

Invited review

Traditional Chinese medicine in treatment of opiate addiction¹Jie SHI², Yan-li LIU³, Yu-xia FANG⁴, Guo-zhu XU², Hai-fen ZHAI², Lin LU^{2,5,6}

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Key words

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Abstract

Traditional Chinese medicine (TCM) includes Chinese medicine and acupuncture. Chinese medicine consists of natural products including plants, animals and minerals. TCM has been practiced in China for more than 2000 years, and for the past 200 years has been used in treatment of drug addiction. Ten Chinese medicines for the treatment of opiate addiction have been approved by the Chinese State Food and Drug Administration (SFDA), and at least 6 are in clinical trials. The general therapeutic principle of Chinese medicine developed was based on its unique theory of “reinforcing healthy Qi and resolving and removing effects of toxicity”. Acupuncture, another essential part of TCM, which was developed based on the principle that “functions of the human body are controlled by the ‘Jing-Luo’ and ‘Qi-Xue’ system”, has been used not only in China, but also in Europe, the USA and other countries, for controlling opiate addiction. There are some advantages in using TCM for opiate detoxification, including less harmful side effects, high safety and ideal effects in the inhibition of protracted withdrawal symptoms and relapse. Co-administration of TCM with modern medicine shows some synergistic effects in detoxification. Many TCM for detoxification also have efficacy in the rehabilitation of abnormal body functions induced by chronic drug use, including improving immune function, increasing working memory and preventing neurological disorder. Given that TCM is effective in the prevention of relapse and causes fewer side effects, it may be used widely in the treatment of opiate addiction.

Introduction

Drug addiction causes a significant burden to individuals and societies throughout the world. In China, it re-emerged as a national problem in the late 1980s^[1,2]. The number of registered drug users increased from 70 000 in 1990 to more than 1 million by the end of 2005^[1], among which 85% were heroin users. There is no effective treatment for heroin addiction although the methadone maintenance treatment (MMT) is thought to be promising in the harm reduction of heroin abuse^[3,4]. However, traditional medicine has recently received wide attention in the treatment of drug addiction. The first international conference for “Herbal Medicine in

the Treatment of Addictions” was held in London on 12–16 February 2006, where traditional medicine was suggested to be potential choice for treating opiate addiction^[5].

Traditional Chinese Medicine (TCM) includes both Chinese medicine and acupuncture and consists of natural products including plants, animals and minerals. The general therapeutic principle of Chinese medicine developed based on its unique theory of “reinforcing healthy Qi and resolving and removing effects of toxicity and focusing on symptom-oriented intervention”. Acupuncture, which was developed based on the principle that “functions of human body are controlled by the ‘Jing-Luo’ and ‘Qi-Xue’ system”, has been used to balance and improve the functions of the different

organs. TCM has been used for more than 200 years in the treatment of opiate addiction in China. Moreover, acupuncture has been used not only in China, but also in Europe, the USA and other countries for controlling opiate and other drug addictions.

Ten Chinese medicines have been already approved for the treatment of opiate addiction by the Chinese State Food and Drug Administration (SFDA), and 6 are undergoing clinical trials. Furthermore, the development, manufacture and distribution of all new developing detoxification Chinese medications must be approved by the SFDA. Chinese medicine is prepared in different ways for clinical practice. In addition to decoction, the traditional preparative method, Chinese medicine is also prepared as liquids, granules, tablets, pills, capsules and suppositories.

In comparison with modern medicine, TCM has less adverse effects, is safe and has ideal effects in treating refractory chronic diseases. TCM can be co-administered with modern medicine or other traditional medicine and thereby reduce toxicity. The advantages of TCM have encouraged its widespread use in acute opiate detoxification during the last decade in China. In addition, many TCM have efficacy in the rehabilitation of abnormal body functions induced by chronic drug use, including improving immune function, increasing working memory, and protecting against neurological disorders. Given that TCM is potentially effective in the prevention of relapse, the core characteristic of addiction^[6-8], it has been suggested that TCM may be the ideal choice in the future for the treatment of opiate addiction.

Chinese medicine in the treatment of opiate addiction

Currently, the SFDA has issued approval of 10 Chinese medicines for use in clinical practice for the treatment of addiction, including the *Fukang* tablet, *Lingyi* capsule, *Yan* Liquid, *Jitai* tablet, *Fuzhengkang* granule, *Anjunning* mini pill, *Kangfuxin*, *Xuanxia* detoxification capsule, *Shifusheng* capsule and *Zhengtongning* granule for opiate acute detoxification^[9-11]. Clinical trials of 6 Chinese medicines are currently underway and pending approval by the SFDA. These include the *Taikangning* capsule, *Jiedukang* capsule, *Yanshen* liquid, *Fuyuan* granule, *Jingan Jiedu* pill, *Jinjiawang* granule and *Junfukang* capsule. Several additional Chinese medicines are undergoing preclinical trials.

Chinese medicines act by targeting multiple processes in the human body. Some *papaveraceae* herbs have been used in traditional prescriptions, such as *Rhizoma corydalis* (*yanhusuo*), *Flos daturae*, *Semen hyoscyami*, *Herba*

chelidonii, and snake venom for pain relief^[12], *Radix ginseng*, *Radix astragali*, *Radix panacis quinquefolii*, *Radix aconite lateralis praeparata*, *Radix angelicae sinensis* and *Cordyceps* for healthy Qi reinforcement, *Rhizoma pinelliae*, *Semen ziziphi spinosae*, *Radix polygalae* for sedation and tranquilization, *Flos lonicerae japonicae*, *Herba taraxaci*, *Gossampinus malabarica* (mumian), pumpkin, *Radix glycyrrhizae*, pine leaves, small flower milkwort herbs with roots (*Jinniucao*), and *Hedyotis diffusa* (*baihua sheshecao*) for body toxin-removing^[13-15]. The treatment effects of these herbs show synergy when used in combination.

The efficacy of Chinese medicine in controlling opiate withdrawal symptoms can be summarized as follows: (1) less than narcotic detoxification agents; (2) similar or even better than non-narcotic detoxification agents (eg clonidine, lofexidine hydrochloride); and (3) moderately effective with limitations in treating patients with severe drug addiction. The therapeutic effects could be subtly different because of their different composition and formulas. For instance, some may be more effective in controlling rhinorrhea, lacrymation and sweating; some for relieving pain, whereas others could be more effective in controlling gastrointestinal (GI) symptoms including nausea and vomiting or suitable for treating insomnia.

Patients with opiate dependence usually experience withdrawal symptoms from d 1 to d 4 following Chinese medicine administration. Chinese medicine is not as effective as methadone, but most residual symptoms are tolerable. Sometimes tranquilizers are required as a supplement. Therefore, TCM treatment should start in advance or as early as possible to control withdrawal symptoms if it is used without other medicines. For drug users with severe opiate dependence and symptoms (eg those with a long history, high dose and long term IV drug users), treatment with only Chinese medicine is inadequate. It is recommended that low-dose, narcotic detoxification drugs, such as methadone or buprenorphine be co-administered together with Chinese medicine. Usually, low-dose, narcotic detoxification drugs are administered from d 1 through to d 5 so that the fast action of the narcotics and the non-dependent long-lasting effects of the Chinese medicine can complement each other. Most Chinese medicines could be used at a low dosage for long-term treatment with the aim of controlling protracted withdrawal symptoms for rehabilitation and for preventing relapse. Generally, Chinese medicines are safe; most have no obvious side effects on respiration, blood pressure, heart rate and liver and kidney functions. Some patients may suffer from a stomach upset, nausea, vomiting and diarrhea, dry mouth, blurred vision, loss of balance, somnolence and

dizziness, but most do not require treatment. Usually, symptoms disappear after dose decrement or after subsequent treatment.

Previously published studies indicate that most Chinese medicines have the following characteristics: (1) sedation, pain relief, local anaesthesia, hypnosis and anti-convulsion; (2) stabilization of blood sugar, improvement of protein metabolism, protection of liver, blood pressure control and anti-hypoxemia; (3) anti-fatigue, anti-stress and anti-shock; and (4) cardiovascular system protection and modulation of immune function. For example, *Radix aconite* (fuzi) is effective in relieving body reeling and head and extremities tremble in opiate withdrawal of rats. *Radix ginseng* is effective in preventing morphine tolerance, addiction and adaptation in the regulation of body functions and in relieving withdrawal symptoms^[16]. *Rhizoma* (yanhusuo) can control nervous vomiting, dilate the coronary artery, antagonize arrhythmia and regulate the function of the GI tract^[17]. Scopolamine, the major chemical component of *Daturae albae, flos* (yang jinhua), is effective in restraining the cerebral cortex, generating anesthetic action, activating the respiration center and improving the metabolism of morphine. It also has benefits in controlling the withdrawal symptoms of morphine and other opiate drugs, preventing the establishment of morphine tolerance and restoring the pain relief effect of morphine in mouse models^[18].

Acupuncture in the treatment of opiate addiction

Acupuncture is an essential part of TCM, performed by inserting thin needles to specific documented points which are believed to represent points of concentration of body energies. In some cases, a small electrical impulse is added to the needles. According to the theory of acupuncture, functions of the human body are controlled by systems of 'Jing-Luo' and 'Qi-Xue'; acupuncture improves the functions of the human body through the control of 'Jing-Luo' and 'Qi-Xue'. The practice of acupuncture has accumulated affluent clinical experience for thousands of years. It spread to Japan in the 6th century, then to Europe in the 17th century. It is now practiced in 120 countries and regions and has become an important modality for treatment throughout the world.

Acupuncture treatment of opiate withdrawal symptoms began in 1972 in Hong Kong, and the use of auricular acupuncture for substance abuse began in Lincoln Hospital, New York in 1983. There are currently over 250 hospitals practicing acupuncture based on the model of Lincoln Hospital^[19]. Acupuncture or electroacupuncture (EA) have been applied with great success to attenuate behavioral signs of

opiate withdrawal in addicts^[20-22]. Acupuncture could improve the curative effects of pharmacotherapy and increase the successful abstinence rate^[23-27], while displaying little or no side effects in comparison with methadone or benzodiazepine and phenoiazine treatment^[28,29].

There are 3 major advantages of employing acupuncture for the treatment of drug addiction. First, acupuncture therapy for addicts is inexpensive, simple and has no side effects^[19]. Second, acupuncture can be used for the prevention of opiate relapse^[30]. Third, acupuncture therapy is safe for pregnant women and parturients^[20].

Although acupuncture as a therapeutic intervention has been widely practiced for the treatment of many functional disorders including substance abuse, little is known about its basic mechanisms of action, particularly with regard to opiate abuse. Recent studies using animal models showed that acupuncture attenuated expression of c-fos, a marker of neuronal activation, in the nucleus accumbens following a nicotine challenge in rats sensitized to nicotine^[31]. Acupuncture at a specific acupoint [Shenmen (HT7)], but not at other acupoints or at control sites, attenuated the GABA_B receptor-mediated increase in ethanol-induced dopamine release in the nucleus accumbens^[32]. Morphine-induced conditioned place preference can be successfully suppressed by 2- or 100-Hz electroacupuncture, presumably via activation of opioid receptors^[33,34]. There is evidence that morphine-induced enhancement of dopamine transmission in the nucleus accumbens is linked to the reinforcing properties of morphine and may be implicated in the development of behavioral sensitization^[35,36]. Thus, morphine-induced elevation of dopamine in the nucleus accumbens may play a major role in the development and maintenance of morphine-seeking behavior. Kim *et al*^[37] reported that acupuncture at the specific acupoint HT7, but not at the control points (TE8 and tail), significantly decreased both dopamine release in the nucleus accumbens and behavioral hyperactivity induced by a systemic morphine challenge. These results suggest that the therapeutic effect of acupuncture on opiate addiction occurs through the inhibition of neurochemical and behavioral sensitization to opiate^[37]. These animal studies have provided important information for understanding the underlying neurobiological mechanisms of acupuncture and electroacupuncture in the treatment of opiate addiction.

It has also been reported that electroacupuncture at the acupuncture point Shen-Shu (BL23) inhibits naloxone-precipitated withdrawal signs in morphine-dependent rats. EA stimulation in freely moving rats attenuated c-fos expression in the central nucleus of the amygdale^[38]. On the other hand, mechanisms of EA may involve enhancement of im-

mune function. Electroacupuncture of the Zusanli (ST 36), Sanyinjiao (Sp 6), Hegu (LI 4) and Neiguan (P 6) points enhanced Natural killer (NK) cell activation following epidural injection of morphine on postoperative patients. These results indicate that mechanisms of acupuncture or electroacupuncture for drug abuse may involve increasing immune function that is dysregulated by opiates^[39]; however, this requires further study.

In both theoretical and practical aspects, many questions regarding acupuncture still remain unclear. Acupuncture practice is based on the therapeutic guidance principle of TCM which involves “reinforcement of healthy Qi and elimination of the effects of toxicity”. However, modern medicine is unable to explain the mechanistic basis of acupuncture. Second, there are many acupoints in human body, and these acupoints have different function according to the theory of TCM. Chronic opiate use produces abnormal functions in different organs or systems of the human body, so it is important to choose effective acupoints for treatment in different phases of opiate abuse. Third, many factors can influence the therapeutic effects, including treatment schedule, motivation to seek acupuncture treatment and psychological state. Margolin *et al*^[40] reported that therapeutic effects were similar when 48 cocaine-dependence addicts were treated with Shanl and real auricular needling^[40]. However, Ma *et al*^[41] found that intensity and frequency of acupuncture may affect efficacy of treatment^[41,42]. Thus, a uniform standard in treatment of opiate addiction using acupuncture should be developed in the future.

Advantages of TCM and their prospects in the treatment of opiate addiction

It is a difficult to find more effective TCM for the treatment of opiate addiction. Numerous reports have been documented highlighting the effective use of TCM for the treatment of drug addiction and other refractory diseases. Drug addiction has been thought to be a brain disease with chronic and relapsed characters; Chinese medicine has shown some advantage in controlling these complex disorders.

An additional advantage of Chinese medicines is their multi-system and multi-target mechanisms of actions. There are many prescriptions used for detoxification, including licorice root and *Rhizoma gastrodiae* for eliminating the effects of toxicity, *ginseng* and *Radix astragali* for reinforcing healthy Qi, *Rhizoma pinelliae* and *Semen Ziziphi spinosae* for relieving withdrawal symptoms^[42]. In addition, *ginseng total saponin* inhibits the development of reverse tolerance to the ambulatory accelerating effects of morphine and pre-

vents the development of dopamine receptor supersensitivity induced by the chronic administration of morphine^[43]. Pseudoginsenoside-F₁₁ inhibits the conditioned place preference induced by morphine in mice^[44]. *L*-tetrahydropalmatine, an active component of *Corydalis yanhusuo*, can attenuate the locomotor-stimulating effects of oxycodone (an opiate receptor agonist) and inhibit the development and expression of oxycodone behavioral sensitization^[38]. In recent studies, *L*-tetrahydropalmatine was found to inhibit physical dependence in morphine-dependent mice and significantly reduce the development of the conditional place preference induced by morphine in mice^[45,46].

Chinese medicine has significant effects on residual withdrawal symptoms. Modern medicine has not developed an ideal therapeutic efficacy for opiate residual withdrawal symptoms which include insomnia, anxiety, pain and complaint. Xu and He reported that a *Shen Fu* detoxification capsule inhibited residual withdrawal symptoms in opiate addicts^[47]. Lu *et al* found that the *Buzheng* pill reduced withdrawal symptoms and heroin cravings in heroin addicts and was more effective than buprenorphine^[48]. It has been shown that *Shen Fu* decoctions inhibit the occurrence of withdrawal symptoms in morphine-dependent mice and rats on d 2 and d 5 after withdrawal, which is consistent with our earlier findings in humans^[49]. In addition, a *Shen Fu* decoction combined with buprenorphine displayed a synergistic inhibitory effect. Thus, Chinese medicines may be the new drugs for residual withdrawal symptoms and cravings.

Due to fewer side effects, Chinese medicines can also be used in combination with other medications. Generally, Chinese medicines can be co-administered with modern medicines or acupuncture. It has recently been reported that 20 out of 26 heroin addicts had no resident withdrawal symptoms and stayed drug free for 1–1.5 years after co-administration of the *Buzheng* pill and acupuncture^[48]. Yang *et al* (1986) found that Chinese medicine, when combined with acupuncture, suppressed the withdrawal scores to –85%^[50]. Zhuang *et al* also reported an effective rate of 98% in heroin addicts when treated with the combination of Chinese medicines and acupuncture^[51].

Finally, TCM may have an advantage in the rehabilitation and prevention of a relapse of opiate addiction. Prevention of drug relapse and completion of rehabilitation is a critical aspect in the treatment for addiction. There are many TCM which may aid in rehabilitation. For example, *ginseng* enhances immune function and metabolism and possesses anti-stress and anti-aging activities. Several *ginsenosides* were proven to be non-organ-specific tumor suppressors and improved learning and memory in patients with

Alzheimer's disease^[52]. More than 28 *ginsenosides* have been extracted from *ginseng*, and might be associated with a wide range of therapeutic actions in the central nervous system and cardiovascular and endocrine systems^[53]. For example, *Shimotsuto*, a basic prescription consisting of Japanese herbs *angelica root*, *cnidium rhizome*, *peony root* and *rehmannia root*, improves working memory impaired by scopolamine in the 8-arm radial task and in the T-maze delayed alternation task in rats^[54]. *Shen Fu* decoction has been found to inhibit the withdrawal symptoms of morphine-dependent mice and rats after precipitated by naloxone both on d 2 and d 6^[55]. After combined treatment with *Shen Fu* decoction and buprenorphine, the withdrawal symptoms of morphine-dependent rats were synergistically inhibited. On the sixth d after withdrawal, spleen and thymus atrophied and phagocytosis, the positive rate of the Fc receptor of macrophage, number of T-lymphocyte in peripheral blood and phytohemagglutinin (PHA)-induced lymphocyte proliferation, percentage of CD⁴⁺ and the ratio of CD⁴⁺/CD⁸⁺ in splenocyte, all markedly decreased^[56]. These findings which show improvement of the immune functions after opiate withdrawal by Chinese medicines, suggest that Chinese medicines not only decreases opiate withdrawal symptoms, but also enhance recovery of normal immune functions depleted by chronic opiate use.

In summary, the fact that TCM are effective in controlling opiate withdrawal symptoms and preventing opiate relapse with fewer side effects suggests a greater use of TCM in the future. It has been anticipated that TCM will foster a \$400 billion market by 2010. The Chinese market will facilitate new TCM product development, and it is believed that TCM may become widely used for detoxification and the prevention of opiate relapse.

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