
Role of Acupuncture in the Treatment of Drug Addiction

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Abstract

This review systematically assessed the clinical evidence for and against acupuncture as a treatment for drug addiction. The existing scientific rationale and possible mechanisms for the effectiveness of acupuncture on drug addiction were also evaluated. We used computerized literature searches in English and Chinese and examined texts written before these computerized databases existed. We also used search terms of treatment and neurobiology for drug abuse and dependence. Acupuncture showed evidence for relevant neurobiological mechanisms in the treatment of drug addiction. Although positive findings regarding the use of acupuncture to treat drug dependence have been reported by many clinical studies, the data do not allow us to make conclusions that acupuncture was an effective treatment for drug addiction, given that many studies reviewed here were hampered by small numbers of patients, insufficient reporting of randomization and allocation concealment methods, and strength of the inference. However, considering the potential of acupuncture demonstrated in the included studies, further rigorous randomized controlled trials with long follow-up are warranted.

Keywords: acupuncture, addiction, heroin, cocaine, treatment

1. Introduction

Acupuncture originated in ancient China and has been used to manage various clinical disorders for thousands of years in China. Acupuncture needles insert into acupuncture points of the body to treat many different disorders. Acupuncture needles are manipulated manually. One of the recent technical developments was to use peripheral electrical stimulation applied

via the acupuncture needles inserted into the acupoints, that is, “electroacupuncture” (EA). Currently, new methods for stimulating the acupuncture points include applying electric current to skin electrodes over the points, directing a laser light onto the points, or using finger pressure to massage selected points (acupressure). In addition, many new points and entire “microsystems” of points have been described for specific body parts, for example, scalp acupuncture and ear acupuncture (auricular acupuncture). In Western countries, acupuncture began to be known in the middle of the 1970s, yet its acceptance has increased rapidly. Many Western patients turn to acupuncture along with conventional medical therapy to make sure they are utilizing all possible medical options. A recent survey of acupuncture released by an NIH Consensus Development Panel indicated that although there are inherent problems of design, sample amount, and appropriate controls in the acupuncture literature, extensive work has shown that acupuncture is beneficial in treating various pain syndromes, postoperative and chemotherapy-induced nausea and vomiting, some forms of bronchial asthma, headache, migraine, and female infertility. For the past 40 years, a number of studies of acupuncture applied, as a medical technique, to the treatment of heroin, alcohol, nicotine, and cocaine addictions have been reported. In light of an increasing trend in the use of acupuncture and utilization of such approaches by patients suffering from drug addiction, we intend to review the existing scientific rationale and clinical data, which indicate that acupuncture may influence the prognosis of drug addicts.

2. Acupuncture: Theory and mechanisms

It has long been a dream to cure diseases by nonpharmacological measures that activate self-healing mechanisms, without using drugs. Recent efforts along these lines were the use of vagal nerve stimulation, repetitive transcranial magnetic stimulation (rTMS), deep brain stimulation, and acupuncture to stimulate certain brain areas. Evidence presented in the present review demonstrates that it is possible to facilitate the release of certain neuropeptides in the central nervous system (CNS) by means of peripheral acupuncture point’s stimulation. In contrast to magnetic stimulation that stimulates the superficial areas of the brain (i.e., the cortex) [1], acupuncture activates various brain structures and/or the spinal cord via specific neural pathways. Any predictions made at this stage should not be overly optimistic. But the clinical efficacy demonstrated using acupuncture to ease postoperative pain [2,3], lower-back pain [4,5], and diabetic neuropathic pain [6], and the successful application of 100 Hz (but not 2 Hz) electroacupuncture for treating muscle spastic pain of spinal origin [7]E certainly hold exciting promise for the future. Gaining knowledge of therapeutic mechanisms is essential to validating therapies such as acupuncture that are difficult to test under double-blind, placebo-controlled conditions. If we try to answer the question “how the acupuncture works or what physical changes occur”, it is appropriate first to give some theoretical background for acupuncture. Clinical treatment with acupuncture is done in light of symptom differentiation and therapeutic methods, by means of needling and moxibustion (lighted punks of *artemis vulgaris*) with certain manipulating methods to stimulate the selected acupuncture points for prevention and treatment of diseases. The theory of meridians and acupuncture points is the basic theory of therapy. In fact, traditional Chinese medicine is based on the concept of the flow of energy or Qi through meridian pathways in the body. Qi is postulated to flow through

the body in precisely located pathways or channels called meridians. These meridians are thought to be connected to various body organs as well as to each other. According to the principles of traditional Chinese medicine, illness results from an imbalance of energy flow within these meridians. Acupuncture was developed according to the principle that human bodily functions are controlled by the “meridian” and “Qi” systems. There are 365 designated acupuncture points located along these meridians. Acupuncture stimulates the points located on “meridians” along which Qi flows, breaking the blockage, and subsequently restoring the flow of energy and healthy body functioning [8].

Acupuncture points on the body have both local and systemic influences. Pain, for example, is treated not only locally but distally as well, via acupuncture points further along the meridian, drawing energy away from the pain. Conditions caused by organ dysfunction such as asthma or drug addiction are differentiated according to the specific symptoms present. Acupuncture points are then selected appropriate to both the symptoms reported and the cause of that individual’s problems.

Although different direction, angle and depth for inserting needles, stimulation intensity, such as rolling, raising, and thrusting, and Deqi may have an effect through different actions, the condition of the patient is the most important factor that influences the effectiveness of acupuncture. Numerous examples reveal that the regulatory effect of acupuncture has the characteristics of holism and bidirectional regulation. In acupuncture theory, bidirectional regulation is referred to a balancing effect of acupuncture interventions when the human body is experiencing a hyperactivity or hypoactivity due to abnormal intrinsic or external factors. The same acupuncture points’ stimulation with different manipulating techniques or stimulation parameters can regulate different functional activities of the body bidirectionally, which means to balance the functions of the body when they become hyperactive with the inhibiting effect and to restore the normal functions of the body when they become hypoactive with the exciting effect. For example, when blood pressure is too high, needling Neiguan (PC.6) can reduce high blood pressure; when blood pressure is too low, needling PC.6 can elevate blood pressure. Acupuncture-induced correction of abnormal blood pressure is observed to be dependent on the nervous, endocrinal, humoral, and dielectric regulation. Take Zusanli (ST. 36) for another example, EA at Zusanli (ST.36) can biregulate gastric activity. For gastric hypermotility, EA at ST.36 can inhibit gastric movement; but for bradygastria, EA at ST.36 can promote the peristalsis of the stomach. In addition, it is notable that some of the acupuncture points can bear special or specific curative effect on certain diseases. For example, Dazhui (GV. 14) abates fever and Zhiyin (BL.67) rectifies the position of fetus [9].

The guidance of the theory of traditional Chinese medicine is traditionally believed to be essential in achieving acupuncture’s therapeutic effect, but the metaphysical explanations may be hard to understand by modern science. In recent years, increasing research publications gave strong evidence that acupuncture could be explained on a physiological and neurobiological rather than a metaphysical basis [10, 11]. For example, in traditional Chinese medicine, the vision-related acupuncture point (VA1) (known as urinary bladder channel of BL67) is believed to be an effective acupuncture point that directly treats eye-related disorders. Various acupoints are related to corresponding specific organs rather than via the central nervous system. Based on the knowledge of Western medicine, it is difficult to believe that acupuncture

treats disorders and diseases by direct control of organs or organ-related disorders and diseases. It is known that many disorders are either controlled or affected by the brain, i.e., specific corresponding brain functional areas. Recently, Cho et al. [12] demonstrated that when acupuncture stimulation is performed at VA1 (vision-related acupuncture point), activation of occipital lobes is seen by functional magnetic resonance imaging (fMRI). Stimulation of the eye by directly using light evokes similar activation in the occipital lobes. It may represent an important step toward understanding oriental acupuncture in relationship to brain function. In addition, the findings by Bruce Rosen of Harvard Medical School at the American Psychosomatic Society Meeting in Orlando showed that acupuncture on pain-relief points cut blood flow to key areas of the brain related with pain within seconds. Researchers applied acupuncture needles to acupuncture points on the hand linked to pain relief in traditional Chinese medicine. Blood flow decreased in certain areas of the brain, which was detected by fMRI within seconds of volunteers reporting a sense of heaviness in their hands, a sign that the acupuncture is working. The needling technique is not supposed to hurt if done correctly. When a few subjects reported pain, the fMRI scannings showed an increase of blood to the same brain areas. It may provide a clear explanation to date for how the ancient acupuncture might relieve pain.

Recently, the neurophysiology of acupuncture has been investigated extensively and reviewed in detail. The principal suggestion is that acupuncture operates largely through neurotransmitters, particularly endorphin-related mechanisms. These studies demonstrate conclusively that acupuncture's effects are related to the release of a variety of neurotransmitters including natural opiates and, furthermore, that this effect is naloxone-reversible. Basic research work carried out has demonstrated that any noxious stimulus will result in endorphin release through the neurophysiological mechanism described as diffuse noxious inhibitory control (DNIC). Therefore, DNIC represents a nonspecific physiological mechanism which triggers the natural opiate system in both man and experimental animal. It has been suggested that DNIC plays a relatively minor role in acupuncture analgesia and that other systems, mediated by serotonin and noradrenaline, may be important. The mechanism of acupuncture in internal diseases, such as asthma, irritable bowel, and the treatment of symptoms such as nausea is completely unknown. Acupuncturists have hypothesized that the autonomic nervous system plays an important, but not as yet ill-defined, part in the underlying mechanisms that are involved in the treatment of such internal problems.

3. Effects of acupuncture on drug dependence

Conventional detoxification methods such as methadone and buprenorphine are effective in reducing illicit opioid use, but problems associated with their use, such as social resistance to the idea of "replacing one drug of abuse with another" and difficulties in tapering patients off the medication due to long-lasting withdrawal effects, make the search for alternative therapies important [13].

Acupuncture's utility for treating drug abuse and dependence is best shown in opioid-dependent patients experiencing withdrawal [14, 15]. Over the past 40 years, acupuncture and

EA have been applied with great success to attenuate behavioral signs of opioid withdrawal in addicts [16-18]. Using acupuncture to treat drug withdrawal symptoms began in 1972. H. L. Wen, a neurosurgeon from Hong Kong, visited China to learn acupuncture anesthesia. Upon returning to his Hong Kong practice, he used electrical stimulation via acupuncture needles to reduce or eliminate the need for anesthetic drugs during surgery. Acupuncture treatment was given over several weeks prior to surgery, as well as during operational procedures. Dr. Wen was unaware that some patients were also heroin, opium, morphine, alcohol, and/or nicotine dependent. The addict patients later volunteered this information, and reported that they also lost their drug cravings after receiving acupuncture. Wen and his colleagues followed up 40 patients for opium and heroin addiction. They confirmed that 39 of 40 patients were considered improved in that they had gained basal weight and reported they did not crave drugs [19-21]. In the United States, Smith and coworkers [22-25] modified Wen's original protocol by eliminating electrical stimulation and by using an abbreviated prescription of five-point auricular acupuncture. This prescription was not designed for withdrawal from any class of drug or any single abused substance. Instead, it effectively reduced cravings, anxiety, and dysphoria of withdrawal in addict patients during withdrawal from a variety of drugs and alcohol. Patients consistently reported the dramatic relief during the early weeks of withdrawal, when the incidence of relapse is highest. By 1974, Smith had used this five-point auricular protocol as the sole detoxification method used in the outpatient clinic at Lincoln Hospital in the Bronx, NY. Over the past 40 years, this acupuncture protocol has grown in popularity. It is currently used to treat alcohol and other drug withdrawal in more than 800 substance abuse treatment centers across the United States and Europe.

Clinical studies and related research on acupuncture have been undertaken by independent groups. Some randomized trials have been done to compare the effects of auricular acupuncture at specific points for the treatment of substance abuse and at sham points [26-28]. Washburn et al. [29] conducted the first controlled study of acupuncture heroin detoxification. One hundred addicted persons were randomly assigned, in a single-blind design, to the standard auricular acupuncture treatment used for addiction or to a "sham" treatment that used points that were geographically close to the standard points. They observed that subjects assigned to the standard treatment attended the acupuncture clinic more days and stayed in treatment longer than those assigned to the sham condition. Zhang et al. [26] also found that acupuncture and electrical stimulation were more effective than clonidine in treating withdrawal syndromes such as insomnia, pain, and anxiety following acute withdrawal symptoms. Clinical studies have also demonstrated that this treatment has fewer side effects. In addition, Meade et al. [30] tested the effectiveness of transcutaneous electric acupoint stimulation (TEAS) as an adjunctive treatment for inpatients receiving opioid detoxification with buprenorphine-naloxone at a private psychiatric hospital. It is shown that TEAS is an acceptable, inexpensive adjunctive treatment that is feasible to implement on an inpatient unit and may be a beneficial adjunct to pharmacological treatments for opioid detoxification. Acupuncture also appears to be a useful adjunct to methadone maintenance therapy (MMT) in heroin addiction. Recently, one study examined the effectiveness of acupuncture for heroin addicts on methadone maintenance by measuring the daily consumption of methadone, variations in the 36-item Short Form Health Survey-36 (SF-36) and Pittsburgh Sleep Quality Index (PSQI) scores. It is shown that acupuncture was also associated with a greater improvement in sleep latency at follow-up. All adverse events were mild in severity [31].

A number of studies have examined the effects of acupuncture on cocaine and alcohol dependence. For example, severe recidivist alcoholic patients treated with acupuncture specifically for the treatment of substance abuse reported less craving for alcohol, fewer drinking episodes, and required fewer admissions to the county detoxification center than did control patients who received acupuncture at nonspecific points [27]. Lipton et al. [32] also reported that patients receiving acupuncture treatment had significantly lower levels of cocaine metabolites than the control subjects. Recently, researchers, headed by S. Kelly Avants, from the division of substance abuse in the Department of Psychiatry at Yale University, divided 82 cocaine addicts into three groups. One third received acupuncture at four specific points around the outer ear, another third received "sham" acupuncture at sites on the ear that would be ineffective, and the remaining third received relaxation therapy consisting of viewing a relaxing video. Treatment sessions were five times a week and lasted eight weeks. The subjects' urine was tested three times a week for traces of cocaine. They found that patients assigned to receive true acupuncture had less cocaine use compared to the two other groups, and there were a higher percentage of patients in the acupuncture group who were clean from cocaine use by the last week of the study than in the two other groups [6].

The effects of acupuncture on drug addiction have also been verified by animal experiments. It has been well shown that acupuncture suppressed morphine withdrawal syndrome and alcohol-drinking behaviors in rats [33-35]. Furthermore, morphine-induced conditioned place preference can be successfully suppressed by 2 or 100 Hz electroacupuncture, a substitute for classic acupuncture [36, 37]. A recent study by Chae et al. [38] found that acupuncture at ST36, but not the other acupuncture points, significantly attenuated the expected increase in nicotine-induced locomotor sensitization to subsequent nicotine challenge. Behavioral response to nicotine challenge in the repeated nicotine treated group (control) was significantly intenser. Stimulation of acupuncture at ST36 just before nicotine challenge as well as during 3 days of withdrawal period completely blocked the effects of nicotine on locomotor activity during the 60 min testing period. In our laboratory, we also found that acupuncture applied at the BL.23 acupuncture point, a novel acupuncture point, could effectively suppress withdrawal syndrome [39,40].

However, some large clinical trials have questioned the effectiveness of acupuncture for drug dependence. In these studies, the acupuncture treatment groups failed to show significant differences from the control group in the treatment of drug dependence [41]. One study has found that acupuncture offered no significant reduction of nicotine withdrawal symptoms or long-term improvement over placebo [42]. Bullock et al. performed a single-blind, randomized, placebo-controlled study to evaluate auricular acupuncture in the treatment of cocaine addiction. Their study had 236 residential and 202 day treatment clients. They did not find any significant treatment differences between true and sham acupuncture. They also found no differences among the three dose levels of true acupuncture [43]. The Cocaine Alternative Treatment Study (CATS) [44] was a large-scale, multi-site study. In this study, 620 patients addicted to cocaine were enrolled from six treatment sites; 412 of the patients were "primary" cocaine-dependent, and 208 were opiate-dependent and maintained on methadone. Patients were randomized to the three treatment conditions: auricular acupuncture, a needle-insertion control condition, and a relaxation control condition. Treatments were offered five times weekly for 8 weeks. The patients maintained on methadone received standard care as offered

in their methadone program. Concurrent drug counseling was also offered to patients in all conditions. The primary outcome measure was cocaine use during treatment and at the 3- and 6-month postrandomization follow-up based on urine toxicology screens and retention in treatment. Results of urine samples showed a significant overall reduction in cocaine use, but no differences by treatment condition. There were also no differences between the conditions in treatment retention (44%–46% for the full 8 weeks). In the last week of treatment, 24, 31, and 29% of patients in auricular acupuncture, needle-insertion control, and relaxation control conditions, respectively, were abstinent from cocaine. This large study does not support the use of acupuncture as a stand-alone treatment for cocaine addiction.

4. Effects of acupuncture on psychological symptoms associated with drug addiction

Easing psychological symptoms associated with heroin use and heroin relapse is an important goal in the treatment of heroin dependence. Notably, as the course of withdrawal followed its natural history and acute symptoms abated, acupuncture continued to reduce anxiety and cravings associated with protracted withdrawal. In fact, patients who had completed addiction programs often continued to enjoy stress reduction induced by occasional “booster” acupuncture treatments. There are many ancient and contemporary papers reporting the successful use of acupuncture for the treatment of patients with depression and anxiety disorders [45-50]. Given that the prevalence of depression and anxiety is very high in cocaine and other drug addicts, and depression and anxiety after prolonged abstinence become the main factors contributing to drug relapse and craving, it is very meaningful to pay close attention to the effects of acupuncture on depression treatment among addicts. In addition, acupuncture has been used to improve psychological status and lessen fatigue [51]. Chang et al. conducted a three-arm randomized controlled trial (RCT) on residents of a homeless veteran rehabilitation program. Sixty-seven enrolled participants were randomly assigned to acupuncture, the relaxation response, or usual care. They found that craving and anxiety levels decreased significantly following one session of acupuncture [52]. In another small, randomized controlled trial, Allen et al. [53] compared symptoms of depression in an acupuncture group, placebo group, and a waitlist control group. The acupuncture group showed greater improvements in depressive scores than the placebo group and the waitlist control group. Roschke et al. [54] studied the effects of adding acupuncture to antidepressant treatment and found that the acupuncture in combination with antidepressant treatment improved the alleviation of depression course compared with pharmaceutical treatment alone. In a clinical trial using TAES for the suppression of opiate craving in humans, a total of 117 heroin addicts who had completed the process of detoxification for more than 1 month were recruited [55]. They were randomly and evenly assigned into four groups. Three groups received TAES treatment of different frequencies (2, 100, or 2/100 Hz). Self-sticking skin electrodes were placed on four acupoints: Hegu and Laogong (palmar side of the Hegu point) in the left (or right) hand to complete a circuit, and Neiguan and Weiguan in the opposite arm to complete a circuit. The control group was processed as in the previous groups except that the intensity was minimal (15 Hz, threshold stimulation for 3 min, and then switched to 1 mA thereafter) to serve as a mock TAES control. Visual analog scale (VAS) was used to assess the degree of craving. There

was a very slow decline of the VAS in the mock TAES control group in a period of 1 month. A dramatic decline of the degree of craving was observed in the groups receiving 2 and 2/100 Hz electric stimulation, but not in the group receiving 100 Hz stimulation. These results observed in humans were in line with the findings obtained in the rat: low-frequency TAES is more effective than high-frequency TAES in suppressing the morphine-induced CPP [56].

However, some studies [6, 30, 57, 58] did not show favorable effects of acupuncture on psychological symptoms associated with opioid addiction (anxiety, depression, and craving). For example, Black et al. [59] conducted a randomized controlled study to test the effect of auricular acupuncture in the treatment of anxiety associated with withdrawal from psychoactive drugs. They found that auricular acupuncture was not more effective than sham or treatment setting control in reducing anxiety. We reviewed the clinical studies that have investigated the clinical effectiveness of acupuncture and focused on psychological symptoms associated with opioid addiction. The clinical studies published in Chinese language journals were assessed carefully and included in our systematical reviews. We found that eight studies [26, 29, 41, 44, 60-62,64] included heroin/opioid craving. Seven studies [27, 28, 32, 60-63] included anxiety. Two studies included depression [60, 65]. All of the four studies [44, 66-68] published in English language journals did not show favorable effects of acupuncture on psychological symptoms associated with opioid addiction (anxiety, depression, and craving). Many studies published in Chinese language journals supported the use of acupuncture for controlling psychological symptoms associated with opioid addiction: craving [26, 41, 63, 69], anxiety [29, 32, 60, 62, 63, 70], and depression [60, 68].

Treatment retention and abstinence are more important goals for the treatment of drug dependence. Effectiveness of the treatment of psychological symptoms associated with drug addiction should be assessed by including longer-term follow-up data. In fact, to determine whether initial improvements from the treatment persist for a reasonable period of time, participant observation should last for at least 3 months. However, most of the studies we reviewed did not provide follow-up data. In these studies, the duration of acupuncture interventions was also shorter than 1 month. In fact, it is unclear whether the extent to which acupuncture has therapeutic effects depends on the duration and frequency of acupuncture. Arguably, longer treatment periods are required for acupuncture to have any chance of showing clinical effects. These variable factors should be taken into account when assessing the effects of acupuncture. Future studies should therefore have sufficiently large samples, extended treatment, and follow-up periods.

5. Possible mechanisms for the effectiveness of acupuncture on drug addiction

It would be reasonable to suggest that an opioidergic mechanism is, at least partially, involved in mediating acupuncture antiwithdrawal. Han and his colleagues from Peking University China have made a detailed survey on the analgesic effect of EA. They found that analgesia induced by 100-Hz EA resulted from accelerating the release of dynorphin from the spinal cord of the rats [11, 71, 72]. In accord with this was the finding that the analgesic effect of 100-Hz EA observed in morphine-dependent rats could be blocked by a high dose of naloxone

only [73]. On the other hand, dynorphin has been shown to be the endogenous ligand of the n-opioid receptor. Indeed, the withdrawal syndrome observed in rats dependent on morphine can be suppressed by high-frequency electroacupuncture, which accelerates the release of dynorphin in the spinal cord and brain [33, 70, 74]. Morphine-induced conditioned-place preference, an experimental model simulating the craving of heroin addicts, can be effectively suppressed by low-frequency electroacupuncture. This effect can be blocked by a small dose of naloxone, indicating the involvement of endogenous opioid peptides [36, 69]. Meanwhile, the clinical study by V. Clement-Jones et al. also showed that EA was associated with a rise in cerebrospinal fluid met-enkephalin levels in all addicts studied [67]. Recently, Wang et al. [75] found that a downregulation of preprodynorphin (PPD) mRNA level was observed in spinal cord, PAG, and hypothalamus 60 hours after the last morphine injection, which could be reversed by multiple sessions, but not a single session of EA. Accompanied with the decrease of PPD mRNA level, there was an upregulation of p-CREB in the three CNS regions, which was abolished by 100 Hz EA treatment. These findings suggest that downregulation of p-CREB and acceleration of dynorphin synthesis in spinal cord, PAG, and hypothalamus may be implicated in the cumulative effect of multiple 100Hz EA treatment for opioid detoxification.

The mesolimbic dopamine system originates in the ventral tegmental area (VTA) and projects to regions that include the nucleus accumbens and prefrontal cortex, which are believed to play a pivotal role in the development of opiate addiction [20]. Opiate abuse-induced changes in the levels of dopamine in the brain are associated with feelings of well-being and pleasure, providing positive reinforcement of continued opiate abuse [76, 39]. Conversely, withdrawal from chronic opiate administration reduces dopamine outflow in the nucleus accumbens [40, 77]. Furthermore, in the treatment of drug craving and relapse to drug use, the core symptoms of addiction, a non-endorphin-mediated mechanism is probably involved. Lu et al. [78] examined alterations in the firing rate of dopaminergic neurons by means of extracellular recording following chronic morphine exposure and applied 100 Hz electroacupuncture treatment to reverse the reduced firing rate of these neurons. They found that the electrophysiological response of VTA DA neurons to morphine was markedly reduced in chronic morphine-treated rats compared to saline-treated controls. A substantial recovery of the reactivity of VTA DA neurons to morphine was observed in rats that received 100 Hz EA for 10 days. Evidence also indicates that acupuncture acts on the nucleus accumbens to inhibit the elevation in dopamine [79, 80]. Yoon et al. demonstrated the acupuncture-mediated inhibition of ethanol-induced dopamine released in the rat nucleus accumbens through the GABA_B receptor [80]. Chae et al. showed that acupuncture treatment at ST.36 attenuated the expected increase in nicotine-induced locomotor activity by reducing postsynaptic neuronal activity in the nucleus and striatum [38].

Δ FosB and FosB are members of the Fos family of transcription factors implicated in neural plasticity in drug addiction. Li et al. [81] found that the intake of and preference for ethanol in rats under 100 Hz, but not 2 Hz electroacupuncture, regimen were sharply reduced. The reduction was maintained for at least 72 hours after the termination of electroacupuncture treatment. Conversely, 100 Hz electroacupuncture did not alter the intake of and preference for the natural rewarding agent sucrose. Additionally, FosB/ Δ FosB levels in the prefrontal cortex, striatal region, and the posterior region of ventral tegmental area were increased

following excessive ethanol consumption, but were reduced after 6-day 100 Hz electroacupuncture. Interestingly, EA can inhibit CB1 receptor upregulation in the prefrontal cortex, striatum, hippocampus, amygdala, and ventral tegmental area in ethanol-withdrawn mice [82]. Furthermore, extracellular signal-regulated kinase (ERK) plays a role in neuronal changes induced by repeated drug exposure. EA can reverse ethanol-induced locomotor sensitization and subsequent ERK expression in mice [83]. These results suggest that acupuncture could play an important role in suppressing the potentiating effects of ethanol and other drugs.

Our recent study [41] showed that acupuncture attenuated elevated c-fos expression in the central nucleus of the amygdala (CeA) during morphine withdrawal in rats. Some studies emphasize that the motivational components of opiate withdrawal appear to be centrally mediated by limbic structures such as the nucleus accumbens and amygdala [2-4]. Therefore, elevated c-fos expression in the CeA might be associated with the motivational components of opiate withdrawal. Our observation that acupuncture suppressed elevated c-fos expression in the CeA indicated that acupuncture might have some therapeutic effects in the treatment of the negative motivations of opiate withdrawal. Of course, further studies must be performed to clarify this issue. In addition, the CeA and the basolateral amygdala have been extensively and differentially involved in associative learning and memory processes, attributing affective salience to environmental stimuli paired with drug effects [5]. One theory of the neural mechanisms of drug abuse focuses on various learning and memory systems in which the normal functions of these complex neural circuits become subverted leading to compulsive drug-seeking behaviors [84, 85]. In this model, drugs of abuse initiate plasticity mechanisms in different learning and memory systems that come to control behaviors of the individual over other preexisting memories. Experience with addictive drugs are encoded and stored like other experiences, except that drugs of abuse only mimic a subset of the actions of natural reinforcers in the brain. Acupuncture can affect learning and memorizing ability [1, 7, 86, 87]. Further work is needed to emphasize whether acupuncture can re-encode experience with addictive drug via affecting learning and memory systems, and modify the addictive behaviors. The amygdala acquires information that promotes approach and interaction with drug-associated stimuli. We also need to know which role the amygdala plays when acupuncture stimulation affects drug-associated learning and memory.

6. Discussion

In terms of lives and productivity, drug addiction remains one of the most serious threats to our public health. Addiction can be defined as the loss of control over drug use, or the compulsive seeking and taking of a drug regardless of the consequences. Available treatments for addiction remain inadequately effective for most individuals. Incorporating acupuncture into existing therapies offers a promising approach. Acupuncture has been widely recognized as a valuable, readily available, and safe means of health care. It is effective, inexpensive, and requires only simple equipment. In this review, we identify and summarize the evidence about

the possible clinical effectiveness of acupuncture on drug addiction, including withdrawal symptoms, drug craving, depression, and anxiety. We also discuss the theory and possible mechanisms for the effectiveness of acupuncture. Some animal and clinical studies have provided supporting evidence for the promising effects of acupuncture. Unfortunately, the data do not allow us to make conclusions that acupuncture was an effective treatment for drug addiction. The evidence for its effectiveness has been inconclusive and difficult to interpret [63]. Some of the clinical studies were unable to detect statistically significant differences in treatment efficacy between their acupuncture treatment and control groups [66-68]. In addition, there are few randomized controlled clinical trials of acupuncture treatment for drug addiction, and the methodological methods used in several clinical trials of acupuncture treatment for drug dependence can be criticized for their poor quality. The quality issues include the following: small numbers of patients, no control subjects, lack of randomized assignment, lack of details regarding specific point locations for needle insertion, and no specification regarding the degree of blinding among research subjects.

In fact, there are some variable factors that need to be taken into account when assessing the effects of acupuncture on drug addiction. (1) The study protocol may influence the assessment of effectiveness of acupuncture. Methods and research designs have been issues of debate among acupuncture clinicians and researchers [88]. For a methodological perspective, randomized controlled trials are considered the gold standard in terms of identifying differences in treatment efficacy [89]. However, unlike the evaluation of a new drug, randomized controlled trials of acupuncture are extremely difficult to conduct, particularly if they have to be blind in design and acupuncture has to be compared with a placebo [90]. The efficacy of acupuncture is difficult to study empirically because of the fundamental divergence between the two schools of thought. The gold standard in Western science is randomized, double-blind, and controlled trials, utilizing one specific protocol for each condition. Randomized controlled trials can be used to answer questions about most clinical problems. However, this approach is not always a practical and cost-effective solution. Sometimes randomized controlled trials are open to error; for instance, patient preference may have an effect on the results as may certain cultural environments. In addition, in some Asian countries such as China where acupuncture is widely used, most patients know a great deal about acupuncture, including the special sensation that should be felt after insertion or during manipulation of the needle. Although various "sham" or "placebo" acupuncture procedures have been designed, they are not easy to perform in these countries. Moreover, acupuncturists consider these procedures unethical because they are already convinced that acupuncture is effective. In fact, most of the placebo-controlled clinical trials have been undertaken in countries where there is skepticism about acupuncture, as well as considerable interest. (2) Another difficulty in evaluating acupuncture practice is that the therapeutic effect depends greatly on the proficiency of the acupuncturists. Their ability and skill in selecting and locating the acupuncture points and in manipulating the needles are different. Needling techniques of inserting, retaining, stimulating, and withdrawing are difficult to standardize. This may partly explain the disparities or inconsistencies in the results reported by different authors, even when their studies were

carried out on equally sound methodological bases. (3) In traditional Chinese medical system, such as acupuncture, where each individual is treated according to specific conditions and symptoms, it may be invalid to use the same protocol for every condition. Individualized protocols are critical to the success of the acupuncture treatment. For example, acupuncture stimulation typically elicits a composite of sensations termed *deqi*, manifesting as soreness, numbness, heaviness, and distention [91]. A body of clinical and experimental evidence indicates that the presence of the *deqi* sensation is a prerequisite for, and often an indicator of, a clinical acupuncture effect. Traditionally, patients are asked to remain aware of the sensation during acupuncture treatment. *Deqi* may be an important variable in studies of the efficacy and mechanism of the action of acupuncture treatment. Our previous study showed that the *deqi* sensations of heroin addicts were significantly higher than those of healthy subjects during acupuncture stimulation, indicating that heroin addicts are “good” responders to acupuncture stimulation [92]. (4) Acupuncture was developed as a branch of traditional Chinese medicine on the basis of oriental philosophy, which takes a holistic approach to regulating the balance of the human body. (Several different schools of acupuncture exist, each with its own principles.) These principles may vary with the types of acupuncture being investigated. The inconsistency in treatment protocols between studies, or the use of combined therapies, makes it impossible to draw a strong causal relationship between therapy and its treatment effect, thus making replication of studies difficult. To this end, traditional knowledge and experience of acupuncture should be duly represented by the investigation team when research is proposed, prepared, and conducted. A good clinical study on acupuncture may be conducted with the understanding and integration of both traditional and modern knowledge of medicine; (5) Most of the clinical research on acupuncture in the United States focused on auricular acupuncture, which is simply the insertion of acupuncture needles into prespecified locations in the ear, whereas studies from China used body acupuncture to treat opiate addiction. These findings are intriguing considering that acupuncture on body and auricular points exhibited different efficacies. According to our clinical experience and the theory of traditional Chinese medicine, body acupuncture may need more attention. Some acupuncture points represent discrete locations in the body, where manual or electrical stimulation can exhibit therapeutic effects on cocaine and other drug addiction [26, 28, 60, 61, 93]. Table 1 provides the summary of main acupoints/sites selected in the reviewed studies. In China, body acupuncture, rather than ear acupuncture, was commonly used for the treatment of drug addiction [26, 28, 60]. The acupuncture points most frequently selected are Zusanli (ST.36), Sanyinjiao (SP.6), Neiguan (PC.6), Shenmen (HT.7), Laogong (PC.8), Waiguan (TE.5), and Hegu (LI.15), located on the four limbs. In our recent work, we showed for the first time that acupuncture applied at the BL.23 acupuncture point, located on the back and commonly used for analgesia and sedation in our clinic, could effectively suppress withdrawal syndrome [40, 41]. Clinically, BL.23 could provide us with a new selection of effective acupuncture points for successful treatment of drug addiction. Further studies on the synergistic combination of BL.23 and other effective acupuncture points, such as Zusanli (ST.36) and Sanyinjiao (SP.6), could assist acupuncturists to use a balanced and appropriate choice for combining points in the treatment of addicts.

Acupoints/sites	Frequency of appearance (N)	Percentage (N/26x %)	Acupoints appearing in the literature
Neiguan (PC6)	12	11.11	6,26, 27, 28, 29, 41,44, 62, 63, 64,65and68
Zusanli (ST36)	10	9.26	6,26, 63, 29, 68, 28, 27, 41, 44, and 62
Sanyinjiao (SP6)	8	7.41	6,26, 27,28,44,62,63,and 68
Shenmen (HT7)	7	6.48	26, 28, 41, 62,63,65, and 68
Hegu (LI4)	6	5.56	6, 26, 27,44, 64, and 68
Shenmen (ear)	4	3.70	3,5, 60, and 68
Kidney (ear)	4	3.70	3,5, 60, and 68
Liver (ear)	4	3.70	3,5, 60, and 68
Lung (ear)	4	3.70	3,5, 60, and 68
Sympathetic (ear)	4	3.70	3,5, 60, and 68
Laogong (PC8)	4	3.70	6,44,65, and 68
Sishencong (EX-HN1)	3	2.78	6, 27, and 65
Jiaji (EX-B2)	3	1.85	28, 62, and 63
Shenshu	3	1.85	28, 62, and 63
Taichong	2	1.85	29 and 63
Baihui (GV20/DU20)	2	1.85	41 and 61
Waiguan (SJ5)	2	1.85	26 and 44
Zhiyang (GV9)	2	1.85	29 and 61
Fengchi	1	0.93	29
Anmian	1	0.93	29
Dazhui (GV14/DU14)	1	0.93	61
Mingmen (GV4)	1	1.85	61
Shendao (GV11)	1	0.93	61
Lingtai (GV10)	1	0.93	61
Shenting	1	0.93	65
Naokong	1	0.93	65
Yintang	1	0.93	65
Yangbai	1	0.93	65
Yongquan	1	0.93	65
Quanzhong	1	0.93	65
Naohu	1	0.93	65
Ben Shen	1	0.93	65

Table 1. Summary of main acupoints/sites selected in the reviewed studies

In summary, acupuncture offer some advantages over existing pharmacological interventions: they are safer, have fewer side effects, and are less expensive. Since deteriorating health often accompanies long-term use of addictive drugs, pharmaceutical interventions with harsh side effects can be detrimental to the general health of long-term drug users. In contrast, acupuncture can enhance immune function and increase metabolism in organs necessary to fight infections and various acute and chronic illnesses. Although the definitive role of acupuncture in the treatment of drug addiction has yet to be established, its basic research and clinical data reviewed here justify further clinical trials to systematically examine the efficacy of acupuncture in treating various conditions related to drug addiction such as withdrawal symptoms, drug craving, anxiety, and depression. The next important step in acupuncture research is to get a better understanding of the neurochemical mechanism of acupuncture in order that the therapeutic effects of acupuncture can be further improved. Also scientifically conducted clinical research is needed to examine the effectiveness of acupuncture treatment of drug addicts. As we mentioned in this review, it has proved difficult to apply and integrate the basic principles and methodology of modern science that ensure the reliability of research subjects to clinical studies on acupuncture. However, researchers should be encouraged to ensure the highest possible standards of study design and reporting in future research in order to improve the evidence base in this field.

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