

REVIEW ARTICLE

Traditional Medicine in the Treatment of Drug Addiction

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Aims: To evaluate clinical trials and neurochemical mechanisms of the action of traditional herbal remedies and acupuncture for treating drug addiction. **Methods:** We used computerized literature searches in English and Chinese and examined texts written before these computerized databases existed. We used search terms of treatment and neurobiology of herbal medicines, and acupuncture for drug abuse and dependence. **Results:** Acupuncture showed evidence for clinical efficacy and relevant neurobiological mechanisms in opiate withdrawal, but it showed poor efficacy for alcohol and nicotine withdrawal or relapse prevention, and no large studies supported its efficacy for cocaine in well-designed clinical trials. Clinical trials were rare for herbal remedies. Radix Puerariae showed the most promising efficacy for alcoholism by acting through daidzin, which inhibits mitochondrial aldehyde dehydrogenase 2 and leads to disulfiram-like alcohol reactions. Peyote also has some evidence for alcoholism treatment among Native Americans. Ginseng and Kava lack efficacy data in addictions, and Kava can be hepatotoxic. Thunbergia laurifolia can protect against alcoholic liver toxicity. Withania somnifera and Salvia miltiorrhiza have no efficacy data, but can reduce morphine tolerance and alcohol intake, respectively, in animal models. **Conclusions:** Traditional herbal treatments can compliment pharmacotherapies for drug withdrawal and possibly relapse prevention with less expense and perhaps fewer side effects with notable exceptions. Both acupuncture and herbal treatments need testing as adjuncts to reduce doses and durations of standard pharmacotherapies.

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INTRODUCTION

Drug abuse and dependence have profound social and economical costs worldwide, and pharmacotherapies for many drugs have had limited efficacy. This limited efficacy has led to exploring complementary approaches to treatment such as traditional herbal medicine and acupuncture, which reach beyond other existing conventional interventions such as therapeutic community treatment (1–3), Alcoholics Anonymous (4, 5), and behavioral therapies such as cognitive behavioral therapy (6, 7). While these nonpharmacological therapies account for up to 45% of the treatment for substance users, herbal medicine and acupuncture to treat drug abuse are relatively new to western medicine (8).

Although the use of herbal medicine can be traced back two thousand years in China, it was applied to treating drug abuse and dependence only about 200 years ago and only in the last 20 years have several well-designed clinical trials improved its acceptance. The results of these clinical trials are inconsistent, however, in part due to the mixtures of herbs, including radix Aconiti Lateralis Preparata, radix Astragali, and Rhizoma Cimicifugae, which were initially prescribed to treat opioid dependent patients (9). Recent neurobiological discoveries, which help provide mechanisms of these herbal medicines and acupuncture, can improve the design and evaluation of clinical trials for these interventions.

HERBAL MEDICINE IN THE TREATMENT OF DRUG ADDICTION

Ginseng

There are two major types of ginseng, *Panax ginseng* (Asian ginseng) and *Panax quinquefolium* (American ginseng). *Panax ginseng* is a well-known Chinese traditional herbal medicine. It has been used for hundreds of years in China and later gained popularity in the West. *Panax ginseng* has been demonstrated to have a profound impact on the central nervous and cardiovascular systems, and it promotes endocrine secretions affecting immune function and metabolism (10). The main active compounds in *Panax ginseng* are called ginsenosides; more than twenty ginsenosides have been isolated, including Rb, Rc, Re, and Rg (11). The active chemical in *Panax quinquefolium* is Pseudoginsenoside-F₁₁ (PF₁₁), an ocotillol-type saponin; this does not exist in *Panax ginseng* (12).

Panax ginseng has been demonstrated to attenuate the behavioral effects of drugs of abuse including morphine, methamphetamine, cocaine, and alcohol in both pre-clinical and clinical studies (13). For example, ginsenosides substantially inhibited conditioned place preference induced by methamphetamine (14) or cocaine (15). Further, ginsenosides significantly attenuated the withdrawal syndromes precipitated by naloxone in morphine-dependent mice (16), and inhibited the conditioned place preference and hyperactivity induced by morphine (17). Unfortunately, *Panax ginseng*'s effects have not been examined in the animal model of drug self-administration, which makes it impossible to draw a definitive conclusion on *Panax ginseng*'s ability to inhibit voluntary drug intake.

Ginseng's inhibitory effect on various drugs of abuse appears to be associated with modulation of dopaminergic transmission. Administration of the *Panax ginseng* extract, ginseng total saponin, can substantially attenuate ambulatory hyperactivity to apomorphine in mice that had repeated exposure to nicotine (18). This finding suggests that ginseng total saponin effectively inhibits post-synaptic dopamine receptor super-sensitivity in nicotine-treated mice (18). A recent study has also reported that ginseng total saponin profoundly inhibited nicotine-stimulated dopamine release in the striatum and Fos protein expression in the nucleus accumbens of mice (19). Taken together, these studies shed new light on *Panax ginseng* as a potentially useful therapeutic agent for the treatment of drug addiction.

Panax quinquefolium, especially PF11, has a different range of effects on drugs of abuse, particularly methamphetamine and morphine. Wu et al. (20) reported that PF11 significantly attenuated the behavioral effects of methamphetamine including anxiety-like behavior in the light-dark box task, increased latency and error counts in the forced swimming task, and prolonged escape latency in the Morris water maze task. Li et al. (21) reported that PF11 significantly inhibited four major effects of morphine: 1) memory impairment in the Morris water maze test, 2) expression of conditioned place preference (at a higher PF11 dose), 3) analgesia tested by tail pinch, and 4) the

development of locomotor sensitization. Neurochemical studies have demonstrated that PF11 antagonizes morphine-stimulated opioid receptor signaling (22) and decreases the concentrations of dopamine and its metabolites in the brain of morphine-treated animals (20). These results suggest that PF11 could reduce relapse in methamphetamine and opiate dependence and protect against methamphetamine-induced neurotoxicity from excessive brain dopamine levels.

Kava

Kava, an extract of the *Piper methysticum* Forst plant, is commonly used by Pacific Islanders and Indigenous Australians. Herbal remedies that contain *kava* have been used for the psychiatric treatment of anxiety and insomnia (23). *Kava* has also been used as a folk medical aid for smoking and alcohol cessation. A village in Fiji developed and implemented an effective community-based smoking cessation program that included the use of *kava* (24). Clinical research has also provided supporting evidence that the administration of *kava* reduces patients' desire for their drug of choice and substantially promotes abstinence in drug-dependent patients (25).

The pharmacological effects of *kava* occur primarily through activation of a lipid soluble group of compounds, called *kava* lactones (23, 26). *Kava* lactones have been found to bind to many sites in the brain and interact with multiple neurotransmitters. They substantially inhibit the uptake of noradrenaline, but not serotonin (27). Glutamate release may also be antagonized by *kava* in an ion-channel dependent fashion (28). *Kava* extract has also been demonstrated to affect the concentration of dopamine and its metabolites associated with altered behaviors in rats (29). These studies highlight *kava* lactones' ability to alter neuronal excitation through direct modulation of voltage-dependent ion channels, resulting in muscle relaxant, anesthetic, anxiolytic, and anticonvulsive properties (23). However, the exact nature of the interaction between *Kava* and drugs of abuse still remains largely unknown.

Because widely used for a long time, *Kava* was thought to be safe. However, hepatotoxicity has been associated with *kava* use perhaps due to mitochondrial toxicity in the liver (30).

Tabernanthe Iboga and Voacanga Africana

Tabernanthe iboga and *Voacanga Africana* are shrubs used widely in traditional African medicine. The root bark of *Tabernanthe iboga* contains ibogaine as its predominant alkaloid, although Ibogaine is one of several naturally occurring alkaloids found in *Voacanga Africana*. Ibogaine is used by indigenous peoples in low doses to combat fatigue, hunger, and in higher doses as a sacrament in religious rituals. In Gabian initiation ceremonies it is used to cause a near-death experience. This chemical's potential "anti-addictive" effect has generated a great deal of interest in recent years (31). American and European addict self-help groups have claimed that ibogaine promotes long-term drug abstinence from heroin, psychostimulants and

cocaine. Anecdotal reports attest that a single dose of ibogaine eliminates withdrawal symptoms and reduces drug cravings for extended periods of time. In a preliminary investigation of this effect, none of the seven opiate-dependent participants receiving *ibogaine* reported significant withdrawal symptoms, and three of the patients remained abstinent for up to 14 weeks following *ibogaine* administration (32). Unfortunately, a clinical trial that specifically examines *ibogaine's* therapeutic benefits in drug-dependent patients has yet to be conducted.

However, accumulating evidence from animal research has provided some insight into the potential use of *ibogaine* in treating substance abuse and dependence (33). *Ibogaine* has been demonstrated to significantly reduce self-administration of morphine (34) and cocaine (35, 36) in animals. *Ibogaine* also reduces mice's preference for cocaine when they are given a choice between either water or a solution containing the drug (37). *Ibogaine* has been reported to antagonize the locomotor effects induced by cocaine (38), nicotine (39), and amphetamine in mice (40). Furthermore, *ibogaine* effectively blocks methamphetamine-induced hyperthermia in mice (41).

While the neurochemical basis for *ibogaine's* putative anti-addictive effects remains largely undetermined, a growing body of literature has suggested that *ibogaine* can modulate multiple transmitter systems in the central nervous system. Radioligand binding assays have shown that *ibogaine* is associated with a wide variety of receptors included the mu, delta, kappa, opiate, 5HT₂, 5HT₃, muscarinic1, 2 receptors, dopamine, norepinephrine, and serotonin uptake sites (42, 43). *Ibogaine* can directly or indirectly modulate the release of multiple neurotransmitters associated with drugs of abuse. For example, *ibogaine* can selectively reduce nicotine receptor-mediated catecholamine release and nicotine-induced dopamine overflow (44). *Ibogaine* blocks dopamine transmission produced by a 5-HT_{1b} antagonist (45) and substantially reduces brain dopamine levels in animals exhibiting robust cocaine-induced locomotor sensitization (46).

Ibogaine binds to multiple sites of the NMDA receptor complex, such as the phencyclidine (47) and MK-801 (48) binding sites. In light of the MK-801's ability to affect the behavioral consequences of addictive substances (49), the NMDA antagonist properties of *ibogaine* have been especially intriguing to researchers in seeking a pharmaceutical candidate to treat drug abuse and dependence. Indeed, the ability of *ibogaine* to block glutamate-induced cell death (31) and attenuate jumping behavior during morphine withdrawal in mice (50) has provided supporting evidence of its association with NMDA receptors. It should also be noted, however, that *ibogaine* has acute non-specific side effects (e.g. tremors, decreased motivated behavior in general) and neurotoxic effects (Purkinje cell loss) manifested in the vermis of the cerebellum. Recently, two novel, synthetic iboga alkaloid congeners, 18-methoxycoronaridine and 18-Methoxycoronaridine, are reported in animal studies to have potent anti-addiction properties with greater safety (36). These findings suggest that some *ibogaine* derivatives are candidates

as safe pharmacological intervention for drug abuse and dependence.

Radix Puerariae

Radix Puerariae, also called Kudzu, is the root of leguminous plant Puerariae that is native to eastern Asia and was imported to the United States where its remarkable hardiness, growing speed, and nutritional value complemented its medicinal potential for alcohol abuse treatment. It was first used for treating alcohol related problems almost a thousand years ago as an amethystic (anti-alcohol intoxication) (Sun Simiao, ~600 A.D.) and anti-dipsotropic (anti-alcohol abuse) agent (Li Dongyuan, ~1200 A.D.). Since then it has been used as an antipyretic, anti-diarrhetic, diaphoretic, anti-hypertensive, and anti-emetic agent (51, 52).

Ten years of pre-clinical studies have shown Radix Puerariae's inhibitory effects on ethanol. In 1993, two crude extracts of Radix Puerariae, daidzin and daidzein, were reported to profoundly suppress free-choice ethanol intake under continuous-access conditions in golden Syrian hamsters; their intake levels returned to baseline following the termination of the treatment (53). Daidzin's inhibitory effect on ethanol consumption was later confirmed in Wistar rats (54). Another active component of Radix Puerariae, puerarin, reduced ethanol intake in Fawn Hooded rats (55) and alcohol-preferring (P) rats (56, 57). Similarly, daily consumption of kudzu root resulted in a significant reduction in alcohol consumption in alcohol-preferring rats (58).

Two controlled clinical trials have examined Radix Puerariae for treating alcohol dependence, but with contradictory results. The first investigation reported no effect of radix Puerariae in reducing alcohol craving or promoting sobriety (59, 60). A later clinical trial found a reduction in the number of beers consumed by heavy drinkers following a week of Radix Puerariae treatment (61).

The neurochemical pathway responsible for Radix Puerariae's inhibition of the behavioral effects of ethanol appears related to Daidzin, which is a potent, selective, and reversible inhibitor of mitochondrial acetaldehyde dehydrogenase (ALDH-2) (62, 63). This enzyme (ALDH-2) is essential to the oxidation of acetaldehyde derived from ethanol metabolism, and without ALDH-2 functioning, the patient will become ill from drinking alcohol in a very similar way to the reaction between alcohol and disulfiram. Daidzin also potently inhibits the formation of 5-HIAA and DOPAC from serotonin and dopamine, respectively, and this inhibition of mitochondrial monoamine metabolism is associated with a concomitant increase in 5-HIAL and DOPAL levels (62, 64, 65). Thus, daidzin appears to suppress alcohol intake by increasing 5-HIAL and by inhibiting ALDH-2 (66). In addition, Puerarin and daidzein, two other compounds drawn from *Radix Puerariae*, have a high affinity for brain benzodiazepine receptors and inhibit [³H] flunitrazepam binding to membranes from cortex, cerebellum and hippocampus (67). Benzodiazepine receptors are located on the

gamma-aminobutyric acid (GABA)-chloride channel complex, and alcohol modulates the brain's inhibitory neurotransmitter GABA through this chloride channel complex. Thus, *Radix Puerariae* could be useful for treating ethanol addiction through its actions on benzodiazepine receptors, its alteration of monoamine metabolism, and its disulfiram-like actions on alcohol (67).

Withania Somnifera

Withania somnifera, commonly called Ashwagandha, is an Ayurvedic medicinal plant that is popularly known as "Indian ginseng," because its biological effects are similar to those of *Panax ginseng*. Ayurveda is the name of the Indian traditional health care system (ayus-life, veda-knowledge, meaning science of life), which is the oldest medical system in the world and is being revived in its complete form under the name of Maharishi Ayurved (68).

This system provides an approach to prevention and treatment of different diseases by a large number of medical procedures and pharmaceuticals. One of the clinical approaches of Ayurveda is Rasayana. Rasayana is not only a drug therapy but also a specialized procedure practiced through rejuvenating recipes in a dietary regimen promoting good habits. The purpose of rasayana is optimization of homeostasis in order to prevent disease and counteract the aging process. The meaning of the word Rasayana (rasa-essence, water; ayana-going) essentially refers to nutrition and its acquisition and circulation in the body tissues (69).

In Ayurveda, *Withania somnifera* is used as a tonic, aphrodisiac, sedative, and Medharasayana ('what promotes learning and a good memory') particularly for geriatric problems (70, 71). *Withania somnifera* has been widely used as a home remedy for a wide range of problems, including consumption, emaciation, debility, dyspepsia, and rheumatism, and its root is used to treat asthma (70, 72). A large number of bioactive compounds can be obtained from *Withania somnifera*'s roots and leaves including withaferin A and 3-i-hydroxy-2, 3-dihydrowithanolide F, which show promising antibacterial and immunomodulating properties (73). Further, glycowithanolides withafurin-A and sitoindosides VII-X isolated from the root of *Withania somnifera* significantly reversed ibotenic acid-induced cognitive deficits, which have been related to Alzheimer's disease (74).

A small number of studies have specifically examined the effects of *Withania somnifera* on addictive drugs. Kulkarni and Ninan (75) reported that repeated administrations of *Withania somnifera* attenuated the development of tolerance to morphine's analgesic effects and suppressed morphine withdrawal jumps in animals. *Withania somnifera* also attenuates several neurobiological changes induced by cold, hypoxia, or restraint stress in animals including the rise in plasma cortisosterone levels, increases in dopaminergic receptor population in the corpus striatum, phagocytic index, and avidity index (76). These anti-stress effects might reduce relapse in drug dependent patients (72).

The precise mechanism for *Withania somnifera*'s effects on morphine probably involves multiple neurotransmitters (76). For example, *Withania somnifera* blocks GABA binding to its receptors and increases chloride influx in the absence of GABA. It also down-regulates 5-HT1 and up-regulates 5-HT2 receptors, and inhibits calcium ion influx in glutamergic ion channels. Furthermore, *Withania somnifera* inhibits acetylcholinesterase. In-depth studies are required to determine how *Withania somnifera* can become used as a non-analgesic herbal medicine to treat stress-induced relapse to drug abuse and dependence.

Thunbergia Laurifolia Linn (Rang Jert in Thailand, also Know as Acanthaceae)

Thunbergia laurifolia Linn is an antipyretic, antidote, and anti-alcoholism treatment in Thai traditional medicine (77–79). To date, no published clinical trial has examined *Thunbergia laurifolia* Linn in treating drug addiction and only a handful of studies have explored the herb's effects in alcohol pharmacotherapy for humans or in animal models. Chanawirat et al. (80) found that extracts of *Thunbergia laurifolia* Linn leaves protected mice from ethanol-induced hepatic injury, and Pramyothina et al. (81) showed that aqueous extract from *Thunbergia laurifolia* Linn was protective against alcohol-induced liver injury in both live rats and primary cultures of rat hepatocytes. Functional magnetic resonance imaging in rats has shown that *Thunbergia laurifolia* Linn increases blood flow signals in nucleus accumbens, amygdala, frontal cortex, and caudate-putamen, which are brain areas related to the reinforcing and rewarding pathways of addictive drugs (82). A recent study showed that *Thunbergia laurifolia* Linn and amphetamine share some similarities in potentiating potassium-stimulated dopamine release from rat striatal slices, suggesting that the herb's potential efficacy for addictive drugs is dopamine-dependent (83).

Salvia Miltiorrhiza

Salvia miltiorrhiza (Danshen in Chinese, or Red Sage root), which belongs to the Labiatae family, has been widely used in Chinese traditional medicine. *Danshen* is a folk treatment for heart disease, hepatitis, haemorrhage, menstrual disorders, miscarriage, oedema, and insomnia, and recent data suggest its utility for substance dependence (48). The name *Salvia* comes from the Latin word meaning 'to heal' which sums up the folkloric belief of its 'magical' therapeutic properties for many kinds of ailments and its popularity in traditional medicine (84).

Standardized extracts of *Salvia miltiorrhiza* inhibited the discriminative stimulus effects of ethanol in rats trained to distinguish ethanol from water (85) and substantially suppressed the acquisition (86), maintenance (85, 87), and reinstatement (88) of alcohol drinking in selectively bred Sardinian alcohol-preferring rats. The therapeutic potential of *Salvia miltiorrhiza* for other addictive drugs such as cocaine, heroin, and nicotine has not been studied.

Salvia miltiorrhiza's inhibition of alcohol intake may involve *Danshen*'s main active components, which include phenanthrenequinones such as tanshinones I, II, cryptotanshinone, and miltirone (86). Miltirone is a low-affinity ligand for central benzodiazepine-GABA_A-binding sites, which are critical for many behavioral consequences of alcohol (89). Miltirone indeed attenuates the acquisition and maintenance of alcohol taking behavior in alcohol-preferring rats (90). Furthermore, miltirone (1–10 AM) partially inhibited the increase in mRNA for the $\alpha 4$ subunit of the GABA_A receptor, which ethanol withdrawal induces in cultured hippocampal neurons (91). Thus, miltirone might ameliorate alcohol withdrawal. Crude water extracts of *Salvia miltiorrhiza* also potentiate potassium-stimulated dopamine release from rat striatal slices to an extent that was comparable to amphetamine suggesting a another mechanism of action that could be useful for substance abuse pharmacotherapy (92).

Banisteriopsis Caapi

Banisteriopsis caapi is a woody vine from the Amazonian basin that makes an hallucinogenic drink known as ayahuasca (English), 'hoasca' (Brazil), 'yage' (Colombia), and 'caapi' (93). Ayahuasca is a Quechua term derived from the juxtaposition of the terms: Aya—"soul," "dead spirit;" Waska—"rope," "vine," and thus is loosely translatable as "vine of the souls" or "vine of the dead". Ayahuasca is a South American psychotropic beverage which is made by boiling the bark of the *Banisteriopsis caapi* (Malpighiaceae) with one of various other psychotropic plants (93, 94).

Ayahuasca contains beta-carbolines, such as harmine, harmaline, tetrahydroharmine (THH), and N,N-dimethyltryptamine (DMT). DMT is an ultra-short-acting hallucinogenic tryptamine (95) present in several plants used as admixtures to the *Banisteriopsis caapi* vine in ayahuasca preparations. Despite being a potent psychoactive chemical, DMT is inactive following oral administration probably due to degradation by gastrointestinal and liver monoamine oxidase (MAO) (96). However, when DMT is combined with inhibitors of MAO enzymes, such as the beta-carbolines in ayahuasca, it is able to reach the systemic circulation and the central nervous system, thus producing its effects (96). The mechanism of DMT action involves brain serotonin binding site of at least three types: 5-HT₂ and 5-HT_{1a} receptors and the 5-HT-protein transporter (97–99).

Some religious groups in Brazil currently use *Banisteriopsis caapi* to treat alcoholism, but its therapeutic efficacy has only been claimed in two clinical reports. In 1996, Mabit reported that *Banisteriopsis caapi* was a possible treatment for cocaine addiction (100). Grob et al. also reported that biweekly usage of *Banisteriopsis caapi* reduces the desire to consume addictive psychoactive agents, such as alcohol, cocaine and amphetamines (101).

Corydalis Yanhusuo

Corydalis yanhusuo is a Chinese traditional analgesic that has sedative, hypnotic, and antihypertensive properties (57). Levotetrahydropalmatine (*l*-THP) is its primary active chemical, and *l*-THP in mice inhibits the hyperactivity induced by oxycodone, an opioid receptor agonist similar to morphine (102). In addition, treatment with *l*-THP can attenuate morphine-induced withdrawal syndromes (103) and conditioned place preference in mice (104). *l*-THP dose-dependently reduces cocaine self administration and attenuates cocaine-induced reinstatement and locomotor activity (105). Supporting these promising pre-clinical findings, a clinical trial conducted in China found that *l*-THP effectively reduced drug craving, withdrawal syndromes, and relapse rates in recovering heroin-dependent patients (19). Thus, *Corydalis yanhusuo* may become an effective pharmacotherapy for drug abuse and dependence.

The neurochemical mechanism for *l*-THP's anti-addictive properties may be antagonism of dopamine transmission. Levotetrahydropalmatine inhibits dopamine D₁ and D₂ receptors and acts on the nigra-striatal neuronal pathways to inhibit both pre- and post-synaptic receptors (106); (107). Electroacupuncture-induced analgesia can be enhanced by *l*-THP presumably via the selective inhibition of dopamine D₁ receptors (108). However, *l*-THP also prevents inhibition of L-type Ca²⁺ channels (106), and inhibition of the L-type Ca²⁺ channel is essential for the development of morphine tolerance, dependence, and sensitization. Thus, *l*-THP could attenuate morphine-induced neural and behavioral plasticity via the blockade of L-type Ca²⁺ channels (109, 110). Finally, pretreatment with *l*-THP inhibits several of these neuronal changes associated with addictive drugs making it an excellent candidate medication for "re-normalization" of brain function that can be disrupted by chronic drug dependence (20).

Lophophora Williamsii (Peyote)

Lophophora williamsii, also known as Peyote, grows wild from Central Mexico, including the Mexican States of Nayarit, Querétaro, San Luis Potosí, Durango, Zacatecas, Nuevo León, Baja California Norte, Chihuahua, Coahuila, Tamaulipas and Sonora, to Texas along Rio Grande from Presidio County to Starr and Jim Hogg Counties. It is commonly used by the Arapaho, Blackfoot, Comanche, Huichol, Kickapoo, Kiowa, Lakota, Navajo, Omaha, and Winnebago Indian Tribes (111, 112).

Peyote is part of a very ancient religious sacrament involving all-night prayer ceremonies in the Native American Church (NAC) (113–115). NAC members accept Peyote as a God-given medicine offering spiritual and physical healing for the betterment of all Native peoples. Peyote, which contains the hallucinogen mescaline (-3,4,5-trimethoxyphenethylamine), is a hallucinogenic cactus producing significant physical, visual, and perceptual changes.

About thirty years ago, the Peyote treatment was incorporated into its alcoholic services program by the United States Public Health Hospital in Clinton, Oklahoma (116). This ritualistic use of Peyote to a properly structured psychotherapeutic session has been demonstrated to be an effective technique for treating alcoholics (117–119). The meeting consists of an orderly, constructive, and stimulating merger of three powerful psychotherapeutic modalities: the master or guide, the ritual or marathon group session, and the psychotropic drug, Peyote. The advantage of this therapeutic procedure is the ability of Peyote to rapidly alter the attitudes and behavior toward alcohol, long before the physical symptoms present. Through the ritual, many individuals testify to unprecedented periods of mental clarity, during which they report visions of their future life as an alcoholic. Later in the period of sobriety, the Peyote ritual potentiates a heightened state of consciousness that once experienced in the ritual becomes incorporated in the person's lifestyle.

Although this mode of treatment is not widely accepted and has not been conclusively proven to be effective; nevertheless, it seems important to consider the mechanism of ethnopsychedelical therapy for alcoholics. It was presumed that the action mechanism of the efficacy of Peyote in the treatment of alcoholism may act through the biomedical nature of the cactus itself.

Furthermore, Halpern (120) investigated the long-term residual psychological and cognitive effects of Peyote and reported that there was no evidence of psychological or cognitive deficits was found among Native Americans using Peyote regularly in a religious setting.

ACUPUNCTURE IN THE TREATMENT OF DRUG ADDICTION

Acupuncture is a traditional Chinese medical technique that was developed over two thousand years ago based on the theory of Chinese medicine that diseases are caused by blockages in the flow of internal energy ("Chi"). Acupuncture stimulates the points located on "meridians" along which Chi flows, breaking the blockage, and subsequently restoring the flow of energy and healthy body functioning (121).

Acupuncture has been used to treat substance abuse worldwide over the past 30 years (122). Using acupuncture to treat acute drug withdrawal symptoms began in 1972 when a Hong Kong neurosurgeon, Dr. Wen, administered acupuncture to surgical patients for anesthesia. He was unaware that some patients were also drug or/and alcohol dependent, and observed that these drug-dependent patients reported losing their drug craving after receiving acupuncture. Dr. Wen and his colleagues confirmed these results on 40 additional patients dependent on opioids (123). Later, the practice of full-body acupuncture was adapted into a five-point auricular acupuncture by Dr. Smith, and this protocol has been used as the sole detoxification method in the outpatient clinic at Lincoln Hospital in the Bronx, NY, USA (124). Due to the revolutionary simplification of auricular acupuncture, it has been widely used to treat addiction to various

substances of abuse. To date, acupuncture is currently used to treat withdrawal syndromes in more than 800 substance abuse treatment centers across the United States and Europe (125). Next, we will review findings on the utility of acupuncture in treating addiction to specific drugs of abuse.

Opiate Addiction

Acupuncture's utility for treating drug abuse and dependence is best shown in opioid-dependent patients experiencing withdrawal (126). Zhang et al. (127) found that acupuncture and electrical stimulation was 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.

These consistently promising clinical results have prompted animal studies to further explore the mechanisms of action for acupuncture in opioid-treated animals. For example, electroacupuncture has been shown to reduce withdrawal behaviors (i.e., jumping) in half of the mice during morphine abstinence (12) and to suppress naloxone-induced morphine withdrawal in rats (128). Electroacupuncture has been the most effective method to reduce morphine withdrawal scores in rats, followed by combined herbs and opioid peptides. Positive outcomes from both clinical and pre-clinical studies have cast acupuncture as a potentially critical support for managing acute and chronic opioid withdrawal and ultimately reducing the likelihood of relapse.

The neurochemical mechanism for acupuncture's ability to attenuate morphine-induced withdrawal syndromes has clarified. Kim et al. (129) reported that acupuncture administered at the bilateral Shenmen (HT7) point significantly decreased both dopamine release in the nucleus accumbens and behavioral hyperactivity induced by morphine. Liu et al. (102) demonstrated that electric acupuncture inserted and fixed at BL.23 significantly attenuated the signs of morphine withdrawal syndrome and c-Fos expression in the central nucleus of the amygdale in rats. Wang et al. (130) indicated that electric acupuncture of 2 Hz presumably decreased conditioned place preference by activating opioid receptors. Since it is accepted that mesolimbic dopamine plays a critical role in modulating various behavioral effects of abused drugs, including morphine, it is reasonable to argue that acupuncture can directly or indirectly influence the neurotransmitters and pathways in the brain to facilitate treatment of opioid abuse and dependence.

Cocaine Addiction

A relatively small number of studies have examined the effect of acupuncture on cocaine abuse and dependence, and there is some controversy over the treatment's effectiveness. Several clinical studies have provided supporting evidence for the promising effects of acupuncture. For example, patients receiving acupuncture treatment are more likely to provide cocaine negative urine samples than control patients (131, 132), and

show significant improvement and negligible side effects relative to control patients (133). Lipton et al. (134) also reported that patients receiving acupuncture treatment had significantly lower levels of cocaine metabolites than the control subjects. However, some large clinical trials have questioned the effectiveness of acupuncture for cocaine dependence. In these studies, the acupuncture treatment groups failed to show significant differences from the control group across a broad spectrum of psychological and physiological assessments (135). After reviewing several databases, D'Alberty (136) concluded that the efficacy of acupuncture in cocaine-dependent patients was not statistically significant, although discrepancies in experimental procedures across studies posed some difficulties in verifying the treatment's overall efficacy. In light of these promising but mixed findings, acupuncture cannot yet be considered an effective adjunct to existing drug treatment programs for cocaine, or other stimulants.

Nicotine Addiction

Acupuncture has also been advocated for smoking cessation, and using mailed questionnaires, Fuller (5) reported that 95% of patients quit smoking after three acupuncture treatments and 32% of the patients remained abstinent since the treatment, with eased nicotine withdrawal syndromes. Acupuncture and education programs also have been combined and shown success in smoking cessation. Bier et al. (137) studied the effects of acupuncture, education, and their combination in 141 adults, and concluded that the combined acupuncture-education group exhibited the greatest relative improvement. However, other studies have found that acupuncture offered no significant reduction of nicotine withdrawal symptoms (49) or long-term improvement over placebo (138). Certainly, the role of acupuncture in the treatment of nicotine dependence is still rather controversial, and additional studies are necessary to assess acupuncture's usefulness in treating nicotine dependence.

Acupuncture's neurochemical mechanism for attenuating smoking may be modulating the neuronal activity in nucleus accumbens and striatum. Acupuncture at *Zusanli* (ST36) in rodents significantly attenuated the increase in nicotine-induced locomotor activity and Fos-like-immunoreactivity in the nucleus accumbens and striatum in response to nicotine challenge (139).

Alcohol Addiction

Acupuncture has also had extensive research in alcoholism. In 1979, Gaa'l and Freebairn used ear-acupuncture relaxation therapy on a group of 62 alcoholics (140). Sixteen (25.8%) patients said that they had maintained total sobriety for over 12 months and 54 (87%) participants said that their life-style, drinking pattern, and physical and mental health had profoundly improved. Bullock et al. (141) performed a randomized trial of ear acupuncture on a group of 54 alcoholic recidivists and found that patients in the treatment group expressed less need for al-

cohol and had fewer drinking and relapse episodes. Lewenberg (142) administered a combination of ear electroacupuncture and a small dose of the antidepressant maprotiline hydrochloride in 50 alcohol-dependent patients, and found that a relatively high percentage of participants remained abstinent up to six months and none of the patients exhibited or reported acute withdrawal symptoms. However, the most recent study by Kunz et al. (143) reported that acupuncture was not superior to the control treatment of aromatherapy in reducing alcohol withdrawal symptoms.

Chronic alcohol administration can deplete extracellular dopamine levels in the nucleus accumbens (144, 145). Zhao et al. (19) reported that in rats' nucleus accumbens, acupuncture at the specific acupoint HT7 significantly inhibited both the decrease of extracellular dopamine levels during ethanol withdrawal and the increase in dopamine levels induced by ethanol injection. These results indicate that stimulation of the specific acupoint HT7 helps to normalize the release of dopamine in the mesolimbic system during chronic ethanol administration and withdrawal.

Moreover, co-administration of traditional herbal medicine and acupuncture may be effective for treating drug abuse and dependence. For example, Zhuang et al. (146) reported 98% efficacy in relief of withdrawal symptoms in heroin addicts when treated with a combination of Chinese herbal medicine and acupuncture. Lu et al. (130) recently reported that 20 of 26 heroin addicts experienced attenuation of withdrawal symptoms and stayed drug free for 1–1.5 years following co-administration of Chinese medicine pills and acupuncture. Taken together, acupuncture combined with herbal medicine deserves further study as a treatment for some types of drug addiction.

CONCLUDING REMARKS

In summary, traditional medical treatments 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, many herbal medicines can enhance immune function and increase metabolism in organs necessary to fight infections and various acute and chronic illnesses.

Despite growing efforts to explore herbal medicine and acupuncture in addictive disorders through both pre-clinical and clinical studies, traditional medicine has insufficient evidence to be used as a primary intervention for substance abuse. However, traditional medicine can complement existing treatments, and future studies should combine traditional medicines with other existing treatments. Basic research to provide evidence for neurochemical mechanisms of action and well-designed controlled trials confirming therapeutic efficacy, are critical to the future use of traditional medicine in treating drug abuse and dependence.

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Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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