

Original Article

Acupuncture for alcohol use disorder

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Abstract: Alcohol use disorder (AUD) is a common medical and social problem, affecting about 240 million people in the world. To address this major health concern, the currently available treatments for AUD need to be improved. Acupuncture, a popular form of complementary and alternative therapy, is emerging as an effective treatment for AUD. This review summarizes how preclinical and clinical studies are related to the application of acupuncture for AUD. These studies suggest that if used correctly, acupuncture may effectively reduce alcohol intake, attenuate alcohol withdrawal syndrome, and rebalance AUD-induced maladaptation in neurotransmitters and hormones in related brain areas. The progress of research in this field is at an early stage. Future investigations with rigorous design and carefully constructed protocols are still needed.

Keywords: Alcohol abuse, complementary and alternative medicine, alcohol withdrawal, negative reinforcement

Introduction

Alcohol use disorder (AUD) is characterized by consumption of large quantities of alcohol despite negative consequences to the individual [1]. It continues to be a leading avoidable risk factor contributing to the global burden of disease [2]. An estimated 240 million people throughout the world are affected [3]. Currently available treatments for AUD remain largely ineffective [4-6], making it necessary to seek new therapies in this field.

Originating in ancient China, acupuncture is an alternative and complementary therapy traditionally practiced by inserting thin solid needles into specific human body points (acupoints) guided by the theory of traditional Chinese medicine. More recently, it has also been practiced by attaching a low energy electrical stimulator to the needle (electroacupuncture) [7]. According to the theory of traditional Chinese medicine, Qi, or “life energy” circulates along the meridians (Jing Luo) and through acupoints. Most acupoints are distributed along the body meridians. In this way, the whole body is connected via a loose neural net-

work, from the superficial skin to the internal organs. Thus, the function of internal organs can be regulated via stimulating certain acupoints. The code of an acupoint tells the meridian it belongs to, and its serial number, e.g., HT7 means the 7th acupoint on the Heart Meridian. **Table 1** and **Figure 1** give an example of the exact locations of commonly used acupoints.

Acupuncture is commonly used to treat a variety of diseases, including alcohol dependence, particularly in East Asian countries [9, 10]. This paper seeks to review preclinical and clinical studies regarding the use of acupuncture as an acceptable therapy to treat aspects of AUD including alcohol intake, alcohol withdrawal syndrome and other changes induced by alcohol administration.

Acupuncture for reducing alcohol intake

Excessive alcohol intake has been identified as an important risk factor for a variety of chronic illnesses. It has been shown that alcohol is causally related to over 60 different medical conditions. Most of the effects of al-

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Table 1. Locations of acupoints on the rat and human

	Rat	Human [8]
HT7	On the wrist crease of the forepaw, radial to the border of ulna	On the anteromedial aspect of the wrist, radial to the flexor carpi ulnaris tendon, on the palmar wrist crease.
PC6	Between ulna and radius, 3 mm proximal to the wrist crease of the forepaw	On the anterior aspect of the forearm, between the tendons of the palmaris longus and the flexor carpi radialis, 2 B-cun proximal to the palmar wrist crease.
SP6	10 mm above the medial malleolus	On the tibial aspect of the leg, posterior to the medial border of the tibia, 3 B-cun superior to the prominence of the medial malleolus.
ST36	Near the knee joint, 5 mm lateral to the anterior tubercle of the tibia	On the anterior aspect of the leg, one finger-breadth lateral to the anterior crest of the tibia, 3 B-cun inferior to bottom of your knee cap.

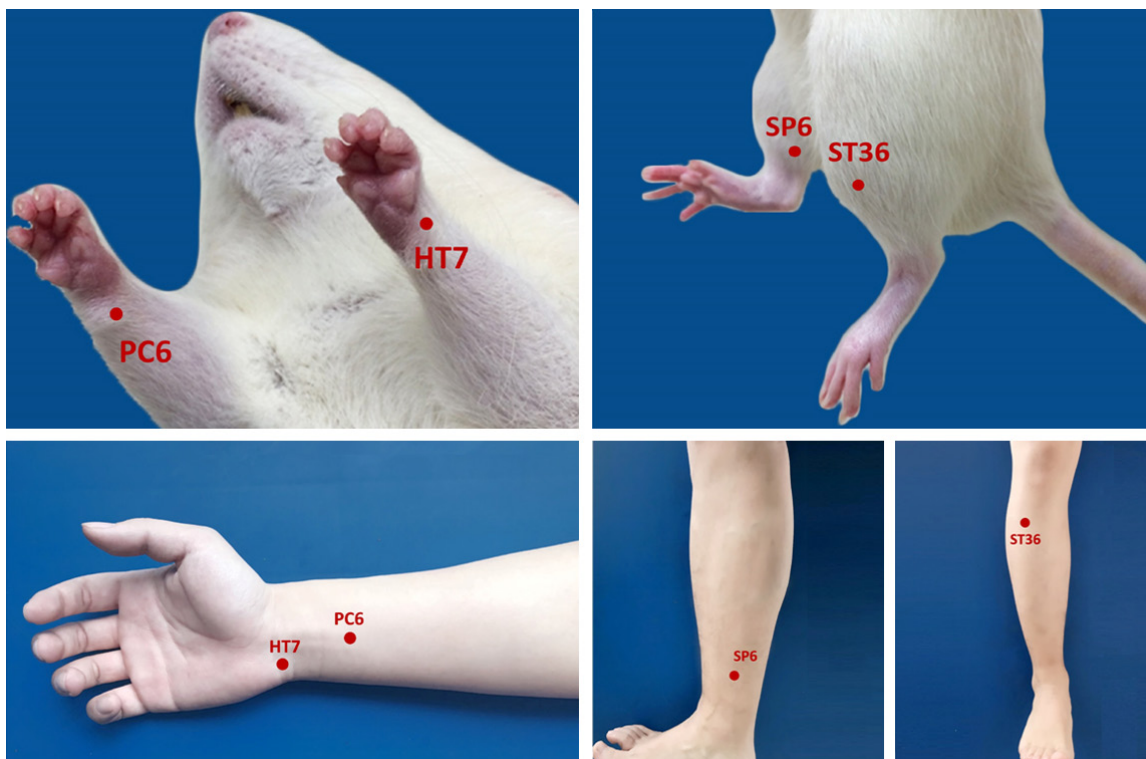


Figure 1. Locations of acupoints on the rat and human.

cohol have been shown to be detrimental. The average volume of alcohol consumption and the patterns of drinking contribute to the disease burden [2]. For most diseases, there is a dose-response relationship between the amount of alcohol intake and the risk of disease, showing increased risk with larger amount of consumption [11]. Therefore, it is crucial to find ways to control the volume of alcohol consumption.

A preclinical study showed that electroacupuncture (EA) bilaterally at a combination of acupoints ST36 (Zusanli) and SP6 (Sanyinjiao) could significantly reduce alcohol intake in alcohol-dependent rats. This inhibitory effect was blocked by the pretreatment with naltrexone,

a mu opioid receptor (MOR) antagonist, indicating that the EA's effect on alcohol intake may involve the activation of endogenous opiate system [12]. Previously, it was observed that a single low frequency EA (2 Hz) treatment (as opposed to high frequency at 100 Hz) at bilateral ST36, but not at the tail acupoints, reduced the voluntary intake of and preference for alcohol, in Sprague-Dawley rats that had been drinking alcohol under an intermittent access two-bottle choice drinking procedure for two months. The Sprague-Dawley rats did not show this effect for sucrose intake. Moreover, repeated low frequency EA treatment reduced ethanol intake and preference, with no rebound increase of ethanol intake when EA treatments were terminated [13]. To

further uncover the underlying mechanism of EA for alcohol abuse, we conducted EA on another group of rats that drank large amount of ethanol under a modified intermittent access two-bottle choice drinking procedure. We found that six-day 100 Hz EA treatment at ST-36 sharply reduced the intake of and preference for ethanol, and the FosB/ Δ FosB levels elevated by repeated cycles of excessive drinking in reward-related brain regions. These results suggest that down-regulation of FosB/ Δ FosB levels may underlie the effect of EA on alcohol addiction [14]. A similar reduction of the intake of alcohol, but not that of sucrose in rats was observed by acupuncture at HT7 (Shenmen) [15]. These inspiring results suggest that acupuncture at certain acupoints could effectively reduce alcohol intake by modulating neurotransmitter and reward pathways in brain.

Acupuncture for relieving alcohol withdrawal syndrome

Alcohol withdrawal syndrome is a complex set of signs and symptoms which occur after abrupt cessation of chronic alcohol consumption. This syndrome is a homeostatic readjustment of the central nervous system from the neuro-adaptation which develops with prolonged alcohol intoxication [16]. Alcohol withdrawal symptoms appear within hours after cessation of alcohol intake and contribute to compensatory relapse behavior [17]. Symptoms of alcohol withdrawal are largely those of autonomic hyperactivity, the reverse of the effects of alcohol intoxication [16]. Symptoms can be both physical, such as tremor, and psychological, such as increased anxiety. Acupuncture has been reported to be effective in relieving both physical and psychological alcohol withdrawal signs. Better understanding of the effect of acupuncture for alcohol withdrawal syndrome and the corresponding mechanisms may be helpful for future clinical application of acupuncture and prevention of relapse behavior.

Acupuncture for physical withdrawal signs

The physical withdrawal signs of alcohol are manifested in various forms, including stereotypic movements, startle, and seizures. A study done by Kim et al. [18] demonstrated that acupuncture at ST36 or SP6 could suppress

the physical signs of alcohol withdrawal such as tail rigidity, hypermobility, and tremor. Additionally, the elevated c-Fos expressions were reduced in the dopaminergic terminal areas, striatum and core of nucleus accumbens, which are known to associate with the control of motor behaviors. A similar effect was observed by acupuncture at HT7, inhibiting locomotor activity, tremor, and grooming during ethanol withdrawal (EW). This suppressive effect can be blocked by intraperitoneal injection of selective GABA_A or GABA_B receptor antagonist [19].

Another physical withdrawal sign attracting researchers' attention is hyperalgesia. Hyperalgesia, defined as increased sensitivity to pain, has been found both in animals and human study participants during EW and may play an important role in relapse [20, 21]. Previously, we tested the paw withdrawal latencies (PWLs) to radiant heat in rats. Results revealed that compared with ethanol-naive rats, PWLs were significantly shorter in rats at 24, 48 and 72 hours and seven days after EW. At 24 hours after withdrawal, a single administration of 2 Hz EA for 20 minutes at ST36 significantly prolonged the PWLs, compared with those of the control group (2 Hz EA at the tail). The effect of EA on PWLs was reversed by bilateral intra-habenula infusion of the MOR antagonist naltrexone, indicating that EA can effectively relieve hyperalgesia during EW via a mechanism involving MORs in the habenula [22].

Acupuncture for anxiety-like behavior during EW

Anxiety symptoms are closely associated with EW thereby providing negative reinforcement leading to relapse [23, 24]. To investigate the effect of acupuncture on anxiety-like behavior in ethanol-withdrawal rats, Zhao et al. conducted a series of experiments, showing that acupuncture at HT7, but not PC6 (Neiguan), effectively attenuated the anxiety-like behavior during EW in rats, which was evidenced by elevated plus maze testing [25-28]. Additionally, changes in the levels of hormones and neurotransmitters triggered by EW were corrected after the acupuncture treatment.

Corticotrophin-releasing factor (CRF) in the central nucleus of the amygdala (CeA) has been

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shown to mediate anxiety-like behavior induced by withdrawal of various addictive drugs [29]. Acupuncture at HT7 can prevent the increase of CRF mRNA expression in the CeA and plasma corticosterone (CORT) concentration. Conversely, injection of CRF into CeA abolishes the effect of acupuncture at HT7 on expression of anxiety-like behavior and over-secretion of plasma CORT [25]. The dysregulation of catecholamine in the CeA during EW, including reduction of dopamine (DA) and its major metabolite 3, 4-dihydroxyphenylacetic acid (DOPAC), and increase of norepinephrine (NE) and its major metabolite 3-methoxy-4-hydroxy-phenylglycol (MHPG), were also normalized by acupuncture at HT7 [26].

cAMP response element-binding protein (CREB) is common to the signaling cascades, which can modulate the transcription of the genes encoding neuropeptide Y (NPY). Studies show that the concentration of phosphorylated CREB and the expression of NPY decreased in the amygdala during EW after chronic ethanol intake. This might be associated with anxiety and alcohol-drinking behaviors [30]. Acupuncture performed at HT7 significantly reversed the decreased levels of NPY protein and mRNA, and CREB phosphorylation in the CeA. Intra-CeA infusions of a selective NPY Y1 receptor antagonist abolished the anxiolytic effects of acupuncture at HT7 [27].

It's well documented that DA projection from the ventral tegmental area (VTA) to the nucleus accumbens is vital in mediating the rewarding effects of ethanol [31]. Additionally, it has a central role in the regulation of anxiety-like behavior [32]. During EW, the reduction of tyrosine hydroxylase (TH) mRNA expression in the ventral tegmental area (VTA), and the levels of TH protein, DA and DOPAC in the nucleus accumbens shell, could be reversed by acupuncture at HT7. Infusion of selective DA1 and DA2 receptor antagonists' solution into the nucleus accumbens shell abolished the anxiolytic effect of acupuncture at HT7 [28].

Collectively, the anxiolytic effect of acupuncture during EW involves multiple hormones, neurotransmitters, and several key brain regions, which all play important roles in ethanol addiction and anxiety. Acupuncture at HT7 achieves an anxiolytic effect by rebalancing the changes triggered by EW and thus ameliorate the anxiety-like behavior as a result.

Acupuncture for spatial learning and memory impairment

Bin et al. [33] showed that after a 5-day ethanol exposure, the spatial learning and memory abilities of rats were markedly decreased as indicated by the prolonged escape latency and decreased time in the target quadrant in the Morris water maze testing. Additionally, decreased Fos expression was detected in the hippocampal CA1 area in rats exposed to ethanol. Consecutive EA treatment at ST36 was shown to successfully reverse these changes. Moreover, significant positive correlations were found between Fos protein expression in the CA1 area and time in the target quadrant, suggesting the possible involvement of CA1 area in the EA effect.

Acupuncture for other changes induced by alcohol administration

Acupuncture for locomotor sensitization

Repeated administration of addictive drugs may result in a progressive, and long-lasting enhancement of the locomotor response termed locomotor sensitization [34]. To study the effect of EA on ethanol-induced locomotor sensitization, Jair and colleagues conducted a series of experiments, showing that EA over a combination of ST36 and PC6 (but not at either ST36 or PC6 individually) reversed the ethanol-induced locomotor sensitization in the acquisition, expression and maintenance phases. These effects were accompanied by inhibition of ethanol-triggered diminution in the *homer1A* mRNA expression in the hippocampus, striatum, and prefrontal cortex [35]. EA given concomitantly at DU14 (Dazhui) and DU20 (Baihui) had similar effect upon locomotor sensitization, which may depend on extracellular signal-regulated kinase signaling [36].

Acupuncture for activity of hypothalamic-pituitary-adrenal axis

The hypothalamic-pituitary-adrenal axis is a major component of the neuroendocrine system, in charge of the response to various stressors. In reaction to stress, CRF neurons residing in the paraventricular nucleus (PVN) of the hypothalamus secrete CRF, which stimulate the release of pituitary adrenocorticotropic hormone (ACTH) and ultimately adrenal CORT [37]. It is reported that acupuncture at

ST36 (but not at the tail) significantly inhibited the increased plasma levels of CORT and ACTH in the ethanol-withdrawal rats [38]. Also, EW-elevated concentrations of NE and MHPG, phosphorylation rate of TH, and expression of CRF protein in the PVN were all prevented by acupuncture at ST36 [38, 39]. Further, given that NE is an important secretagogue of CRF in the PVN, post-acupuncture injection of NE into PVN remarkably reverses the inhibitory effects of acupuncture on the over-secretion of plasma CORT in EW rats [39]. Altogether, it is suggested that acupuncture at ST36 can block the EW-induced hyperactivity of the HAP axis, which may be mediated by inhibiting the hyperactivity of hypothalamic Norepinephrine system.

Acupuncture for mesolimbic DA system

Acupuncture has a dual-directional regulating effect on the accumbal DA levels. Studies show that acupuncture at HT7, but not at control points (PC6 or tail), had a significant inhibitory effect on accumbal DA increase induced by acute systematic ethanol administration or ethanol challenge in EW period [40, 41]. Interestingly, acupuncture at HT7 also prevented accumbal DA decrease during the withdrawal period after chronic ethanol treatment [19, 41]. The differential effects of acupuncture on DA release were both blocked by intraperitoneal injection of selective GABAB antagonist SCH 50911 [19, 40]. Nevertheless, DA release in the nucleus accumbens was not affected by acupuncture at HT7 in the vehicle (saline)-treated rats [40, 41]. A further study showed that acupuncture at HT7 significantly reduced the suppression of VTA GABA neuron firing rate produced by acute ethanol administration, which was blocked by naloxone, suggesting that opioid receptors and VTA GABA neurons may take part in acupuncture's role in modulating mesolimbic DA release [15].

Acupuncture for endocannabinoid system

The endocannabinoid system plays a vital role in the development of ethanol dependence and relapse [42]. Study showed that the CB1R in the prefrontal cortex, striatum, hippocampus, amygdala and ventral tegmental area increased in EW mice. EA at acupoint combination ST36 and PC6 (2 Hz), or DU14 and DU20 (100 Hz) could effectively and specifically inhibit this CB1R upregulation [43].

Clinical studies

Clinical studies focus mainly on the application of body acupoints, ear acupoints or their combination to the treatment of alcohol craving and related discomfort.

Using placebo needle acupuncture as control, a randomized trial showed that real-needle acupuncture therapy at KI9 (Zhubin) could effectively reduce alcohol craving for the alcohol-dependent subjects, measured using a Visual Analogue Scale [44]. Yang et al. [45] conducted a functional MRI study among drinkers who were accustomed to light to heavy alcohol consumption. They observed that stimulation at HT7 induced activation on the bilateral post-central gyrus, inferior parietal lobule, inferior frontal gyrus, claustrum, insula, and anterior lobe of cerebellum, as well as the left posterior lobe of the cerebellum, brain areas associated with alcohol-related diseases. These results support that HT7 stimulation as an additional treatment for alcohol dependence. By comparison, acupuncture at control acupoint LI5 (Yangxi) only activated the right inferior parietal lobule and left claustrum.

Auricular acupuncture, which stimulate ear acupoints instead of body acupoints, has attracted great attention in recent years. A significant percentage of alcoholics who received ear-acupuncture relaxation therapy felt that their lifestyle, drinking pattern and physical and mental health improved after treatment [46]. Bergdahl et al. [47] interviewed subjects about their experience with auricular acupuncture treatment during the abstinence period following the elimination of problematic alcohol and illicit drug use. All subjects responded positively following the acupuncture treatment, noting a reinforced sense of relaxation and well being, peacefulness and harmony, and new behaviors without any negative side-effects. Female alcoholics were reported to have a stronger reduction of anxiety one month after acupuncture treatment at traditional ear points compared with the incorrect (placebo/sham) points in control group [48]. Lewenberg applied a combination of ear electroacupuncture and small doses of antidepressant maprotiline hydrochloride in 50 alcoholics and found that a relatively high percentage of subjects became abstinent without exhibiting or reporting any acute withdrawal symptoms [49].

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In some studies, body acupoints and auricular acupoints were manipulated simultaneously. Bullock et al. [50, 51] showed that severe recidivist alcoholics receiving acupoint-specific treatment expressed less need for alcohol, had fewer drinking episodes and fewer admissions to the detoxification center compared to the control patients receiving non-specific treatment. The effect was long-lasting and significant. Karst et al. [52] performed acupuncture at ear-body acupoint combination as a supplemental therapy to standard medication with carbamazepine. After ten daily treatments, the experimental needle group showed significant superiority over the placebo needle group at withdrawal symptoms on day 14, supporting acupuncture as an adjunctive treatment for alcohol withdrawal symptoms.

Systematic review results support that among patients with AUD, acupuncture treatment has a more significant effect than control interventions on alcohol-related symptoms and behaviors [53]. Southern et al. [54] also support the use of acupuncture as a potentially effective treatment for the reduction of alcohol cravings and withdrawal symptoms.

Nevertheless, not all studies support the clinical use of acupuncture for AUD. Worner et al. [55] cautioned against the routine use of acupuncture in alcoholics due to the lack of a significant outcome between point-specific acupuncture, sham transdermal stimulation and standard care groups. Rampes et al. [56] did not find any major advantage in using specific auricular acupuncture points for alcohol addiction compared with the non-specific points. Bullock et al. [57] found that acupuncture did not contribute significantly to the reduction of alcohol use compared to standard therapy alone. Kunz et al. [58] reported that acupuncture did not show any significant benefits over the use aromatherapy in its specific effects on reducing alcohol withdrawal symptoms.

Discussion

Acupuncture is an ancient and effective therapy based on the theory of traditional Chinese medicine. By modulating the movement of Qi through body meridians, acupuncture helps to restore the harmony and fluency of Qi. Different from the modern pharmacological manipulation, acupuncture has several features that

make it a unique approach for the AUD. Firstly, acupuncture mainly targets dysfunction to make an effect, without disturbing the normal state, which can be seen from the absence of influence of acupuncture on the accumbal DA release in saline-treated rats [40, 41]. Secondly, acupuncture works against changes, rather than towards a certain direction. From lines of findings about the accumbal DA release [40, 41], we can see that the effect of acupuncture is dual-directional, which means that inserting the needle in the same acupoint can play two opposite effects according to the existing changes within the body. The core function of acupuncture is to reverse the pathologic changes of the disease process, promoting a return to the normal bodily balance of Qi. These features of acupuncture contribute to its safety and wide applicability. Also, the effect of acupuncture is acupoint-specific. Selection of acupoint and frequency of treatment depends largely on the traditional acupuncture theory, clinical experience, and experimental study results. Additionally, even the same acupoint attached to electrical stimulation of different frequencies may produce different effects [13, 43]. However, despite the significant amount of pre-clinical and clinical evidence suggesting the efficacy of acupuncture therapy, the exact and predominant mechanisms underlying its effects are not defined.

In addition to its use in alcohol dependency, acupuncture has also been applied to the treatment of other addictive drugs, including cocaine, opioids, and opiates, nicotine, and morphine [59]. There are several milestones in the development of acupuncture for substance abuse. The initial use of acupuncture to attenuate drug withdrawal signs began in 1972 following an incidental discovery by Dr. Wen, a neurosurgeon in Hong Kong. This discovery was followed by the creation of a standardized acupuncture protocol by Michael Smith, head of the United States National Acupuncture Detoxification Association (NADA), for the treatment of drug abuse [60-62]. In 2005, Ji-Sheng Han in Peking University, China introduced a protocol on the use of acupuncture for withdrawal symptoms and relapse [62]. This effort significantly promoted the application of acupuncture for drug abuse. Schwartz et al. [63] reported that subjects who joined programs implementing acupuncture therapy were

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less likely to be readmitted for substance abuse detoxification within six months compared to those in the residential detoxification programs.

Chinese herbs are an essential component of traditional Chinese medicine. They have been used for alcohol-related disorders with some positive results [64]. Co-administration of acupuncture with traditional Chinese herbal medicine may be effective for the treatment of drug abuse and dependence [60].

Although acupuncture has become an increasingly popular method for the treatment of alcohol addiction, there are still many methodological problems in the research in this field [65]. As was described by Worner [55], the enrolled subjects were mainly of lower socioeconomic class. It remains to be clarified whether this kind of sample has an influence on the study results. Furthermore, the existing studies typically choose only one or two acupoints in each experiment as opposed to the typical clinical practice of selecting a group of acupoints for needle insertion. Another inherent problem frequently suggested throughout several studies was the choice of control groups, which potentially can reverse the final study results. The rationality of placing sham or placebo acupuncture, or even electrocardiogram pads as a control intervention needs further discussion. Inappropriate choice of outcome measurements may also alter or even overlook the effect of acupuncture for drug dependence [66].

To summarize, acupuncture is an inexpensive, safe therapy for AUD if administered by trained personnel. It may effectively reduce alcohol intake, attenuate alcohol withdrawal syndrome, and rebalance the altered release of neurotransmitters and hormones in addiction-related brain areas. However, the development of research in this field is very slow or even stagnant. Rigorously designed and detailed studies are still necessary to help us fully understand the mechanisms of acupuncture.

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Disclosure of conflict of interest

None.

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