Natural and complementary therapies for substance use disorders

Angela J. Dean

Purpose of review

To review recent studies that have examined the efficacy of natural and complementary therapies as treatments for substance use disorders and their complications.

Recent findings

Despite increasing interest in natural and complementary therapies for substance use disorders, rigorous clinical studies in this area are few in number. Recent clinical studies, although preliminary, have reported potential therapeutic effects for hypericum in the treatment of smoking cessation, for prickly pear extract in the prevention of alcohol hangover and magnesium supplementation as an adjunct to methadone treatment. Other clinical studies have reported negative findings for ginkgo as an adjunctive treatment for cocaine dependence, for artichoke in prevention of alcohol hangover, and acupuncture for alcohol withdrawal. Relevant findings from animal studies are also discussed. Neither vitamin E nor Liv 52 had a useful effect in alcohol-related liver disease. A study of silymarin in baboons, which was undertaken in an attempt to untangle the conflicting findings of human studies, reported a potential for this compound to prevent liver injury. There is increasing awareness of safety issues associated with complementary therapies. Safety issues pertinent to substance use treatment are discussed in this review.

Summary

Several pharmacological and psychosocial treatments for substance use disorders are solidly evidence-based and improve both individual and public health outcomes. At this stage, there remains insufficient evidence to support the use of natural and complementary therapies as a primary intervention for substance use disorders. Further clinical trials are required to clarify the potential role of particular agents.

Keywords

addiction, complementary therapies, drug dependence, herbal medicine, substance use disorders

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Mater Child and Youth Mental Health Service and Mater Pharmacy Services, Mater Hospital, Brisbane, Queensland, Australia

Correspondence to Angela Dean PhD, Research Fellow, Kids in Mind Research, Mater Child and Youth Mental Health Service, Raymond Terrace, South Brisbane, Qld 4101, Australia
Tel: +61 7 3840 1007; fax: +61 7 3840 1644; e-mail: angela.dean@mater.org.au

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Abbreviation

OFI *Opuntia ficus indicia*

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Introduction

Many existing pharmacological and psychosocial interventions for substance use disorders are solidly evidence-based. Yet, there is a need to identify additional treatments. There is growing recognition that evidence-based treatments do not produce adequate therapeutic benefits in every patient. Additionally, barriers such as financial cost, lack of availability, or perceptions of existing treatments as unappealing may limit rates of treatment uptake. Developing new treatments within a pluralistic treatment model may attract a larger number of substance users into treatment. The use of natural and complementary therapies fits well within a range of existing theoretical frameworks for understanding and treating drug dependence. They could fulfil a variety of roles:

(1) As adjunctive treatments to existing pharmacological or psychosocial interventions.
(2) As treatment alternatives for substance users who are not eligible for existing treatments, who are nonresponsive to existing treatments, or who refuse existing treatments.
(3) As treatment options in countries or regions where evidence-based interventions are not routinely available.
(4) As treatment options for disorders where there is no current gold standard treatment.

It has been estimated that up to 45% of substance users employ natural and complementary therapies [1]; surveys suggest that more than three-quarters of substance users contacting treatment services find complementary or alternative treatments acceptable [2,3].

Natural and complementary therapies are a diverse and heterogeneous group of treatments; many, such as relaxation therapies, are already widely utilized within substance use treatment settings. This review will focus on pharmacological rather than behavioural therapies and incorporate literature published in English dating from 2003 to 2004.

Reducing hazardous alcohol intake

A series of animal studies has examined the potential for various plant-derived compounds to reduce alcohol intake. No clinical studies were identified within the review period that examined complementary medicines as a primary intervention targeting drug consumption.

Danshen (*Salvia miltiorrhiza*) is native to China and used within traditional Chinese medicine. One research group has published three series of controlled experiments where Danshen was shown to reduce acquisition of ethanol intake in rats with no prior exposure [4]; reduce ethanol intake in rats with established ethanol intake [5]; and prevent increases in voluntary ethanol intake occurring after a brief period of abstinence, used as an animal model of relapse [6]. Danshen has not been subjected to any human trials, and is at an early stage of research into its effects.

The Kudzu plant (*Pueraria lobata*) has been used traditionally in China to treat alcohol intoxication and hangover [7]; recent animal research explores the potential for two isoflavone derivatives – daidzin and puerarin – to reduce alcohol intake [8•,9]. Two recent studies add to existing findings, reporting that Kudzu root extracts led to significant reductions in alcohol consumption in rats with established alcohol intake [10], and that puerarin produced reductions in alcohol intake, but only temporarily [11]. A previous clinical trial reported no effect of Kudzu on craving or abstinence rates in chronic alcohol dependence [12]. Future research needs to identify the differences in pharmacological activity between single isolated constituents and whole plant extracts.

Hypericum (*Hypericum perforatum*, or St John's Wort), is widely used as a herbal antidepressant, with a large number of controlled trials supporting its use in the treatment of mild (but not severe) depression [13,14]. Animal studies suggest that acute administration of hypericum can reduce voluntary alcohol intake and act synergistically with opiate antagonists [8•]. Two recent studies examining the effects of hypericum on alcohol intake in rats confirm previous research and demonstrate that the constituent hyperforin contributes to observed reduction in alcohol intake [15,16]. Hyperforin is currently considered to be the primary contributor to antidepressant effects [17]. The mechanism behind effects on alcohol intake is not established. Hypericum inhibits reuptake of various neurotransmitters, including monoamines, γ-aminobutyric acid (GABA) and glutamate [17]. The effects on ethanol intake may also be secondary to anxiolytic or sedative activity. Without human studies, these findings have little direct application to the clinical setting. However, hypericum seems a likely candidate for advancing into clinical testing, given the large body of human data for other indications and availability of standardized formulations.

Substance withdrawal syndrome

The traditional aim of detoxification is to achieve a safe and humane withdrawal from a drug of dependence [18]. Although unlikely to produce long-term abstinence in itself, detoxification is an attractive treatment option for many substance users, and may permit individuals to reduce their drug use, or prepare them for other treatment programs [18].

Pharmacological interventions

Pharmacological management of substance withdrawal is standard practice in many countries, and an important component of comprehensive treatment provision. Use of complementary medicines with relevant pharmacological properties fits well within existing models of withdrawal management.

Hypericum (*Hypericum perforatum*) has also been investigated for its effects on nicotine withdrawal. Similar pharmacological effects to existing treatments such as bupropion has partly contributed to the interest in hypericum. In a clinical study, 45 adult smokers were randomized to receive an oral spray containing hypericum or placebo spray, in addition to brief counselling sessions and nicotine replacement patches. Although abstinence rates were similar in each group after 1 month, hypericum was associated with lower craving scores, and less anxiety, restlessness and sleeplessness compared with controls [19]. An animal study also reports that high doses of hypericum attenuated effects of nicotine withdrawal in mice [20]. This effect was greatest when hypericum was initiated prior to nicotine cessation rather than delayed until emergence of withdrawal symptoms.

Numerous complementary medicines are utilized for their putative sedative properties. Some, such as valerian (*Valeriana officinalis*), have evidence to support their use in insomnia. Sedative compounds have a potential role in the management of agitation, insomnia or anxiety associated with substance withdrawal. Pilot studies have reported beneficial effects of passionflower (*Passiflora incarnata*) for opiate withdrawal [21], or melatonin for benzodiazepine [22] or nicotine [23] cessation. However, there are few recent clinical studies of these agents focusing on withdrawal management. One review [24] discusses the mechanisms of passionflower in the treatment of substance use disorders, focusing on one particular constituent, a benzoflavone moiety, which animal studies have shown to reduce withdrawal severity from various substances. Unfortunately, this review does not address the comparative effects between this constituent and whole plant preparations typically utilized for sedative and anxiolytic effects. The potential to reduce

morphine withdrawal signs in mice has been reported for rosemary (*Rosmarinus officinalis*) [25] and the corn poppy (*Papaver rhoeas*), which may possess opioid and anticholinergic effects [26]. Positive effects in animal studies do not necessarily translate to clinical effectiveness. These studies may contribute to our understanding of the pharmacology of these compounds; however, without ongoing research, they provide little to inform treatment.

Acupuncture

There are many research studies of acupuncture in substance users, however findings have been conflicting. A recent study in a prison population compared auricular acupuncture with sham auricular needling to determine whether acupuncture could assist in reducing discomfort or drug use [27•]. The sample was heterogeneous, with various drugs used (amphetamines 51%; heroin 12%; cannabis 10%) and varying degrees of dependence severity. No differences between treatments were observed. Another trial examined the effects of acupuncture on alcohol withdrawal symptoms in inpatients [28•]. Participants were randomized to either auricular needle acupuncture, laser stimulation of the ear, or a sham laser condition. Those receiving needle acupuncture had shorter withdrawal duration and lower need for adjunct sedative medications, but this was not significant after controlling for baseline differences. There were no group differences between laser and sham-laser interventions. This finding is consistent with a growing body of evidence reporting no differences between acupuncture and control groups [29]. The Cochrane metaanalysis on acupuncture for smoking cessation concludes that 'there is no evidence for the specific effectiveness of acupuncture, acupressure, laser therapy or electro-stimulation for smoking cessation greater than a placebo effect' [30]. One of the challenges for acupuncture research has been defining what is an appropriate 'placebo' and the subsequent difficulty in conducting controlled, blinded studies. Three recent reviews discuss research and clinical issues associated with acupuncture for substance use [31•–33•].

Alcohol hangover

Two clinical studies have examined plant-derived products for the prevention of alcohol-related hangover. The most recent of these examined the effects of an extract from the fruit of the prickly pear (*Opuntia ficus indicia*, OFI) [34•]. Using a double-blind, crossover design, 64 volunteers were randomly allocated to take a single dose of OFI or placebo, 3 h prior to alcohol ingestion. Overall, the risk of a serious hangover was halved in the group receiving the active treatment. Additionally, OFI treatment was associated with better overall well-being, and lower ratings of nausea, anorexia and dry mouth compared with placebo. After alcohol ingestion, C-reactive protein levels increased in the placebo condition; this increase was attenuated in patients receiving OFI. The investigators attribute observed therapeutic effects to the antiinflammatory activity of OFI.

The second clinical study [35•] examined extracts from the globe artichoke (*Cynara scolymus*), an agent which is sometimes marketed as a hangover cure, and has possible cholerectic properties. Using a similar design, 15 participants were randomly assigned to standardized globe artichoke extract (LI 120, 960 mg) or placebo immediately before and after alcohol consumption. There were no observed differences between artichoke extract and placebo on any of the outcome measures. Small sample size may have contributed to lack of significant effects.

Adjuncts to conventional treatment

Many users of natural and complementary medicines do so in conjunction with conventional treatments rather than take them as a true alternative. Two clinical studies have examined complementary medicines as adjuncts to conventional interventions for substance use.

Ginkgo biloba has an emerging evidence base to support its use as a cognitive enhancer in disorders of cognitive impairment such as dementia. Hypothesizing that improved cognitive function would improve treatment engagement, Kampman and colleagues [36•] conducted a trial in dependent cocaine users receiving outpatient psychological treatments. Participants were randomly allocated to one of three groups: ginkgo (standardized extract Egb761, 240 mg daily), piracetam (another nootropic agent, 4.8 mg daily) or placebo. After 8 weeks, there were no differences between the three interventions on any outcomes, including relapse rates, positive urine drug screens, craving, or addiction severity scores. In fact, there was a trend in some comparisons for placebo to be superior to the other treatments. Although small sample size may have contributed to lack of observed effects for ginkgo or piracetam, the trend for effects to be in the opposite direction to what was hypothesized suggests that results do not reflect a type II error. This was a small study; however, the negative finding highlights the need for efficacy to be tested in a controlled setting.

The second study examined the effect of magnesium supplementation as an adjunct to methadone maintenance treatment [37•], prompted by a series of animal studies reporting positive effects of magnesium on cocaine self-administration, and development of morphine tolerance. In a randomized, double-blind pilot study, 18 methadone maintenance patients with ongoing illicit opiate and cocaine use were given either magnesium (732 mg daily of magnesium-L-aspartate hydrochloride, equivalent to 61 mg of elemental magnesium) or placebo for 12 weeks. All participants received 30 min of counselling each week. Magnesium treatment was

associated with fewer opiate-positive urine screens and lower craving ratings for cocaine. This preliminary finding needs to be confirmed in larger studies. Although the methadone doses received by study participants were within an adequate range (85–100 mg), it would also be interesting to compare the effects of this or other therapies with other strategies for methadone patients, such as increasing methadone dose or enhancing psychosocial interventions.

Alcohol-related liver disease

Greater understanding of the role of oxidative stress in the pathogenesis of liver disease has fuelled interest in a range of complementary medicines of alcohol-related liver disease, especially those agents with antioxidant effects.

Silybum marianum

Silymarin refers to a group of flavolignan compounds derived from milk thistle (*Silybum marianum*) that exert antioxidant effects [38]. Clinical studies report some positive effects in the treatment of alcohol-related liver disease, however results have been conflicting [38]. In order to control for sample heterogeneity that has complicated interpretation of previous research, such as variability in alcohol consumption and disease severity, Lieber and colleagues [39•] conducted a controlled study in a baboon model of alcohol-related liver disease. During 2 years of alcohol consumption, increases in markers of oxidative liver injury that were observed in the control group were attenuated in baboons receiving regular silymarin over the same time period. Silymarin treatment was also associated with lower triglycerides and plasma ALT levels and significantly less steatosis, fibrosis and cirrhosis.

Emerging data for silymarin for alcohol-related liver disease are promising. The potential clinical role for silymarin is strengthened by the absence of standard pharmacological interventions. Future controlled trials need to determine whether silymarin can provide additional therapeutic benefit above abstinence, and whether its primary role is for those patients who have trouble achieving abstinence. Additionally, this study demonstrates that silymarin has the capacity to prevent liver injury – in contrast to previous studies which examine the treatment of existing injury. If research continues to demonstrate that silymarin can prevent alcohol-induced liver disease, options for use of silymarin as a harm reduction approach in high-risk drinkers may need to be examined.

A number of clinical studies have reported negative findings for alcohol-related liver disease, including vitamin E [40], Liv 52 [41] and polyenylphosphatidylcholine [42]. With regard to the latter trial, subgroup analyses suggest a potential effect in high-risk groups. However, results of all three trials were limited by small sample sizes, variability in disease severity and levels of drinking during the study. Larger studies that control for these factors would clarify these findings.

Safety issues relevant to substance use

Although complementary medicines are often perceived to be safe and free of unwanted effects, evidence continues to emerge that safety cannot be assumed. Hypericum can induce activity of a range of drug-metabolizing enzymes such as cytochrome P4503A4 and p-glycoprotein [43•]. As a result, regular use of hypericum may lead to reduced serum concentrations and effectiveness of substrate drugs, such as HIV protease inhibitors and the oral contraceptive pill [43•,44,45]. Of particular importance is a recent report describing such an interaction between hypericum and methadone [46•]. In four patients, addition of hypericum led to significant reductions in methadone serum concentrations, with two patients reporting withdrawal symptoms. Co-administration of hypericum and serotonergic agents such as antidepressants or methylenedioxymethamphetamine (MDMA, or Ecstasy) may also lead to serotonin toxicity [47]. Similarly to conventional antidepressants, hypericum may produce withdrawal symptoms after abrupt cessation of higher doses [48].

Ephedrine is a naturally occurring alkaloid found in plants of the *Ephedra* genus (*Ma Huang*), which is structurally similar to amphetamines and possesses potential for abuse. Recent reports add to existing descriptions of ephedra-induced psychiatric adverse effects, including psychosis [49,50]. Use of *Ephedra* group alkaloids may also produce false-positive urine drug screening for amphetamines when analysed using radioimmunoassay techniques [51]. Other herbs such as hypericum, Siberian ginseng and valerian do not appear to produce false positive urine drug tests using enzyme immunoassay analyses [52].

A systematic review assesses 15 epidemiological studies which investigate whether acupuncture is a risk factor for hepatitis transmission [53•]. Five studies reported an association between acupuncture and hepatitis C, where acupuncture led to a modest increase in risk of hepatitis C transmission. Although these studies had their limitations, it does highlight the importance of using disposable needles during acupuncture. Another systematic review examines the safety of plant-derived compounds implicated in hepatotoxicity [54•].

Conclusion

Despite growth in research into complementary therapies, at this stage there remains insufficient evidence to support the use of complementary therapies as a primary intervention for substance use. Should we discourage

substance users from using complementary therapies? When making these judgements, it is important to consider the broader clinical context. Treatments with demonstrated efficacy should be promoted where available. However, 'gold-standard' interventions such as methadone maintenance remain unappealing for many opiate users. Additionally, treatment options with demonstrated efficacy may not be widely available or accessible in some regions. When little evidence exists to support an intervention, patients should be told this, as part of an informed decision-making process. Monitoring changes in target symptoms such as drug consumption or drug craving is a technique commonly incorporated into existing substance use treatments, and is an important component of gauging treatment response. A systematic approach to treatment utilizing outcome monitoring is especially important when trialing a nonevidence-based intervention.

Continuing research is needed to clarify the potential role of particular interventions. Positive effects in animal studies do not necessarily translate to clinical effectiveness. Therapies which have shown promise in human studies need to be subjected to larger, adequately powered controlled trials. It would be desirable for future clinical research to examine complementary medicines not in isolation, but to compare them with both existing treatments and strategies that optimize existing treatments. Substance dependence is a chronic disorder; research needs to incorporate longer-term treatment outcomes and conform to the current standards by which we evaluate conventional interventions.

In conclusion, no complementary therapies have yet been fully demonstrated to be effective for substance abuse treatment. The limitations of existing research augur well for researchers rather than clinicians. It is likely that any potential role for complementary medicines will be as part of a multi-dimensional approach to service provision, rather than as sole interventions. More research is required to define this role. In the meantime, it is important that our enthusiasm for new treatments does not generate a situation where substance use disciplines endorse a lower standard of clinical evidence than would be acceptable in other fields of medicine.

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