 21(11): 1593–1596.
97 Zou M. Clinical observation on therapeutic effect of combination of acupuncture and ginger-partition moxibustion for treatment of patients with cardiac arrhythmia. *Zhongguo Zhen Jiu*. 2009; 29(11): 876–878. Chinese with abstract in English.
98 Litscher G, Cheng G, Cheng W, Wang L, Niu Q, Feng X, Gaischek I, Kuang H. Sino-European transcontinental basic and clinical high-tech acupuncture studies—part 2: acute stimulation effects on heart rate and its variability in patients with insomnia. *Evid Based Complement Alternat Med*. 2012; 2012: 916085.
99 Wang L, Cheng W, Sun Z, Xu Y, Cheng G, Gaischek I, Kuang H, Litscher G. Ear acupressure, heart rate, and heart rate variability in patients with insomnia. *Evid Based Complement Alternat Med*. 2013; 2013: 763631.
100 Agelink MW, Sanner D, Eich H, Pach J, Bertling R, Lemmer W, Klieser E, Lehmann E. Does acupuncture influence the cardiac autonomic nervous system in patients with minor depression or anxiety disorders? *Fortschr Neurol Psychiatr*. 2003; 71(3): 141–149. German with abstract in English.
101 Fasmer OB, Liao H, Huang Y, Berle JØ, Wu J, Oedegaard KJ, Wik G, Zhang Z. A naturalistic study of the effect of acupuncture on heart-rate variability. *J Acupunct Meridian Stud*. 2012; 5(1): 15–20.
102 Hwang DS, Kim HK, Seo JC, Shin IH, Kim DH, Kim YS. Sympathomodulatory effects of Saam acupuncture on heart rate variability in night-shift-working nurses. *Complement Ther Med*. 2011; 19(Suppl 1): S33–S40.
103 Wang H, Litscher G, Shi X, Jiang YB, Wang L. Effects of acupuncture on heart rate variability in beagles; preliminary results. *Evid Based Complement Alternat Med*. 2013; 2013: 419212.
104 Kurono Y, Minagawa M, Ishigami T, Yamada A, Kakamu T, Hayano J. Acupuncture to Danzhong but not to Zhongting increases the cardiac vagal component of heart rate variability. *Auton Neurosci*. 2011; 161(1–2): 116–120.
105 Chen NY, Zhou Y, Dong Q, Zhou CX. Observation on therapeutic effect of acupuncture in the treatment of German hypertension patients. *Zhen Ci Yan Jiu*. 2010; 35(6): 462–

466. Chinese with abstract in English.
106 Yin C, Du YZ. Observation of anti-hypertensive effect on primary hypertension treated with acupuncture at Renying (ST9) mainly. *Zhongguo Zhen Jiu*. 2012; 32(9): 776–778. Chinese with abstract in English.
107 Wu HC, Lin JG, Chu CH, Chang YH, Chang CG, Hsieh CL, Tsai AH, Ueng KC, Kuo WW, Lin JA, Liu JY, Huang CY. The effects of acupuncture on cardiac muscle cells and blood pressure in spontaneous hypertensive rats. *Acupunct Electrother Res*. 2004; 29(1–2): 83–95.
108 Dong YS, Xing SL. Effect of acupuncture needle-retention duration at Baihui (GV20) and Sishencong (EX-HN1) on blood pressure in hypertension patients. *Zhen Ci Yan Jiu*. 2012; 37(3): 233–236. Chinese with abstract in English.
109 Chen H, Dai J, Zhang X, Wang K, Huang S, Cao Q, Wang H, Liang Y, Shi C, Li M, Ha T, Ai L, Li S, Ma J, Wei W, You Y, Liu Z, Tian J, Bai L. Hypothalamus-related resting brain network underlying short-term acupuncture treatment in primary hypertension. *Evid Based Complement Alternat Med*. 2013; 2013: 808971.
110 Gao XY, Li YH, Liu K, Rong PJ, Ben H, Li L, Zhu B, Zhang SP. Acupuncture-like stimulation at auricular point Heart evokes cardiovascular inhibition via activating the cardiac-related neurons in the nucleus tractus solitarius. *Brain Res*. 2011; 1397: 19–27.
111 Guo J, Wang LP, Liu CZ, Zhang J, Wang GL, Yi JH, Cheng JL. Efficacy of acupuncture for primary insomnia: a randomized controlled clinical trial. *Evid Based Complement Alternat Med*. 2013; 2013: 163850.