

REVIEW

Complementary and alternative medicine in the treatment of substance use disorders—a review of the evidence

RISHIKESH V. BEHERE,¹ KESAVAN MURALIDHARAN¹ & VIVEK BENEGAL²

¹Department of Psychiatry, and ²Deaddiction Centre, Department of Psychiatry, National Institute of Mental Health and Neurosciences, Bangalore, India

Abstract

Issues. Substance use disorders are chronic relapsing disorders, leading to significant impairment in psychosocial functioning. Conventional therapies have not been able to alter the outcome of these disorders significantly and frequent relapses continue to occur, despite the development of newer medications, like baclofen, ondansetron, etc. Hence, there is a need to look at complementary and alternate systems of medicine. **Approach.** This article is a review of the evidence for complementary and alternate systems of medicine in substance use disorders. Articles were searched using the Medical Subject Headings (MeSH) database of the PubMed search engine and further non-indexed information was obtained from the Google search engine. The article is organised in parts, each reviewing a different system of medicine in the following order—alternate medical systems, biologically based therapies, energy-based interventions and mind–body interventions; as classified by the National Center for Complementary and Alternative Medicine, National Institutes of Health, USA. **Key Findings.** The currently available evidence is limited and not very encouraging. At present only acupuncture, herbal therapies and mind–body interventions have shown some positive results in human trials and hold promise for the future. **Implications.** This review emphasises the paucity of research into this important field especially the lack of rigorous human trials. **Conclusion.** More systematic studies are required before these systems of medicine can be widely recommended in the treatment of substance use disorders. [Behere RV, Muralidharan K, Benegal V. Complementary and alternative medicine in the treatment of substance use disorders—a review of the evidence. *Drug Alcohol Rev* 2009;28:292–300]

Key words: substance use disorder, complementary medicine, energy-based therapy, mind–body intervention, biological therapy.

Introduction

Substance use disorders are chronic relapsing conditions, leading to significant morbidity and impairment in psychosocial functioning [1,2]. Management of substance use disorders has always been a challenge, with combinations of medications and psychosocial interventions being the main stay of treatment. Advances in the understanding of the neurobiology of addiction have presented newer avenues in the medical management of substance use disorders. Established medications include disulfiram, acamprosate, naltrexone,

opioid maintenance and nicotine replacement therapies [3,4]. Newer drugs like ondansetron, topiramate and baclofen have shown promise but more evidence still needs to be garnered regarding their efficacy [5–7]. Despite the changes in treatment modalities, treatment outcomes have not changed much and relapse is common [8,9].

The limitations of conventional therapies and an ongoing need for treatments with long-term efficacy in maintaining abstinence and preventing relapse to drug and alcohol abuse has resulted in attempts at using complementary and alternative systems of medicine in

Rishikesh V. Behere MD, Senior Resident, Kesavan Muralidharan MD, Assistant Professor, Vivek Benegal MD, Additional Professor of Psychiatry. Correspondence to Dr Rishikesh V. Behere, Senior Resident, Department of Psychiatry, National Institute of Mental Health and Neurosciences, Bangalore—560029, India. Tel: +91 80 26995250; Fax: +91 80 2656 4830/2121; E-mail: rvbehere@gmail.com

Received 7 February 2008; accepted for publication 29 March 2008.

the management of these disorders. Even in developed countries like USA, a National Health Interview Survey in 2002 found that 62% of population use at least some form of alternative therapies [10]. This survey found that people preferred alternative medicine for reasons of 'dissatisfaction with western medicine', 'personal control' and 'philosophical congruence'.

The National Center for Complementary and Alternative Medicine (NCCAM) [11] at the National Institutes of Health, USA, classifies complementary and alternative medicine (CAM) therapies into five major categories (NCCAM, National Institute of Health): (i) *whole medical systems*, for example, homeopathic and naturopathic medicine, Ayurveda or traditional Chinese medicine (acupuncture, acupressure); (ii) *biologically based practices*, such as use of herbs, special macronutrient diets, mega doses of vitamins, minerals and other dietary supplements; (iii) *energy medicine* which are of two types: (a) bioelectromagnetic-based therapies: these use energy fields including unconventional use of electromagnetic fields, for example, transcranial magnetic stimulation (TMS), transcranial direct current stimulation; and (b) Biofield therapies: these are intended to affect energy fields that purportedly surround and penetrate the human body. Therapies include qigong, Reiki and therapeutic touch; (iv) *mind-body medicine*, such as meditation, yoga, spiritual healing, art, music, therapy and biofeedback; and (v) *manipulative and body-based practices*, such as chiropractic or osteopathic manipulations, therapeutic massage.

Complementary and alternative medicines are interventions that by definition are not accepted by conventional practitioners, because they have not yet been shown to be effective clinically. Hence, there is a need to review the efficacy of these interventions before they can be widely recommended. This article is an attempt to review the alternative systems of medicine that are available for the treatment of substance use disorders and examine the evidence for their efficacy.

Method

The PubMed search engine was used to search articles, using the MeSH database search terms complementary therapies, homeopathy, 'medicine, ayurvedic', acupuncture, 'Mind-Body and Relaxation Techniques', yoga, TMS, biofeedback, 'substance-related disorders'. Additional information from non-indexed sources was searched with the Google search engine.

Once retrieved, we have included all available articles. There were hardly any randomised controlled trials or methodologically rigorous studies to do a systematic review. The NCCAM classification structure is used to report the available results.

Results

Whole medical systems

Ayurveda. Ayurveda is the traditional and ancient system of Indian medicine. The classical Ayurvedic literature of '*charaka samhita*' mentions the use of various medicinal wines to treat illnesses arising out of alcohol use.

A few Ayurvedic preparations have been tested in animal models for their impact on various substances. These include an Indian herbal brew known as *asavam* (SKV) [12] and *BR-16A*, [13–15] a multicomponent herbal preparation. The results are summarised in Table 1.

Anticig. An herbal formulation based on traditional Ayurvedic compositions has been introduced as an 'anti-dote to the poisoning effects of tobacco and related products like cigarettes' [16]. As well as being effective in tobacco cessation, the herbal nicotine-free pharmaceutical composition comprises an effective amount of sterilised dried plant powder/extracts obtained from *Ocimum sanctum*, *Myristica fragrans*, *Elettaria cardamomum*, *Syzygium aromaticum*, *Acorus calamus*, *Zingiber officinale*, *Cinnamomum zeylanicum*, and optionally with pharmaceutical additives to form solid dosage forms like tablets.

A single open trial using Anticig was carried out on 35 subjects [16]. The medication was prescribed ad libitum (one tablet of 500 mgs of the plant drug), one tablet as and when the subject desired to smoke. A total of 62% reportedly maintained abstinence after 8 weeks of use of the medication and 73% reported reduction in craving. Further evidence is currently not available.

Homeopathy. Homeopathy is a widely practiced system of medicine based on the principle of 'like treats like'. *Nux vomica* & *Hyoscyamus* has been described for the treatment of alcohol-related withdrawal and delirium tremens. Extracts of strychnous *nux-vomica* has been found to reduce voluntary alcohol intake in rats [17]. A possible proposed mechanism of action is that the drug interacts with membrane aquaporins facilitating water influx into cells [18].

We did not come across any evidence for efficacy of these drugs in humans.

Acupuncture. In this system of medicine, life energy (called 'qi') is believed to flow throughout the body in specific channels, or 'meridians', ideally in a smooth, unobstructed and balanced cycle. Imbalances in this basic energy system eventually lead to disease. The metal acupuncture needles which are inserted at

Table 1. Summary of important studies on efficacy of complementary and alternative medicine in substance use disorders

Type of CAM therapy	Author	Type of study	Results
Whole medical systems			
Ayurveda			
Asavam (SKV)	Shanmugasundaram <i>et al.</i> , 1986 [12]	Animal study	Reduction in voluntary ethanol intake in rats.
BR 16-A	Kulkarni & Verma, 1992 [15]; Kulkarni & Verma, 1993 [13]; Kulkarni & Sharma, 1994 [14]	Animal studies	Prevented tolerance and naloxone precipitated withdrawal, alcohol withdrawal anxiety, withdrawal from benzodiazepines, in rats, respectively.
Anticig	Haran <i>et al.</i> , 2005 [16]	RCT	33 out of 35 subjects completed the treatment program of 8 weeks and 22 of these subjects were able to maintain complete abstinence by the end of 8 weeks.
Homeopathy			
Nux Vomica	Sukul <i>et al.</i> , 2001 [17]	Animal study	Reduction in voluntary alcohol intake in rats
Acupuncture			
	Bullock <i>et al.</i> , 1989 [23]	RCT	8 week placebo-controlled trial on alcohol-dependent patients 12 of 21 alcohol-dependent patients' maintained abstinence at 6 months.
	Avants <i>et al.</i> , 2000 [24]	RCT	82 cocaine-dependent, methadone-maintained patients they found better abstinence rates.
	Margolin <i>et al.</i> , 2002 [26]	RCT	Large single blind RCT on 620 cocaine-dependent patients. No significant difference found between groups at 6 month follow-up.
	Bullock <i>et al.</i> , 2002 [29]	RCT	Large, single blind, RCT on 503 alcohol-dependent patients. Acupuncture was not found to have any additional benefit over conventional treatment.
	Gates <i>et al.</i> , 2006 [33]	Cochrane review	Currently no evidence that auricular acupuncture is effective for the treatment of cocaine dependence.
	Tian & Krishnan, 2006 [34]	Pilot placebo controlled trial	Showed positive response of adjuvant acupressure to usual treatment
Biologically based practices			
Kudzu			
	Shebek & Rindone, 2000 [43]	RCT	No significant differences in craving or abstinence rates between the two groups after a 1 month trial
	Lukas <i>et al.</i> , 2005 [44]	Open trial	Showed significant reduction in alcohol consumption in naturalistic setting.
St Johns's wort			
	Perfumi <i>et al.</i> , 1999 [49]; Rezvani <i>et al.</i> , 1999 [50]; Coskun <i>et al.</i> , 2006 [51]	Animal studies	Reduction in voluntary alcohol intake and alcohol withdrawal in rats.
Tabernathe iboga			
	Alper <i>et al.</i> , 1999 [62]	Open trial	Significant reduction in opioid withdrawal symptoms.
Salvia miltiorrhiza			
	Serra <i>et al.</i> , 2003 [66]; Brunetti <i>et al.</i> , 2003 [67]	Animal studies	Reduction in voluntary alcohol intake on intragastric administration.
Magnesium			
	Margolin <i>et al.</i> , 2003 [70]	RCT	Significant reduction in craving & better abstinence rates in 18 methadone-maintained patients.
Melatonin			
	Zhdanova & Piotrovskaya, 2000 [74]; Garfinkel <i>et al.</i> , 1999 [75]	Open trial	Significant reduction in acute nicotine and benzodiazepine withdrawal, respectively.
Bioelectromagnetic-based therapies			
TMS			
	Eichhammer <i>et al.</i> , 2003 [78]	Double-blind crossover trial	rTMS over left dorso lateral prefrontal cortex (DLPFC) showed significant reduction in cigarette smoking without change in levels of craving.
	Camprodon <i>et al.</i> , 2007 [79]	Open trial	rTMS over right DLPFC found to reduce craving in cocaine-dependent individuals 4 h later.
Mind-body medicine			
EEG-Biofeedback			
	Scott <i>et al.</i> , 2005 [88]	RCT	RCT on 120 patients of multiple substance dependence showed abstinence rate of 77% in test group at end of 1 year and significant improvement of tasks of variable attention.
	Shafii <i>et al.</i> , 1975 [90]	Open trial	54% discontinuation in consumption of hard liquor after 2-3 years practice of transcendental meditation.
Yogas			
	Vedamurthachar <i>et al.</i> , 2006 [92]	RCT	Sudarshan Kriya Yoga showed significant reduction in depression, ACTH and cortisol levels in 60 alcohol-dependent patients during a 2 week detoxification regime.

ACTH, adrenocorticotrophic hormone; EEG, electroencephalogram; RCT, randomised controlled trial; TMS, transcranial magnetic stimulation.

specific points in the body create a difference in electrical potential between inside and outside, thus stimulating extra cellular ion flow [19]. Auricular acupuncture is used in treatment of substance use disorders.

Acupuncture is believed to have an effect on monoamine systems. Recent evidence with animal experiments shows that it significantly reduces dopamine release in nucleus accumbens and normalises the mesolimbic dopaminergic system in rats sensitised to morphine [20] and alcohol [21]. Acupuncture might also reduce c-Fos like immunoreactivity by modulating post-synaptic neural activation in the striatum and nucleus accumbens [22].

Bullock *et al.* [23] conducted a controlled study on 40 patients. Both groups underwent an 8 week program of acupuncture in addition to attending AA meetings. Acupuncture was given at points specific for treatment of substance use disorders in patient group and at non-specific points for the control group. A total of 21 patients completed the acupuncture course and 12 of them maintained complete abstinence at 6 months, however, only 1 of the 40 controls had completed the 8 week course. Avants *et al.* [24] in a more recent study of 82 cocaine-dependent methadone-maintained patients found better abstinence rates with auricular acupuncture group as compared with needle insertion control condition or a no-needle relaxation control [24]. Acupuncture has also been found to ameliorate acute opioid withdrawal symptoms [25]. However, other clinical trials have found no significant differences between active acupuncture conditions and comparison conditions in reducing cocaine use [26] and reducing use of or craving for cocaine [27]. A randomised trial of electroacupuncture was not found to improve nicotine withdrawal symptoms [28]. Bullock *et al.* [29] in a large randomised, placebo-controlled single blind study on 503 alcohol patients did not find any additional benefit with acupuncture over conventional treatment. Trümpler *et al.* [30] in a pilot randomised controlled trial of laser, sham and needle auricular acupuncture failed to find any significant advantage for laser acupuncture. Various review articles have failed to confirm efficacy of acupuncture as a sole mode of treatment [31,32]. A recent Cochrane review [33] states that 'There is currently no evidence that auricular acupuncture is effective for the treatment of cocaine dependence. The evidence is not of high quality and is inconclusive. Further randomized trials of auricular acupuncture may be justified.'

There is recent evidence that when used as an adjunct, there is a positive response to the specific auricular acupressure treatment on psychological distress, craving and drug/alcohol use measures [34]. Although there have been many studies of its potential usefulness, many of these studies provide equivocal results

because of limitations of design, sample size and other factors like standardising the site for needle placement. The issue is further complicated by inherent difficulties in the use of appropriate controls, such as placebos and sham acupuncture groups [35]. The National Acupuncture Detoxification Association's 5-point protocol [31] is an attempt at standardising the sites for needle placement in test and control groups for research purposes.

Biologically-based practices

Herbal medicines

Kudzu. Kudzu (*Pueraria lobata*) is one of the earliest medicinal plants used in traditional Chinese medicine. It has many profound pharmacological actions including anti-intoxication effects and antidipsotropic (anti-alcohol abuse) activity [36]. It has been examined in various animal and human studies for its efficacy in reducing alcohol consumption.

It has three isoflavonoids—daidzin, daidzein, puerarin [37,38]. Daidzin is a potent and selective inhibitor of human mitochondrial aldehyde dehydrogenase (ALDH-2). It is postulated that daidzin's antidipsotropic effects are mediated by unknown physiological pathways catalysed by ALDH-2 different from that of the classical ALDH inhibitor disulfiram [37].

Animal studies have shown kudzu extracts reduce voluntary ethanol intake in Syrian golden hamsters [38] and rats [39–42]. Shebek *et al.* [43] conducted a randomised double-blind placebo-controlled clinical trial ($n = 38$, patients = 21, controls = 17) using twice daily dose of 1.2 gm of kudzu root extract. They failed to show any significant differences in craving or abstinence rates between the two groups after a 1 month trial. Lukas *et al.* [44] in a study where heavy alcohol users were treated with 25% concentration of the isoflavonoids for 7 days and then allowed to drink alcohol in a laboratory naturalistic setting, found that kudzu treatment resulted in significant reduction in the number of beers consumed and a decrease in the volume of each sip. These changes occurred in the absence of a significant effect on the urge to drink alcohol.

St Johns Wort. *Hypericum perforatum* is an herb native to Europe which has been widely studied for treatment of depression. Its constituents are Hyperforin, Hypericin, Flavonoids and Tannins [45]. The postulated mechanisms of actions have been increased striatal acetylcholine levels [46] inhibition of serotonin, norepinephrine and dopamine reuptake in hippocampus, hypothalamus and nucleus accumbens in rat brains and also neuronal inhibition by gamma-aminobutyric acid (GABA) [47,48].

Efficacy has been studied only in rat experiments in which it is found to reduce voluntary alcohol intake [49,50] and alcohol withdrawal symptoms [51]. No evidence is available for efficacy in humans.

Tabernathe iboga. It is a plant native to central Africa and is recognised to have potential in treating withdrawal as well as reducing craving for substances. Its constituents are ibogaine and its metabolite noribogaine. The postulated mechanism of action is that ibogaine causes up regulation of glial cell derived neurotrophic factor in the dopaminergic neurons in the ventral tegmental area which reduces alcohol consumption in rats. It has been found to reduce extra cellular levels of dopamine in the nucleus accumbens, and also to act as a mu-[52] and kappa-opioid receptor agonist, NMDA [53] and nicotinic receptor antagonist and also to block serotonin uptake [54] which might explain the effects of ibogaine on all substance use disorders.

Ibogaine's ability to attenuate opioid withdrawal in the rat was first published by Dzoljic *et al.* [55]. It has also been shown subsequently to diminish morphine self-administration [56] cocaine self-administration [57], and to reduce alcohol consumption in rat models [58]. A synthetic analogue 18-methoxycoronaridine has been found to have effects similar to that of ibogaine in preclinical studies [59,60]. Many case series and open label studies have been reported regarding ibogaine's efficacy in humans. Sheppard [61] described use of single dose of ibogaine 700–1200 mg in seven opioid-dependent subjects who reported significant decrease in withdrawal symptoms within 38 h. Alper *et al.* [62] conducted an open-label trial in 33 opioid-dependent subjects, 25 of which reported attenuated withdrawal symptoms after 24 h. Ibogaine has certain acute effects on administration, which include visual phenomenon described as a wakeful dream like state, ataxia, tachycardia and hypertension. Fatal cardiac arrhythmias have also been reported [63].

Salvia miltiorrhiza. This is also a traditional Chinese medicinal herb. It contains Miltirone [64] which has been found to inhibit up regulation of GABA-A receptor in rat hippocampal neurons during ethanol withdrawal [65]. Preclinical studies in rats show that intragastric administration of the active compound reduces voluntary ethanol intake [66,67], as compared with intraperitoneal administration suggesting an additional mechanism of inhibiting alcohol absorption [68].

Biological supplementation

Blum and colleagues have described [69] amino acid supplementations with D & L isomers of phenylalanine and L-Tryptophan in doses of 500–1500 mg per day to

reduce craving for alcohol, cannabis and nicotine as they are essential in synthesis of brain monoamines and endorphins.

Magnesium is an endogenous NMDA receptor blocker. Its supplementation in a randomised double-blind pilot study in 18 methadone-maintained patients was found to reduce craving and improve abstinence rates [70]. This preliminary finding needs to be confirmed in larger studies.

In animal models melatonin has been found to reduce alcohol intake [71] and reduce chronic ethanol-induced free radical damage and lipid peroxidation [72,73]. In human studies, melatonin has been found to reduce acute nicotine [74] and benzodiazepine [75] withdrawal effects.

Energy medicine

Bioelectromagnetic-based therapies

Transcranial magnetic stimulation. TMS is a method of inhibiting or activating neurons by external application of electromagnetic fields and is a useful non-invasive research tool to study cortical activity. There is some recent evidence for therapeutic implications in depression and auditory hallucinations. Using investigative TMS, it has been showed that alcohol [76] and chronic cocaine use [77] reduces excitability of the cortex. Preliminary studies on 14 patients using repetitive TMS of the left dorso lateral prefrontal cortex as a treatment method for nicotine dependence found significant reduction in cigarette smoking without change in levels of craving [78]. One session of 10 Hz repetitive TMS over right dorso lateral prefrontal cortex was found to reduce craving in cocaine-dependent individuals 4 h later [79].

Biofield therapies

Other energy-based therapies include qigong and therapeutic touch. Qigong is an ancient Chinese health practice which involves rhythmic body movements to balance the same energy 'qi' as described in acupuncture. There has been one study wherein 86 heroin addicts were randomised to a qigong group ($n = 34$), medication group ($n = 26$) receiving tapering dose of lofexidine or a control group ($n = 26$) receiving only symptomatic treatment for withdrawal symptoms. The Qigong group interestingly had urines negative for morphine by day 5 whereas the test was negative only by day 9 in the treatment group suggesting a role for qigong in detoxification of morphine dependence although the role of a placebo effect cannot be ruled out [80].

Mind body medicine

Electroencephalogram biofeedback

Electroencephalogram (EEG) biofeedback is a variation of the general principle of biofeedback where in the subject receives feedback on her/his physiological responses by which s/he learns to gain voluntary control over autonomic responses. Here EEG is used as an agent to provide feedback on brain wave patterns.

Studies on biological markers of alcoholism have found alcoholics and sons of alcoholics to have EEG wave patterns in the fast alpha (9–12 Hz) and beta (12–20 Hz) range [81–83]. Biofeedback aims at the patient learning to convert her/his brain wave activity from the alpha to theta range.

In an early case report [84] and an experimental study on 14 subjects, Saxby *et al.* [85] found alpha theta biofeedback reduced craving, depression and anxiety scores. Autogenic relaxation by biofeedback has been shown to develop internal locus of control in adolescents [86] and also has been proposed as an alternative treatment method for adolescents, especially those with stimulant abuse and attention and conduct problems [87]. In a recent randomised controlled study on 120 multiple substance abusers who received 50 sessions of biofeedback significant changes in the test of variable attention and Minneosta multiphasic personality inventory were found. Furthermore, at end of 1 year 77% in the test group were abstinent compared with 44% in the control group [88]. Methodological issues regarding the procedure and conduct of these studies have been raised [89]. However, these preliminary findings need to be replicated in larger randomised controlled trials.

Yoga, meditation and spirituality

Yoga and meditation have long been described for the treatment of substance use disorders. Shafii *et al.* [90] in a study on 216 patients practicing transcendental meditation found that 60% reported discontinuation of wine and beer consumption after 2–3 years of practice and 54% of subjects versus 1% of controls had stopped consumption of hard liquor. Gelderloos *et al.* [91] in a review of 24 studies on transcendental meditation found it to be an effective intervention which brought about in addition long-term changes in improved well-being, self-esteem and personal empowerment. The above studies, however, used self-report questionnaires on alcohol use by subjects and had no objective evidence for reduced substance use. An Indian study has found that Sudarshan Kriya Yoga, a form of yoga based on specific breathing techniques, significantly reduced depression scores on the Beck's depression inventory

and also serum adrenocorticotrophic hormone, and cortisol levels in 60 alcohol-dependent patients undergoing a detoxification regime over a 2 week period [92].

A study on spirituality and mindfulness found spirituality scores negatively correlated with substance use whereas interestingly mindfulness scores were positively correlated with binge drinking patterns [93]. A comparison of faith-based versus traditional substance abuse treatment programs by Neff *et al.* [94] found that although both scored similarly on domains of 'safe supportive environment, group activities and cohesion and role modeling' they differed on domains of 'spiritual beliefs and structure and discipline'.

Other mind–body interventions

A community-based rehabilitation program called 'drumming out drugs' has been evaluated by qualitative research method [95]. A component of group activities involving playing drums is added to rehabilitation programs. Interviews with participants indicate that it improves self-esteem and instils a feeling of being part of a community. A physiological mechanism proposed is that rhythmic auditory stimulation produces brain wave patterns in the theta range [96].

Manipulative and body-based practices

In a randomised control trial of 50 patients, massage therapy added as an adjunct to regular medical detoxification significantly reduced scores on the alcohol withdrawal scale in the early stages of the detoxification process in comparison to a 'rest' condition [97].

Conclusion

A number of alternative therapies are being tried in the treatment of substance use disorders. Although a few preliminary studies show encouraging results, none of the alternative therapies have significant evidence as of now. Of the evidence reviewed, acupuncture, EEG biofeedback and herbal therapies (kudzu, ibogaine) hold promise for the future. Mind body interventions, which are innocuous in nature and have shown efficacy in preliminary studies, warrant more attention. Studies of CAM face methodological difficulties relating to standardisation of procedures, provision of a control arm and blinding for double-blind randomised controlled trials. This review emphasises the paucity of research into this important field especially the lack of rigorous human trials.

The popularity of CAM, in the context of the limitations of traditional medicine is on the rise. Hence,

efforts to establish efficacy and standardised treatment procedures are warranted to make these interventions more effective.

References

- [1] McCabe RJ. Alcohol-dependent individuals sixteen years on. *Alcohol Alcohol* 1986;21:85–91.
- [2] Marshall EJ, Edwards G, Taylor C. Mortality in men with drinking problems: a 20-year follow-up. *Addiction* 1994; 89:1293–8.
- [3] Mann K. Pharmacotherapy of alcohol dependence: a review of the clinical data. *CNS Drugs* 2004;18:485–504.
- [4] Suh JJ, Pettinati HM, Kampman KM, O'Brien CP. The status of disulfiram: a half of a century later. *J Clin Psychopharmacol* 2006;3:290–302.
- [5] Johnson BA, Roache JD, Javors MA, et al. Ondansetron for reduction of drinking among biologically predisposed alcoholic patients: a randomized controlled trial. *JAMA* 2000; 284:963–71.
- [6] Addolorato G, Caputo F, Capristo E, et al. Baclofen efficacy in reducing alcohol craving and intake: a preliminary double-blind randomized controlled study. *Alcohol Alcohol* 2002;37:504–8.
- [7] Johnson BA, Ait-Daoud N, Bowden CL, et al. Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. *Lancet* 2003;361:1677–85.
- [8] Vaillant GE. A 60-year follow-up of alcoholic men. *Addiction* 2003;8:1043–51.
- [9] Mann K, Schafer DR, Langle G, Ackermann K, Croissant B. The long-term course of alcoholism, 5, 10 and 16 years after treatment. *Addiction* 2005;100:797–805.
- [10] Astin JA. Why patients use alternative medicine: results of a national study. *JAMA* 1998;279:1548–53.
- [11] National Centre for Complementary and Alternative Medicine, National Institute of Health. What is CAM? Available at: <http://www.nccam.nih.gov/health/whatiscam/> (accessed February 2007).
- [12] Shanmugasundaram ER, Subramaniam U, Santhini R, Shanmugasundaram KR. Studies on brain structure and neurological function in alcoholic rats controlled by an Indian medicinal formula (SKV). *J Ethnopharmacol* 1986;17:225–45.
- [13] Kulkarni SK, Verma A. Protective effect of BR-16A (Mentat), a herbal preparation on alcohol abstinence-induced anxiety and convulsions. *Indian J Exp Biol* 1993; 5:435–9.
- [14] Kulkarni SK, Sharma A. Reversal of diazepam withdrawal induced hyperactivity in mice by BR-16 A (mentat), a herbal preparation. *Indian J Exp Biol* 1994;32:886–8.
- [15] Kulkarni SK, Verma A. Evidence for nootropic effect of BR-16A (Mentat), a herbal psychotropic preparation, in mice. *Indian J Physiol Pharmacol* 1992;36:29–34.
- [16] Haran JC, Lal A, Nujum Z, Edayaranmula JJ. Efficacy and safety of 'Anticig' anti-smoking ayurveda tablet in chronic smokers—secondary trial in a specialized substance abuse prevention centre setting. 2005. Available at: http://www.anticig.com/who_cer1.html (accessed June 2007).
- [17] Sukul NC, Ghosh S, Sinhababu SP, Sukul A. Strychnos nux-vomica extract and its ultra-high dilution reduce voluntary ethanol intake in rats. *J Altern Complement Med* 2001;7:187–93.
- [18] Sukul NC, De A, Sinhababu SP, Sukul A. Potentized mercuric chloride and Nux vomica facilitate water permeability in erythrocytes of a fresh-water catfish *Clarius batrachus* under acute ethanol intoxication. *J Altern Complement Med* 2003;9:719–25.
- [19] Freeman WL. Acupuncture. In: Freeman WL, Lawlis GF, eds. *Complementary and alternative medicine—a research based approach*. Missouri: Mosby, 2001:311–44.
- [20] Kim MR, Kim SJ, Lyu YS, et al. Effect of acupuncture on behavioral hyperactivity and dopamine release in the nucleus accumbens in rats sensitized to morphine. *Neurosci Lett* 2005;387:17–21.
- [21] Zhao RJ, Yoon SS, Lee BH, et al. Acupuncture normalizes the release of accumbal dopamine during the withdrawal period and after the ethanol challenge in chronic ethanol-treated rats. *Neurosci Lett* 2006;395:28–32.
- [22] Kim JH, Chung JY, Kwon YK, et al. Acupuncture reduces alcohol withdrawal syndrome and c-Fos expression in rat brain. *Am J Chin Med* 2005;33:887–96.
- [23] Bullock ML, Culliton PD, Orlander RT. Controlled trial of acupuncture for severe recidivist alcoholism. *Lancet* 1989; 1:1435–9.
- [24] Avants SK, Margolin A, Holford TR, Kosten TR. A randomized controlled trial of auricular acupuncture for cocaine dependence. *Arch Intern Med* 2000;160:2305–12.
- [25] PK L, GP L, DP L, Lu DP, Lu WI. Managing acute withdrawal syndrome on patients with heroin and morphine addiction by acupuncture therapy. *Acupunct Electrother Res* 2004;29:187–95.
- [26] Margolin A, Kleber HD, Avants SK, et al. Acupuncture for the treatment of cocaine addiction: a randomized controlled trial. *JAMA* 2002;287:55–63.
- [27] Lipton DS, Brewington V, Smith M. Acupuncture for crack-cocaine detoxification: experimental evaluation of efficacy. *J Subst Abuse Treat* 1994;11:205–15.
- [28] White AR, Resch KL, Ernst E. Randomized trial of acupuncture for nicotine withdrawal symptoms. *Arch Intern Med* 1998;158:2251–5.
- [29] Bullock ML, Kiresuk TJ, Sherman RE, et al. A large randomized placebo controlled study of auricular acupuncture for alcohol dependence. *J Subst Abuse Treat* 2002;22:71–7.
- [30] Trümpler F, Oez S, Stähli P, Brenner HD, Jüni P. Acupuncture for alcohol withdrawal: a randomized controlled trial. *Alcohol Alcohol* 2003;38:369–75.
- [31] D'Alberto A. Auricular acupuncture in the treatment of cocaine/crack abuse: a review of the efficacy, the use of the National Acupuncture Detoxification Association protocol, and the selection of sham points. *J Altern Complement Med* 2004;10:985–1000.
- [32] Ki YH, Schiff E, Waalen J, Hovell M. Efficacy of acupuncture for treating cocaine addiction: a review paper. *J Addict Dis* 2005;24:115–32.
- [33] Gates S, Smith LA, Foxcroft DR. Auricular acupuncture for cocaine dependence. *Cochrane Database Syst Rev* 2006; (1):CD005192.
- [34] Tian X, Krishnan S. Efficacy of auricular acupressure as an adjuvant therapy in substance abuse treatment: a pilot study. *Altern Ther Health Med* 2006;12:66–9.
- [35] NIH Consensus Development Panel on Acupuncture. Acupuncture. *JAMA* 1998;280:1518–24.
- [36] Keung WM, Vallee BL. Kudzu root: an ancient Chinese source of modern antidipsotropic agents. *Phytochemistry* 1998;47:499–506.
- [37] Keung WM, Klyosov AA, Vallee BL. Daidzin inhibits mitochondrial aldehyde dehydrogenase and suppresses ethanol intake of Syrian golden hamsters. *Proc Natl Acad Sci USA* 1997;94:1675–9.

- [38] Keung WM, Vallee BL. Daidzin and daidzein suppress free-choice ethanol intake by Syrian golden hamsters. *Proc Natl Acad Sci USA* 1993;90:10008–12.
- [39] Overstreet DH, Lee DYW, Rezvani AH, Pei YH, Criswellm HE, Janowsky DS. Suppression of alcohol intake after administration of the Chinese herbal medicine, NPI-028, and its derivatives. *Alcohol Clin Exp Res* 1996;20:221–7.
- [40] Lin RC, Guthrie S, Xie CY. Isoflavonoid compounds extracted from *Pueraria lobata* suppress alcohol preference in a pharmacogenetic rat model of alcoholism. *Alcohol Clin Exp Res* 1996;20:659–63.
- [41] Heyman GM, Keung WM, Vallee BL. Daidzin decreases ethanol consumption in rats. *Alcohol Clin Exp Res* 1996;20:1083–7.
- [42] Benlhabib E, Baker JI, Keyler DE, Singh AK. Kudzu root extract suppresses voluntary alcohol intake and alcohol withdrawal symptoms in P rats receiving free access to water and alcohol. *J Med Food* 2004;7:168–79.
- [43] Shebek J, Rindone JP. A pilot study exploring the effect of kudzu root on the drinking habits of patients with chronic alcoholism. *J Altern Complement Med* 2000;6:45–8.
- [44] Lukas SE, Penetar D, Berko J, *et al.* An extract of the Chinese herbal root kudzu reduces alcohol drinking by heavy drinkers in a naturalistic setting. *Alcohol Clin Exp Res* 2005;29:756–62.
- [45] Wright CW, Gott M, Grayson B, Hanna M, Smith AG, Sunter A, Neill JC. Correlation of hyperforin content of *Hypericum perforatum* (St John's Wort) extracts with their effects on alcohol drinking in C57BL/6J mice: a preliminary study. *J Psychopharmacol* 2003;17:403–8.
- [46] Buchholzer ML, Dvorak C, Chatterjee SS, Klein J. Dual modulation of striatal acetylcholine release by hyperforin, a constituent of St. John's wort. *J Pharmacol Exp Ther* 2002;301:714–19.
- [47] Kientsch U, Burgi S, Ruedeberg C, Probst S, Honegger UE. St John's wort extract Ze 117 (*Hypericum perforatum*) inhibits norepinephrine and serotonin uptake into rat brain slices and reduces 3-adrenoceptor numbers on cultured rat brain cells. *Pharmacopsychiatry* 2001;34(Suppl. 1):S56–60.
- [48] Rommelspacher H, Siemanowitz B, Mannel M. Acute and chronic actions of a dry methanolic extract of *Hypericum perforatum* and a hyperforin-rich extract on dopaminergic and serotonergic neurones in rat nucleus accumbens. *Pharmacopsychiatry* 2001;34(Suppl. 1):S119–126.
- [49] Perfumi M, Ciccocioppo R, Angeletti S, Cucculelli M, Massi M. Effects of *Hypericum perforatum* extraction on alcohol intake in Marchigian Sardinian alcohol-preferring rats. *Alcohol Alcohol* 1999;34:690–8.
- [50] Rezvani AH, Overstreet DH, Yang Y, Clark E, Jr. Attenuation of alcohol intake by extract of *Hypericum perforatum* (St. John's Wort) in two different strains of alcohol-preferring rats. *Alcohol Alcohol* 1999;34:699–705.
- [51] Coskun I, Tayfun Uzbay I, Ozturk N, Ozturk Y. Attenuation of ethanol withdrawal syndrome by extract of *Hypericum perforatum* in Wistar rats. *Fundam Clin Pharmacol* 2006;20:481–8.
- [52] Bhargava HN, Cao YJ, Zhao GM. Effects of ibogaine and noribogaine on the antinociceptive action of mu-, delta- and kappa-opioid receptor agonists in mice. *Brain Res* 1997;752:234–8.
- [53] Popik P, Layer RT, Fossom LH. NMDA antagonist properties of the putative antiaddictive drug, ibogaine. *J Pharmacol Exp Ther* 1995;275:753–60.
- [54] Glick SD, Maisonneuve IS. Mechanisms of antiaddictive actions of ibogaine. *Ann NY Acad Sci* 1998;844:214–26.
- [55] Dzoljic ED, Kaplan CD, Dzoljic MR. Effects of ibogaine on naloxone precipitated withdrawal syndrome in chronic. Morphine dependent rats. *Arch Int Pharmacodyn Ther* 1988;294:64–70.
- [56] Glick SD, Rossman K, Steindorf S, Maisonneuve IM, Carlson JN. Effects and aftereffects of ibogaine on morphine self-administration in rats. *Eur J Pharmacol* 1991;195:341–5.
- [57] Cappendijk SLT, Dzoljic MR. Inhibitory effects of ibogaine on cocaine self-administration in rats. *Eur J Pharmacol* 1993;241:261–5.
- [58] Rezvani A, Overstreet D, Lee Y, *et al.* Attenuation of alcohol intake by ibogaine in three strains of alcohol preferring rats. *Pharmacol Biochem Behav* 1995;52:615–20.
- [59] Rezvani AH, Overstreet DH, Yang Y. Attenuation of alcohol consumption by a novel nontoxic ibogaine analogue (18-methoxycoronaridine) in alcohol-preferring rats. *Pharmacol Biochem Behav* 1997;58:615–19.
- [60] Maisonneuve IM, Glick SD. Anti-addictive actions of an iboga alkaloid congener: a novel mechanism for a novel treatment. *Pharmacol Biochem Behav* 2003;75:607–18.
- [61] Sheppard SG. A preliminary investigation of ibogaine: case reports and recommendations for further study. *J Subst Abuse Treat* 1994;11:379–85.
- [62] Alper KR, Lotsif HS, Frenken GM, Luciano DJ, Bastiaans J. Treatment of acute opioid withdrawal with ibogaine. *Am J Addict* 1999;8:234–42.
- [63] Lotsif HS. Ibogaine in the treatment of chemical dependence disorders: clinical perspectives. *MAPS Bulletin* 1995;3:19–26.
- [64] Colombo G, Serra S, Vacca G. Identification of miltirone as active ingredient of *Salvia miltiorrhiza* responsible for the reducing effect of root extracts on alcohol intake in rats. *Alcohol Clin Exp Res* 2006;30:754–62.
- [65] Mostallino MC, Mascia MP, Pisu MG, Busonero F, Talani G, Biggio G. Inhibition by miltirone of up-regulation of GABAA receptor alpha4 subunit mRNA by ethanol withdrawal in hippocampal neurons. *Eur J Pharmacol* 2004;494:83–90.
- [66] Serra S, Vacca G, Tumatis S, *et al.* Anti-relapse properties of IDN 5082, a standardized extract of *Salvia miltiorrhiza*, in alcohol-preferring rats. *J Ethnopharmacol* 2003;88:249–52.
- [67] Brunetti G, Serra S, Vacca G, *et al.* IDN 5082, a standardized extract of *Salvia miltiorrhiza*, delays acquisition of alcohol drinking behavior in rats. *J Ethnopharmacol* 2003;85:93–7.
- [68] Colombo G, Agabio R, Lobina C, *et al.* *Salvia miltiorrhiza* extract inhibits alcohol absorption, preference, and discrimination in sP rats. *Alcohol* 1999;18:65–70.
- [69] Blum K, Ross J, Reuben C, Gastelu D, Miller DK. Nutritional gene therapy: natural healing in recovery. *Counselor The magazine for addiction professionals*. 2001. Available at: <http://www.counselormagazine.com/content/view/204/63/> (accessed June 2007).
- [70] Margolin A, Kantak K, Copenhaver M, Avants SK. A preliminary, controlled investigation of magnesium L-aspartate hydrochloride for illicit cocaine and opiate use in methadone-maintained patients. *J Addict Dis* 2003;22:49–61.
- [71] Rudeen PK, Symmes SK. Pineal gland and melatonin influence on chronic alcohol consumption by hamsters. *Pharmacol Biochem Behav* 1981;14:143–7.
- [72] El-Sokkary GH, Reiter RJ, Tan DX, Kim SJ, Cabrera J. Inhibitory effect of melatonin on products of lipid peroxi-

- dation resulting from chronic ethanol administration. *Alcohol* 1999;34:842–50.
- [73] Baydas G, Tuzcu M. Protective effects of melatonin against ethanol-induced reactive gliosis in hippocampus and cortex of young and aged rats. *Exp Neurol* 2005;194:175–81.
- [74] Zhdanova IV, Piotrovskaya VR. Melatonin treatment attenuates symptoms of acute nicotine withdrawal in humans. *Pharmacol Biochem Behav* 2000;67:131–5.
- [75] Garfinkel D, Zisapel N, Wainstein J, Laudon M. Facilitation of benzodiazepine discontinuation by melatonin: a new clinical approach. *Arch Intern Med* 1999;159:2456–60.
- [76] Kahkonen S, Wilenius J, Nikulin VV, Ollikainen M, Ilmoniemi RJ. Alcohol reduces prefrontal cortical excitability in humans: a combined TMS and EEG study. *Neuropsychopharmacology* 2003;28:747–54.
- [77] Boutros NN, Lisanby SH, Tokuno H, *et al.* Elevated motor threshold in drug-free, cocaine-dependent patients assessed with transcranial magnetic stimulation. *Biol Psychiatry* 2001;49:369–73.
- [78] Eichhammer P, Johann M, Kharraz A, *et al.* High-frequency repetitive transcranial magnetic stimulation decreases cigarette smoking. *J Clin Psychiatry* 2003;64:951–3.
- [79] Camprdon JA, Martinez-Raga J, Alonso-Alonso M, Shih MC, Pascual-Leon A. One session of high frequency repetitive transcranial magnetic stimulation (rTMS) to the right prefrontal cortex transiently reduces cocaine craving. *Drug Alcohol Depend* 2007;86:91–4.
- [80] Li M, Chen K, Mo Z. Use of qigong therapy in the detoxification of heroin addicts. *Altern Ther Health Med* 2002;8:50–4, 56–9.
- [81] Schuckit MA. Biological markers in alcoholism. *Prog Neuropsychopharmacol Biol Psychiatry* 1986;10:191–9.
- [82] Ehlers CL, Schuckit MA. EEG fast frequency activity in the sons of alcoholics. *Biol Psychiatry* 1990;27:631–41.
- [83] Porjesz B, Rangaswamy M, Kamarajan C, Jones KA, Padmanabhapillai A, Begleiter H. The utility of neurophysiological markers in the study of alcoholism. *Clin Neurophysiol* 2005;116:993–1018.
- [84] Fahrion SL, Walters ED, Coyne L, Allen T. Alterations in EEG amplitude, personality factors, and brain electrical mapping after alpha-theta brainwave training: a controlled case study of an alcoholic in recovery. *Alcohol Clin Exp Res* 1992;16:547–52.
- [85] Saxby E, Peniston EG. Alpha-theta brainwave neurofeedback training: an effective treatment for male and female alcoholics with depressive symptoms. *J Clin Psychol* 1995;51:685–93.
- [86] Sharp C, Hurford DP, Allison J, Sparks R, Cameron BP. Facilitation of internal locus of control in adolescent alcoholics through a brief biofeedback-assisted autogenic relaxation training procedure. *J Subst Abuse Treat* 1997;14:55–60.
- [87] Trudeau DL. Applicability of brain wave biofeedback to substance use disorder in adolescents. *Child Adolesc Psychiatr Clin N Am* 2005;14:125–36.
- [88] Scott WC, Kaiser D, Othmer S, Sideroff SI. Effects of an EEG biofeedback protocol on a mixed substance abusing population. *Am J Drug Alcohol Abuse* 2005;31:455–69.
- [89] Graap K, Freides D. Regarding the database for the Peniston alpha-theta EEG biofeedback protocol. *Appl Psychophysiol Biofeedback* 1998;23:265–72, 273–5.
- [90] Shafii M, Lavley R, Richard R. Mediation and prevention of alcohol abuse. *Am J Psychiatry* 1975;132:942–5.
- [91] Gelderloos P, Walton KG, Orme-Johnson DW, Alexander CN. Effectiveness of the transcendental meditation program in preventing and treating substance misuse: a review. *Int J Addict* 1991;26:293–325.
- [92] Vedamurthachar A, Janakiramaiah N, Hegde JM, *et al.* Antidepressant efficacy and hormonal effects of Sudarshana Kriya Yoga (SKY) in alcohol dependent individuals. *J Affect Disord* 2006;94:249–53.
- [93] Leigh J, Bowen S, Marlatt GA. Spirituality, mindfulness and substance abuse. *Addict Behav* 2005;30:1335–41.
- [94] Neff JA, Shorkey CT, Windsor LC. Contrasting faith-based and traditional substance abuse treatment programs. *J Subst Abuse Treat* 2006;30:49–61.
- [95] Winkelman M. Complementary therapy for addiction: ‘drumming out drugs’. *Am J Public Health* 2003;93:647–51.
- [96] Neher A. Auditory driving observed with scalp electrodes in normal subjects. *Electroencephalogr Clin Neurophysiol* 1961;13:449–51.
- [97] Reader M, Young R, Connor JP. Massage therapy improves the management of alcohol withdrawal syndrome. *J Altern Complement Med* 2005;2:311–13.