

Acupuncture for Detoxification in Treatment of Opioid Addiction

Sly Wu, AWN Leung, DTW Yew

Abstract

Opioid is a popular drug of abuse and addiction. We evaluated acupuncture as a non-pharmacological treatment with a focus on managing withdrawal symptoms. Electrical stimulation at a low frequency (2 Hz) accelerates endorphin and enkephalin production. High-frequency stimulation (100 Hz) up-regulates the dynorphin level that in turn suppresses withdrawal at the spinal level. The effect of 100-Hz electroacupuncture may be associated with brain-derived neurotrophic factor activation at the ventral tegmental area, down-regulation of cAMP response element-binding protein, and enhanced dynorphin synthesis in the spinal cord, periaqueductal grey, and hypothalamus. Clinical trials of acupuncture for the management of different withdrawal symptoms were reviewed. The potential of acupuncture to allay opioid-associated depression and anxiety, and its possible use as an adjuvant treatment were evident. A lack of effect was indicated for opioid craving. Most studies were hampered by inadequate reporting details and heterogeneity, thus future well-designed studies are needed to confirm the efficacy of acupuncture in opioid addiction treatment.

Key words: Acupuncture; Electroacupuncture; Heroin; Opioid-related disorders; Substance withdrawal syndrome

*Ms Sharon L. Y. Wu, BSc, MCM, School of Chinese Medicine, The Chinese University of Hong Kong, Hong Kong SAR, China.
Prof. Albert Wing-Nang Leung, BSc, PhD, BCM, School of Chinese Medicine, The Chinese University of Hong Kong, Hong Kong SAR, China.
Emeritus Prof. David Tai-Wai Yew, PhD, DSc, MD, Schools of Biomedical Sciences and Chinese Medicine, The Chinese University of Hong Kong, Hong Kong SAR, China.*

Address for correspondence: Ms Sharon L. Y. Wu, Schools of Biomedical Sciences and Chinese Medicine, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong SAR, China.
Tel: (852) 9616 0680; Email: sharonlywu@gmail.com

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Introduction

In the past 4 years (from 2012 to the third quarter of 2015), heroin has remained the most commonly abused drug in Hong Kong. According to the Central Registry of Drug Abuse, heroin use is reported by over 50% of reported abusers.¹ Heroin abuse imposes a high risk of mortality^{2,3} and morbidity.⁴ Its combined use with alcohol or barbiturates may fatally depress respiration.⁵ Injection of the drug is associated with the risk of gangrene, blood clot formation, acquired immunodeficiency syndrome, hepatitis, tuberculosis, and sexually transmitted diseases. The sociological, psychological, and medical costs are high to both the individual and society.

Methadone maintenance therapy (MMT) has been prescribed in Hong Kong since 1972. Its ready availability as well as stable effect with long half-life make it the

dominant treatment of detoxification.⁶ Nevertheless, MMT is a substitution therapy and contributes to a high relapse rate after detoxification.^{7,8} A prolonged reliance on a maintenance dose confers tolerance to its autonomic effects (constipation, urinary hesitancy, reduced libido and potency, perspiration).⁹ Combined use of methadone with other drugs imposes serious risk. As a result, other methods are being sought to improve treatment. The agonist-antagonist mix buprenorphine is thought to be a less addictive and safer substitute with fewer interactions with other euphoriant drugs.^{10,11} Nonetheless, respiratory depression may occur with therapeutic doses so it should be used with caution in patients with compromised respiratory function.¹² Use of a symptomatic medication such as clonidine is hampered by its hypotensive and sedative effects.¹³ Tramadol and estazolam may cause various side-effects, with the latter having the potential to cause changes in behaviour.

Development of Acupuncture as a Treatment for Opioid Addiction

The application of acupuncture in addiction treatment commenced following an incidental discovery by Wen, a neurosurgeon in Hong Kong.¹⁴ In 1972, a 50-year-old male patient was admitted to Kwong Wah Hospital with brain concussion. He was known to have been abusing opium for 5 years and was offered cingulotomy for his drug abuse problem. Acupuncture anaesthesia was used instead of local anaesthesia. Acupuncture points employed were IL-4 and SI-3 (right hand), EH-4 and TB-9 (arm), as well as the auricular brainstem and *Shenmen* (神門).

During electrostimulation of the acupuncture needles, the patient voluntarily reported complete disappearance of his withdrawal symptoms. Wen¹⁵ went on to pursue the plausible link between acupuncture and relief of withdrawal symptoms, and concluded that acupuncture could provide effective relief in heroin withdrawal syndrome.

Another milestone was the codification of the National Acupuncture Detoxification Association (NADA) protocol and establishment of its training procedure. Wen and Cheung's protocol¹⁶ was introduced at the Lincoln Recovery Center in the Bronx, New York in 1974. The Director of the Center, Dr Michael O. Smith, founded the NADA and developed Wen and Cheung's protocol¹⁶ into the well-known 5-point ear acupuncture protocol.¹⁷ Acupuncture points employed in the NADA protocol are bilateral 'sympathetic', 'Shenmen', 'kidney', 'liver', and 'lung'. The protocol has since been introduced into many western clinical settings and approximately 30 countries worldwide. Training in its application has also gained recognition — individuals who complete 70 hours of NADA training are known as "acupuncture detoxification specialists".¹⁸

During the abundant research into acupuncture analgesia since the late 1950s, it has become clear that acupuncture can induce an antinociceptive effect by accelerating the production and release of opioid peptides in the central nervous system (CNS). Han et al^{19,20} from Beijing Medical University, China, concluded that the antinociceptive effect was frequency-dependent, with low-frequency (2 Hz) stimulation accelerating production of endorphin and enkephalin, and high-frequency stimulation (100 Hz) up-regulating the dynorphin level. Their finding that acupuncture precipitated release of endorphins led to the idea of using it to relieve withdrawal syndrome of addicts during abstinence.

Effect of Electroacupuncture on Relief of Withdrawal Syndrome: Animal Studies

Despite the original belief that 2 Hz should be more effective in reducing withdrawal, Han and Zhang²¹ later found that 2 Hz was only marginally effective in suppressing 2 of 5 withdrawal signs in rats, while all 5 signs were significantly reduced with 100-Hz electroacupuncture (EA).^{21,22} Dynorphin was shown to suppress withdrawal syndrome in heroin-dependent humans²³ and morphine-dependent animals through the κ -opioid receptors in the spinal cord.²⁴ Cui et al²⁵ later revealed that spinal intrathecal administration of a κ -opioid receptor agonist trans-3,4-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-benzenacetamide hydrochloride (U-50,488H, 2.5-10 μ g) U-50488 suppressed naloxone-precipitated withdrawal syndrome. On the contrary, the κ -opioid antagonist norbinaltorphimine (1.25-5 μ g) induced naloxone-precipitated withdrawal syndrome in a dose-dependent manner. A single dose of dynorphin was effective in suppressing both withdrawal and tolerance in morphine-dependent

mice.²⁶ The findings of other studies^{22,25,27,28} suggested that an endogenous κ -agonist, probably dynorphin, suppresses morphine withdrawal at the spinal level.

These findings explained the immediate effect of a single EA treatment. Wang et al²⁹ presented work on the cumulative effect. Multiple sessions of 100-Hz EA were more effective and long-lasting than a single session in suppressing morphine-induced withdrawal syndrome in rats. Hooke et al²⁶ provided evidence that the effect of dynorphin on suppressing withdrawal could be enhanced by repeat dosing. A down-regulation of preprodynorphin (PPD) mRNA level in the spinal cord, periaqueductal grey matter and the hypothalamus was observed after injection of morphine, and reversed by multiple sessions of EA. Accompanied by down-regulation of the PPD mRNA level, up-regulation of cAMP response element-binding protein (p-CREB) was observed in 3 CNS regions, and was abolished by 100-Hz EA treatment.²⁹ These findings indicate that acceleration of dynorphin synthesis and down-regulation of p-CREB may be implicated in the cumulative effect of multiple 100-Hz EA treatments for opioid detoxification.

Neurons containing dopamine (DA) in the ventral tegmental area (VTA), in particular the nucleus accumbens (NAc), and their target areas in the limbic forebrain play the most important role in the brain reward circuit. All drugs of abuse increase DA-mediated transmission in the NAc. Chronic morphine causes reduction in size of DA neurons in the VTA³⁰ and reduces the dendritic spine density of medium spiny neurons in the NAc.³¹ Hypofunction of DA neurons in the VTA is thought to contribute to acute and protracted opiate withdrawal.³² In rats with morphine withdrawal for 14 days, the ultrastructure of VTA DA neurons was altered and their size decreased.^{33,34} At the same time, the firing rate and burst firing of the VTA DA neurons were not altered with intravenous injection of morphine.³⁵ Rat experiments showed that 100-Hz EA could suppress morphine withdrawal, facilitate recovery of VTA DA neurons and normalise their reactivity to morphine, and up-regulate brain-derived neurotrophic factor (BDNF) protein level in VTA.^{33,34} This implies that the detoxification effect of 100-Hz EA may be associated with endogenous BDNF activation.

Effect of Acupuncture on Relief of Withdrawal Syndrome: Clinical Studies

Depression and Anxiety

Psychological symptoms are the strongest factor that contributes to relapse from heroin withdrawal.^{36,37} Comorbidity between substance abuse, depression, and anxiety is very common³⁸ and many studies take depression and anxiety as the outcome measures. A meta-analysis of acupuncture for opioid addiction-associated depression by Zhang et al³⁹ included 2 trials that compared the effects of acupuncture with placebo acupuncture and with no treatment. Their results showed a statistically significant benefit of acupuncture in alleviation of depressive

symptoms compared with both placebo acupuncture and no treatment. From the included trials, Hou et al⁴⁰ randomly assigned 60 addicts who fulfilled the ICD-10 criteria to an acupuncture or control group. The acupuncture group received needling on bilateral *Neiguan* (内关; PC-6), *Shenmen* (HT-7), *Zusanli* (足三里; ST-36), *Sanyinjiao* (三阴交; SP-6), *Jiaji* T_{5,7} (夹脊穴; EX-T_{5,7}), and *Shenshu* (肾俞; BL-23), with EA of 3 to 5 Hz, sparse wave applied on *Zusanli*, *Sanyinjiao*, *Jiaji* T₇, and *Shenshu*. The EA was performed daily for 20 minutes, 5 times a week for 3 weeks. The control group received no treatment. The acupuncture group showed significantly lower Hamilton Depression Rating Scale⁴¹ than the control group. In the second trial from the analysis, Mu et al⁴² evaluated the effects on anxiety and depression by randomising 120 heroin addicts who fulfilled the DSM-IV criteria to acupuncture on bilateral *Neiguan*, *Shenmen*, *Zusanli*, *Sanyinjiao* and *Taichong* (太冲; LR-3) [Group 1], bilateral *Jiaji* T_{5,9,11} and *Shenshu* (Group 2), sham electrostimulation group (Group 3), or control group (Group 4). For the first 2 groups, selected acupoints *Neiguan*, *Shenmen*, *Zusanli* and *Sanyinjiao* (Group 1), as well as *Jiaji* T_{5,11} and *Shenshu* (Group 2) received electrostimulation of 5 Hz, 5 mA for 20 minutes, 3 times a week for 10 weeks. The third group received sham stimulation on *Zusanli*, *Sanyinjiao*, and *Jiaji* T_{5,11} for 20 minutes, 3 times a week for 10 weeks. The control group received no treatment. For the 2 experimental EA groups, patient scores in the Zung Self-rating Depression Scale were lower than the sham and control groups ($p < 0.05$). Anxiety scores as indicated by the Zung Self-rating Anxiety Scale in the 2 EA groups were also lower than the sham and control groups ($p < 0.01$ and $p < 0.05$ respectively). The effect of acupuncture on depression did not significantly differ between the 2 EA groups. Nonetheless for anxiety, acupuncture Group 2 (who received regular needling on bilateral *Jiaji* T₉ and EA on *Jiaji* T_{5,11} and *Shenshu*) showed significant improvement compared with their Group 1 counterparts (i.e. regular needling on *Taichong* and EA on *Neiguan*, *Shenmen*, *Zusanli*, and *Sanyinjiao*) after 10 weeks of treatment.

In addition to the above study by Mu et al,⁴² a meta-analysis by Zhang et al⁴³ pooled 7 more trials that examined the effect of acupuncture on opioid-associated anxiety. Acupuncture achieved a greater improvement than placebo acupuncture, drug,^{44,45} or no-treatment therapies,^{42,46} although no statistical difference was found for acupuncture with drug versus drug alone.^{47,48} The study duration ranged from 10 days to 10 weeks. Regardless of the plausible clinical effectiveness, most studies were hampered by their small study population, and lack of reporting of attrition rates and method of allocating patients. The studies also differed in their treatment regimen, type of waveforms if EA was the selected intervention, insertion depth (possibly due to different selected acupoints), and manipulation methods. This heterogeneity rendered it impossible to draw conclusions about the effectiveness of acupuncture as a treatment for psychological symptoms associated with opioid addiction.

Other limitations that hindered the comprehensiveness of most existing studies include insufficient reporting of adverse events, practitioners' background, or response of patients. Commonly reported adverse events associated with acupuncture included needle pain (1-45%), tiredness (2-41%), and bleeding (0.03-38%); fainting and syncope were uncommon (0-0.3%), whereas feelings of relaxation were common (86%).⁴⁹ Practitioners' background is important as it helps to ensure accurate representation of a clinical setting in the studies. Physician experience suggests that better therapeutic acupuncture effects are obtained by doctors with several years, or even decades, of clinical training.⁵⁰ Traditionally, the evocation of *deqi* response (得气疗效) is often sought from patients but is not always reported in the studies. *Deqi*, the sensation of numbness and fullness at the site of stimulation, is believed to be important for acupuncture analgesia.^{51,52} Scientific evidence showed that *deqi* was predictive of a positive outcome in osteoarthritis,⁵³ and significant correlations were found of analgesia with numbness and soreness rating,⁵⁴ suggesting that attributes of *deqi* sensation could be useful indicators of effective treatment.

There is evidence of no significant effect of acupuncture on opioid withdrawal-associated psychological symptoms.⁵⁵⁻⁵⁷ All of these studies used auricular acupuncture instead of conventional body acupuncture. The original protocol of Wen and Cheung¹⁶ employed 4 body acupoints in addition to 2 ear points. It is certainly worth investigating the synergistic effects of a different combination of acupoints. Further studies of the presence and absence of needle manipulation, and type of stimulation would help practitioners to design appropriate and balanced treatment for opioid withdrawal symptoms.

Sleep Disturbance

Another significant symptom in opioid withdrawal is sleep disturbance, positively correlated with relapse to heroin abuse. Clinically, individuals who are more deprived of sleep drop out of treatment earlier.⁵⁸ Transcutaneous electrical acupoint stimulation has been shown to exert an immediate hypnotic effect in a third of heroin addicts.⁵⁹ Animal studies showed that during acute morphine withdrawal, rapid eye movement (REM) sleep, non-rapid eye movement (NREM) sleep, and total sleep time decreased, while sleep latency was prolonged. On the contrary, both 100-Hz EA and 2-Hz EA significantly increased REM sleep, NREM sleep, and total sleep time.⁶⁰ These studies may aid in the design of treatment that improves sleep profile and thus reduces risk of relapse. Chong et al⁶¹ compared opioid-associated sleep-related symptoms in 60 individuals. The experimental group was needled at bilateral *Neiguan*, *Shenmen*, *Zusanli*, *Sanyinjiao*, *Jiaji* T_{5,7} and *Shenshu*, and electrostimulation was applied on *Zusanli*, *Sanyinjiao*, *Jiaji* T₇, and *Shenshu* with continuous wave (3-5 Hz) for 20 minutes, 5 times a week for a total of 15 times. The control group received no treatment. Sleeping difficulties, such as difficulty falling asleep and easy awakening, could be alleviated by

acupuncture with the above protocol ($p < 0.01$). Zhu et al⁶² utilised the same acupuncture points as Chong et al⁶¹ but employed sparse wave EA (10 Hz, 5 mA) for 20 minutes, 3 times a week for 10 weeks. They performed acupuncture at points on the back before moving on to acupoints on the limbs, and observed lowered scores for sleep-related symptoms ($p < 0.001$).

Effect on Acupuncture on Craving

Craving is another important trigger of heroin relapse. Acupuncture was shown to suppress morphine self-administration in animals.⁶³ Lee et al^{64,65} demonstrated that acupuncture at *Yanggu* (阳谷; SI-5) reduced morphine-seeking (craving) behaviour following abstinence after both a fixed ratio (FR) schedule and progressive ratio (PR) schedule, with c-Fos expression in both VTA and NAc suppressed.⁶⁶ *Shenmen* (HT-7) was also tested and showed attenuation of morphine self-administration at both low dose (0.1 mg/kg)⁶⁷ and high dose⁶⁸ on a FR schedule. The active lever press decrease for FR schedule and breakpoint suppression for PR schedule were reversed by pretreatment with the selective GABA_A antagonist bicuculline or the selective GABA_B antagonist SCH50911, suggesting acupuncture on SI-5-mediated morphine craving through the GABAergic pathway.

Researchers also studied EA on other acupoints. *Zusanli* (ST-36) and *Sanyinjiao* (SP-6) were shown to significantly reduce cue-induced reinstatement of heroin seeking in rats, with attenuation of FosB expression in the NAc core,⁶⁹ and other regions including anterior and posterior cingulate cortex, central nucleus of amygdala, NAc shell, VTA, and locus coeruleus.^{70,71}

It is known that environmental cues can activate specific brain regions in heroin addicts, and functional magnetic resonance imaging (fMRI) can reveal these craving-related brain regions.⁷² Cai et al⁷³ examined the influence of acupuncture on cue-elicited brain activation in heroin addicts. Comparisons were made between addicts and controls presented with heroin cue exposure, heroin cue exposure plus acupuncture at *Zusanli*, with or without needle twirling. Heroin cues elicited significant activation of craving-related brain regions, mainly in the frontal lobes and callosal gyri. In the heroin addict group, acupuncture without needle twirling did not significantly affect the range of cue-induced brain activation, but it significantly changed the extent of activation. Acupuncture with needle twirling, on the contrary, significantly decreased both the range and extent of activation during heroin cue exposure, when compared with the group without needle twirling. Unfortunately, the experiment was limited by small sample size, lack of non-addict control subjects, and the 2-dimensional images often provided by brain fMRI. Nonetheless, since *Zusanli* can rapidly suppress activation of craving-related brain regions, more studies should investigate its potential as an intervention for opioid craving.

Mu et al⁷⁴ evaluated craving clinically and performed a follow-up study to examine relapse rate. They compared the effects of acupuncture on bilateral *Neiguan*, *Shenmen*, *Zusanli*, *Sanyinjiao* (Group 1) and that on bilateral *Jiaji* T₅₋₇ and *Shenshu* (Group 2). Needles were applied on these acupoints, whereas electrostimulation was done in the selected acupoints: *Zusanli* and *Sanyinjiao* (Group 1), *Jiaji* T₇ and *Shenshu* (Group 2) with sparse wave on 5 Hz, 5 mA for 20 minutes, 3 times a week for 10 weeks; a sham group had electrodes fixed on *Zusanli* and *Sanyinjiao* without actual stimulation, and a control group received no treatment. Craving recall (as measured by visual analogue scale) was lower in both acupuncture groups compared with the sham and control groups ($p < 0.01$). Serum β -endorphin and dynorphin-A levels were also higher in the 2 acupuncture groups ($p < 0.01$). Comparison of the 2 experimental groups revealed that EA on bilateral *Jiaji* T₅₋₇ and *Shenshu* seemed to alleviate heroin protracted withdrawal to a greater extent than bilateral *Neiguan*, *Shenmen*, *Zusanli*, and *Sanyinjiao* ($p < 0.01$). All groups were followed up 6 months after discharge. Of 120 cases, 98 were successfully contacted. The relapse rate in the *Jiaji* T₅₋₇ and *Shenshu* group was 77.3%; that of *Neiguan*, *Shenmen*, *Zusanli*, *Sanyinjiao* group was 88.5%, whereas that of sham group was 90.5% and controls being 95.7%. The relapse rate of the *Jiaji* T₅₋₇ and *Shenshu* group was significantly lower than the *Neiguan*, *Shenmen*, *Zusanli*, *Sanyinjiao* group, as well as the sham and control groups ($p < 0.05$). It is known that the usual relapse rate within 6 months of detoxification is $> 95\%$,⁷⁵ with protracted withdrawal symptoms a prominent factor in relapse.⁷⁶

Regardless of the supporting evidence for the potential of acupuncture as an intervention for craving, existing meta-analysis showed no significant benefit of acupuncture.³⁹ More high-quality clinical trials are needed to determine whether and how acupuncture influences craving and relapse in human addicts.

Properties of Acupoints

As shown in the systematic review by Zhang et al³⁹ the acupoint *Neiguan* (PC-6) is the most frequently used point for management of psychological symptoms in heroin addiction treatment, followed by *Zusanli*, *Sanyinjiao*, *Shenmen*, and *Hegu* (合谷; LI-4).³⁹ These acupoints were also the most commonly used points in a systematic review by Lin et al.⁵⁰ *Neiguan* is located 3 finger breadths below the wrist on the inner forearm in between the 2 tendons. It is the Luo-connecting point of the Pericardium channel that links to its exterior-interior Heart channel. From the Chinese medicine perspective, the pericardium is an organ system known to help defend the heart against pathogens and illnesses. The heart system is related to not only cardiovascular illnesses but also psychological problems. Thus, acupuncture on *Neiguan* can theoretically help alleviate the psychological attributes of protracted withdrawal such as anxiety and depression. Studies have shown that involvement of

Neiguan helped augmented treatment of depression and anxiety.^{77,78} Furthermore, *Neiguan* has branches that reach the Triple energiser meridian. It targets Qi depression (气机壅滞) or sputum accumulation and thus can also treat other protracted withdrawal symptoms such as abdominal distension, anorexia, belching, vomiting, and tightness of the chest. *Neiguan* is best known in the West for treating nausea and vomiting. Acupressure on *Neiguan* has been shown to improve gastro-intestinal motility in women following transabdominal hysterectomy.⁷⁹

Zusanli is the He-sea point (合穴) of the Stomach channel in the Five-shu points (五输穴). It is known for treating symptoms of the digestive system and for its pain-relieving effect.⁸⁰ *Sanyinjiao* is the Yuan-primary point (原穴) of the Spleen channel, as well as the crossing point of the 3 channels namely Liver, Spleen, and Kidney; it serves the body by nourishing Liver-yin (肝阴), Spleen-yin (脾阴) and Kidney-yin (肾阴), respectively. *Shenmen* is the Yuan-primary point of the Heart channel, and is reported to treat insomnia⁸¹ and anxiety.⁸² *Hegu* is the Yuan-primary point of the Large Intestine channel. It is an important acupoint in acupuncture anaesthesia.

Acupuncture as Adjuvant Treatment

In addition to the promising yet inconclusive findings about the efficacy of acupuncture in the treatment of opioid addiction, researchers have also studied acupuncture as an adjuvant treatment. Instead of replacing allopathic medications during opioid detoxification, studies examined whether acupuncture could augment treatment efficacy in its ancillary role. Some studies reported significant decrease in the dose requirement of buprenorphine or methadone to alleviate opioid withdrawal symptoms,^{83,84} others suggested that combined treatment may result in a lower relapse rate.⁸⁵⁻⁸⁷ A meta-analysis by Liu et al⁸⁸ revealed that patients who received acupuncture combined with opioid agonist treatment scored lower for opioid withdrawal symptoms than individuals who received opioid agonist treatment only, on the first day and last 3 days of a 10-day tapered dose. There was no significant difference between the 2 groups in relapse rate at 6 months. The existing evidence suggests that acupuncture as an adjuvant treatment may have the potential to decrease dosage of agonist needed and alleviate the agonist's side-effect. Nonetheless, stronger evidence and more high-quality research are needed to allow firm conclusions to be drawn.

Conclusion

Early studies concluded that electrical stimulation at a low frequency (2 Hz) accelerates endorphin and enkephalin production, whereas high-frequency stimulation (100 Hz) up-regulates dynorphin level. Later evidence suggested that 100-Hz EA is effective in reducing withdrawal symptoms, with a suggestion that dynorphin suppresses withdrawal at the spinal level. The effect of 100-Hz EA may be associated

with BDNF activation at the VTA, while a cumulative effect of multiple 100-Hz stimulation may be related to acceleration of dynorphin synthesis and down-regulation of p-CREB.

Meta-analysis of clinical trials indicated the potential of acupuncture as a treatment for opioid-associated depression and anxiety, but no statistically significant beneficial effect was reported for opioid craving. Most studies are limited by small sample size, insufficient reporting of methodology, and variations in treatment regimens. Analysis is thus inconclusive. Despite this, animal studies demonstrated an influence of acupuncture on withdrawal symptoms. In the treatment of sleep disturbance, EA at both 100 Hz and 2 Hz significantly increased REM sleep, NREM sleep, and total sleep time. For craving, drug-seeking behaviour was suppressed by acupuncture and was reversed by pretreatment with selective GABA antagonists, suggesting mediation of morphine craving through the GABAergic pathway. Acupuncture demonstrated considerable potential as an adjuvant treatment, but analysis provided no evidence of it being otherwise superior to pharmacological treatment alone. Regardless of the inconsistencies in therapeutic effect, key acupoints for opioid addiction have been identified. Considering the potential demonstrated by animal studies, further high-quality studies that investigate the synergistic effects of a combination of acupoints may enable treatment to be refined.

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