Review Article

De-addictives: Evaluation Methods and its Choice of Remedies from Various System of Medicines – An Update

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ABSTRACT

Addiction is a characteristic psychological and physiological dependence on a substance or practice that is beyond professional control. It is a chronic brain disorder that causes obsessive substance use despite harmful consequences. Addiction causes major destructive effect to human being along with its social consequence. Abrupt withdrawal of any addicted substances produces psychological disorder. Natural substances have various effect on the body, even though many of them can lead to addiction, others have long been used in the treatment and detoxification. In this review, the methods of evaluation and various modalities of treatment for de-addiction are discussed. Some of the laboratory method for finding various de-addictive drugs in animals' model, different form of treatments with herbals such as – Ginseng, *Tabernanthe iboga* and *Voacanga africana*, *l*-THP, Datura, *Nigella sativa* etc; synthetic drugs (Methadone, Buprenorphine, Naltrexone, Disulfiram, Acamprosate) and therapies (Acupuncture, Aromatherapy, Yoga, Nutritional and Horticulture therapy) were reviewed and found to have significant effect in substance dependence. Refined preclinical model such as CPP, drug self-administration and cue induced paradigm or models etc, are used to understand the neurobiological effect of addictive substances in the brain and its different form of treatment can be used depends on the symptoms and severity of the condition with appropriate system of medicine.

Keywords: Antiaddiction, Conditioned Place Preference, Herbs, Acupuncture therapy, Aromatherapy.

INTRODUCTION

Addiction can be defined as a chronic brain disease which include craving and relapsing response that is usually characterized by compulsive substance or drug seeking for use in despite of harmful consequences. The substance or drug with addiction property have high tendency to cause long lasting changes in the structure, function and working property of the brain and can leads to harmful and bizarre behaviours which is usually seen in substance induced addictive patients.

Addiction can be of two types-firstly is the "substance" type of addiction which includes addiction to certain drugs or substance such as narcotic analgesics (e.g. heroin, morphine, codeine, Hallucinogens (e.g. cannabis), Depressants (e.g. amylobarbitone), Stimulants (e.g. methylamphetamine, cocaine, ecstasy), Tranquillizers (e.g. chlordiazepoxide, benzodiazepine) and others like Ketamine, Alcohol, Tobacco etc. Secondly is the "behavioural" type of addiction which includes compulsive buying, sexual addiction, internet addiction, pathological gambling, compulsive exercise and eating disorder[1].

Imaging studies on animals and human have shown the three stages of addiction cycle with key elements such as ventral tegmental area and ventral striatum as a focal point for the binge/intoxication stage, amygdala in the withdrawal/negative affect stage, and orbitofrontal cortex–dorsal striatum, prefrontal cortex, basolateral amygdala and hippocampus in the preoccupation/ anticipation stage. The network which are involving in craving are the cingulate gyrus, the dorsolateral prefrontal, and the inferior frontal cortices which acts by disrupting the inhibitory control[2].

Treatment of addiction usually start with medical, psychosocial assessment and detoxification or relieving of withdrawal symptoms and help patients to attain a drug-safe state. Even with clinical progress in treating of physical withdrawal syndromes usually produced by abusive substance, efficacious treatments for all drug addictions are inadequate to control the main addiction, craving and relapse problems toward such substances.

1. METHODS FOR ANTIADDICTIVE STUDY

Methods and models used for study of drug abuse and dependence:

Free-choice bottle model

A technically simple, noninvasive and non-operant self-administration method constrained to oral administration, commonly used in alcohol addiction research where subject can choose whether to drink alcohol and the amount ingested[3]. The method is also used to outlook the pharmacological treatment for prevention of excessive alcohol drinking[4].

Liquid diet

This method is commonly used in alcohol addiction research where ethanol or addictive substance is added in high concentration to a liquid diet and animals are allowed to access *ad libitum* of the diet or forcing to take the substance present in the diet which is the main sources of nutrition, the amount of substance given and its consumption are recorded and calculated[5,6] . The method of feeding alcohol as part of a liquid diet will leads to blood alcohol levels that usually mimic the clinical conditions and allows experimental repetitions of many pathological complications caused by alcohol, such as alcoholic fatty liver disease, various alcohol-induced metabolic derangements, and the interaction of ethanol with industrial solvents and many others commonly used drugs, and nutrition[5].

Operant self-administration

The most common and direct procedure for evaluation of reinforcing properties of a substance by testing whether animal will work (lever press) to gain the substance. This model is based on the statement that drug can increase the possibility of the abnormal behavior[7].

In this model, initially the animal is surgically implanted with an intravenous catheter and permit to acquire drug self-administration on either lever pressing or nose poking then subsequently extinguished. After certain period of extinguished, the ability of acute exposure to triggering stimuli or Cues is measure as a response where drug seeking can be determined. the manifestation of reinstatement is considered if animal responds at a rate above extinction and show selectivity on the operandum that is previously delivered the drug (e.g., presses on lever that deliver the drug rather than the vehicle lever)[8].

Alcohol vapor

The model is based on the vapor's inhalation, developed for an attempt of induction of a state of alcohol dependence in animals. Alcohol vapor inhalation is a non-invasive procedure which allows the control of dose, duration and the pattern of exposure to addictive substances as per requirements. On cessation of exposure of animals to alcohol vapor, animals exhibit a sign of tolerance and physical dependence which can be further tested for multitude of motivational, acute withdrawal and protracted abstinence related behavioral pattern[9]. Gilpin *et al* had exposed rats to alcohol vapor for a period of 4 hours and the alcohol concentration in the brain and blood samples was measured and found that maximum level of alcohol is attained in blood and brain. Further, eight hours after termination, blood and brain alcohol levels returns back to pre-vapor baseline[10].

Conditioned Place Preference (CPP)

The most common method used to study conditioned preference that apply environmental stimulus as the conditioned stimulus. The testing apparatus is composed of boxes with two distinct compartments with different stimulus dimension, flooring, wall color or cue and separated by a removable door. The third compartment which is not paired with drug is also present in the apparatus.

In this method the subjects are initially trained to associate one compartment of a choice apparatus with drug injections and a second compartment with drug vehicle injection, after training i.e, on a drug free test day, subject is given a choice between the two compartments, and typically it will spend more time in the drug paired environment[8].

CPP protocol consist of three phases: pre-conditioning, conditioning and post-conditioning (test). In pre-conditioning animals (rat or mouse) are placed in neutral compartment and allowed to access the entire apparatus for 15minutes per day for a period of 3 days; In the conditioning phase the same animal received alternate injections of drug and vehicle and exposed to either one suitable compartment respectively. For conditioning test, animal is placed in neutral compartment and allowed to access the entire apparatus. The time spent in each compartment is recorded, increase in time spent in compartment paired with drug indicates the development of CPP or vice versa. Similarly, this method can be subsequently used for reinstatement of CPP that is carried out by exposing the animal to a relapse trigger such as stress, drug or others non-drug stimuli[11].

Stress-induced relapse

The state where negative effect such as anxiety, anger, stressful life event and depression can easily trigger relapse to drug seeking and drug taking in humans. Thus, the model is used to mimic this kind of human situation[12].

Stress can be induced by various factors. In case of animal models, intermittent foot-shock is one of the most successfully used stressors. The mechanism of relapse here involved the region such as lateral tegmental noradrenergic nuclei and their projections through ventral noradrenergic bundle to central nucleus of amygdala, hypothalamus and finally a common glutaminergic corticostriatal pathway[13].

Cue-induced relapse

Exposure to environment cues such as sound, sight and other sensory stimuli which are previously associated with drug-use are the common risk factor to relapse of addiction in human. The situation of drug-seeking behavior can be studied using animal model with different cues including- discrete cue, discriminative cue and contextual cues. In discrete cue-induced model, animals are first trained to self-administer a drug and a reward is given each time whenever animal is paired with discrete cues. In discriminative cue-induced, animals are trained to self-administer a drug or saline in the presence of distinct discriminative stimuli. Finally, in contextual cue method, animals are first trained to self-administer the drug in

presence of cue (light, tone, odor) in the drug paired context which act as occasion setter for drug reinforced behavior. Re-exposure of animals to drug-paired context can reinstate drug-seeking. These methods are differed in their tactile, visual, olfactory and visual features[14].

HERBS/PLANTS USED IN THE TREATMENT OF ADDICTION

Ginseng Extract

Panax ginseng (Fam: Araliaceae)

Analgesic effect of opioids like morphine in a non-opioid dependent manner was blocked by ginseng extract. Hence, can inhibit the tolerance and dependence on morphine. The suppressive provide effect which is developed due to morphine tolerance on exposure to foot-shock stress is prevented by ginseng. Ginseng extract was found to have inhibitory action on behavioral sensitization to Morphine, Methamphetamine and Cocaine. It also inhibits the appearance of the recurrent phenomenon of the effect of Methamphetamine and Cocaine on re-administration. This provide evidence that ginseng is clinically useful in prevention of opioids and psychostimulant abuse and dependence[15].

Tabernanthe iboga and *Voacanga africana*

Tabernanthe iboga and *Voacanga africana* are shrubs used in African traditional medicine. Both the plants contain a naturally occurring alkaloid called ibogaine. This ibogaine is used by ancient people in a very low dose to overcome fatigue, hunger and sometimes in high dose for some religious rituals. The anti-addictive effect of this alkaloid has brought a great interest in recent years[16]. American and European addict self-help groups have claimed that ibogaine can promotes the long-term drug abstinence from Heroin, psychostimulants and Cocaine. Anecdotal have report that a single dose of ibogaine can abolishes withdrawal symptoms and reduces drug cravings for extended periods of time[17].

Ibogaine has been demonstrated and found to significantly reduce self-administration of morphine and cocaine in animals. It also antagonizes the locomotor effect which is induced by cocaine, nicotine and amphetamine in mice[18].

Ibogaine binds to multiple sites of the NMDA (N-methyl-D-aspartate) receptor complex. Acute non specific side effects (e.g. tremors, decreased motivated behavior in general) and neurotoxic effects (Purkinje cell loss) of ibogaine was indicated in the vermis of the cerebellum. The NMDA antagonist properties of ibogaine have been fascinating to researchers in seeking a pharmaceutical candidate to treat drug abuse and dependence[19].

L-Tetrahydropalmatine (*l*-THP)

Levo-tetrahydropalmatine is the primary active chemical constituents present in the plant *Corydolis yanhusuo* and some other plant which belongs to a species of the genera Stephania and Corydalis. *Corydolis yanhusuo* is a Chinese traditional medicine having a number of clinical indications such as sedative, hypnotic and antihypertensive property. The pharmacological activity of *l*-THP includes the antagonism of Dopamine receptor (D1, D2 and D3), alpha adrenergic receptors and serotonin receptors. Therefore, due to this blockade activity *l*-THP can be consider as an antiaddictive agent. The neurochemical mechanism of *l*-THP as anti-addictive property is because of its inhibiting action on Dopamine receptors and its action on nigrostriatal neuronal pathways as inhibitors of both pre and post synaptic receptors. Subsequently due to the antagonistic action on dopamine receptors as well as adrenergic and serotonin receptors, *l*-THP may have the utility for treating opioid addiction[20, 21].

Camellia sinensis

Camellia sinensis is commonly known as green tea and it is a worldwide popular herb. The active constituents called (-)-epigallocatechin gallate is obtained from this herb and found to attenuate the withdrawal symptom and dose-dependent to morphine. It also has an inhibitory effect on an increased cAMP concentration in the locus coeruleus and dopamine receptor signaling due to morphine[22].

Caulis sinomenii

Caulis Sinomenii is a Chinese plant commonly known as Qing Feng Teng. It has an effective analgesic, anxiolytic and sedative action and improving the drug dependence which is related to abnormal monoaminergic transmission. It can modulate the histamine level in central nervous system and also suppress the acquisition of place preference of mice using morphine induced conditioned place preference method[23].

Nigella sativa

Nigella sativa is an annually flowering plant commonly known as black cumin belonging to the family Ranunculaceae. Sangi *et al* has done a study on this plant and found that it is very effective in the prevention and treatment of addiction, infections, weakness and pain which is seen after addiction. No serious side effect is detected with this drug. Apart from these it also has antiallergic, antibacterial activity. This plant is rich in amino acids with nutritional characteristic and sympatholytic activity. Hence, it could be appropriate for treating the withdrawal symptoms[24].

Berberine

Berberine is an isoquinoline alkaloid obtained from different species of genus Berberis such as *Berberis vulgaris*, *Berberis candidula* etc. Berberine has the property to weaken the sympathetic system. Hence, can reduce diarrhea and nausea, anticonvulsant and anti-spasm effect. It has calcium channel inhibitor property hence can abolish tachycardia in withdrawal phase[1]. Pre-treatment with berberine preceding to morphine administration can lessen depression and anxiety like symptoms which is associated with morphine discontinuation, mostly by modulating the hypothalamic

corticotropin releasing factor and noradrenergic system in the CNS. Therefore, berberine may be useful as an alternative medicine for treatment of morphine related withdrawal symptoms[25].

Datura

Datura is a plant belonging to Solanaceae family containing hyoscine and scopolamine as chemical constituents that has analgesic and anti-inflammatory effect[26]. This plant can reduce the incidence of withdrawal symptoms due to its anticholinergic effect through limbic system, neuronal circuits and autonomic system. It was also found to reduce morphine withdrawal symptoms like diarrhea and bruxism or jaw clenching in male rats[27].

Chamomile

Chamomile is the most popular herbal tea obtained from dried flower heads of plants -*Matricaria recutita* L., *Chamomilla recutita* L., *Matricaria chamomilla.* The main constituents of this plants are phenolic compound, flavonoids like apigenin, quercetin, patuletin, luteolin and glucosides. Kesmati *et al* studied on aqueous and hydroalcoholic extract of chamomile on morphine withdrawal and found that the hydroalcoholic extract of chamomile contains apigenin and chrisin can induced sedative effects on some of morphine withdrawal symptoms like rearing and grooming. They suggest that these constituents act on neurochemical systems of dependence in the CNS thereby, reduce the symptoms of morphine withdrawal syndrome[28].

Peganum harmala

Peganum harmala is a plant known as wild Syrian rue belonging to the family Zygophyllaceae. Beta-carboline alkaloid such as harmalol, harmine and harmaline are the important constituents presents in this plant[29].

Peganum harmala is characterized as one of the monoamine oxidase and serotonin inhibitors. The alkaloid harmaline plays an important role in eliminating some of the withdrawal symptoms by influencing the opioid circuits, receptors, limbic system and autonomic nervous system in the brain. Studies have found that oral administration of *Peganum harmala* powder can reduce the incidence of withdrawal symptom[30].

***Piper methysticum Forst* plant extract**

Piper methysticum extract is herbal remedy commonly known as kava, traditionally used by pacific islander and indigenous Australians for psychiatric treatment of anxiety and insomnia; smoking and alcohol cessation[31].

Supporting evidence has also provided by the clinical research that administration of kava reduces the patients desire towards their drug of choice and significantly promotes self-restraint in drug-dependent patients. Hence, can be considered as an alternative anti-craving medicine[32].

Pharmacological action of kava is due to activation of lipid soluble group called kava lactones that can bind to many brain sites and interact with multiple neurotransmitters and inhibit the update of noradrenaline, glutamate release and affect the concentration of dopamine and its metabolites associated with behavior alteration in rats[33].

Radix Puerariae

Radix Puerariae is the root of a plant Peurariae belonging to the family Leguminosae. Almost thousand years ago this plant was used as an anti-alcohol intoxication, anti-dipsotropic agent[34].

Preclinical studies of *Radix Puerariae* have shown to have inhibitory effects on ethanol. Its crude extract diadzin and daidzein are found to suppress free choice ethanol intake in golden Syrian hamsters and Wistar rats. On termination of treatment the intake levels returned to baseline. Regular consumption of *Radix Puerariae* root resulted in significant reduction in alcohol consumption in alcohol preferring rats[35].

***Thunbergia Laurifolia* (Linn.)**

Thunbergia Laurifolia is one of Thailand traditional medicine known for its anti-alcoholism, antipyretic and antidote treatment. Chanawirat *et al* found that the leaf extract has protective effect on mice from ethanol-induced hepatic injury[36].

Thunbergia Laurifolia increase the blood flow to brain areas such as nucleus accumbens, amygdala, frontal cortex and caudate-putamen which are related to reinforcing and rewarding pathway of addictive drugs[37].

2. SYNTHETIC DRUGS USED FOR TREATMENT OF ADDICTION

Opioid Addiction

Methadone

It is a long acting synthetic opioid agonist that prevent and reduce withdrawal symptoms and craving in individual who is opioid addicted. The effect of illicit opioids can also be blocked by this drug. No euphoric effect can be produced and it can also prevent addiction from any high feeling due to cross tolerance mechanism on Heroin injection. Heroin addicts are recommended to take one oral daily maintenance dose for normal function. Methadone is an FDA approved drug for long term treatment of opioid addiction[38].

Buprenorphine

Buprenorphine is a synthetic opioid medication with partial agonist on opioid receptors. It has the capability to reduce or eliminate withdrawal symptoms associated with opioid dependence and with less risk of overdose. Buprenorphine is available in the market as a single drug or in combination with naloxone (e.g.; Suboxone), implant and injection[39].

Naltrexone

Naltrexone is an opioid antagonist that block opioids from binding to their receptors and thereby can prevents euphoric effect. It was used to reverse opioid overdose and treatment of opioid addiction. This is based on the mechanism that repeated absence of abusive opioid and its desired effect can gradually diminish craving and addiction[40].

Tobacco addiction

Bupropion

Bupropion is an antidepressant drug which is also prescribe as an aid in smoking cessation. It produces mild stimulant effects by blocking the reuptake of neurotransmitters such as norepinephrine and dopamine. Bupropion has the tendency to reduce the severity of nicotine craving and withdrawal symptoms. It increases the chance of quitting smoking by approximately 1.6-fold. The exact mechanisms of its action in smoking cessation is not clear but has FDA approval for smoking cessation treatment[41].

Varenicline

Varenicline is the latest FDA approved medication for smoking cessation. It acts either as a partial agonist or antagonist on the nicotine receptors in the brain that involved with the rewarding effects of nicotine- It stimulates the nicotine receptors but not sufficiently trigger the dopamine release which is important for nicotine rewarding effect. The activation of dopamine by nicotine can be block by Varenicline. Hence, can reduce cravings and supporting abstinence from smoking[42].

Nicotine replacement therapy (NRT)

Nicotine replacement therapy is a treatment to help people quit smoking by giving the product that supply low dose of nicotine and with less toxins. The goal of this therapy is to cut down craving for nicotine and eliminate the nicotine withdrawal symptoms. Numbers of formulations are available including- transdermal nicotine patch, nicotine spray, nicotine gum and lozenges. Research found that combining the patch with other replacement therapy is more effective than a single therapy[43].

Alcohol addiction

Disulfiram

Disulfiram is used in the treatment of chronic alcoholism by producing acute sensitivity to alcohol. The mechanism of action is by inhibiting the enzyme acetaldehyde dehydrogenase that interferes with alcohol degradation resulting in accumulation of acetaldehyde and in turn produces a very unpleasant reaction that includes flushing, nausea, throbbing headache, vomiting and palpitation if a person drinks alcohol. Hence, it used as a second line treatment for alcohol dependence[42].

Acamprosate

Acamprosate is a drug used in treating alcohol dependence. Its mechanism of action is by binding on the GABA and glutamate neurotransmitter systems thereby, reduce the symptoms of protracted withdrawal such as insomnia, anxiety, restlessness and dysphoria. It is very effective in patient with severe dependence[44].

Topiramate

Topiramate is an anticonvulsant drug and usually prescribed as off-label (non-FDA approval) for helping alcohol-dependent individuals to stop drinking and in alcohol use disorders. Topiramate shown to reduce alcohol cravings in patient with alcohol use disorders. The exact mechanism of its action is unknown but the possible mechanism suggested that it work by increasing inhibitory (GABA) neurotransmission and reducing the stimulatory (glutamate) neurotransmission[45].

3. OTHER THERAPIES FOR ADDICTION

Acupuncture therapy

Acupuncture is a Chinese traditional medical technique developed based on the theory that diseases are caused by blockages in the flow of internal energy. Acupuncture stimulates the point related to energy flow and breakage of blocking that subsequently restore the energy flow and healthy body functioning[46].

Over the past many years, acupuncture has been used to treat addiction to various substance of abuse. Up to date acupuncture is used to treat withdrawal syndrome in many treatment centers across US and Europe[47].

Zhang *et al* found that acupuncture treatment and electrical stimulation Is more effective than clonidine in withdrawal syndromes of opioid addiction such as insomnia, anxiety, pain and clinical study have revealed that this treatment has fewer side effect[48].

Clinical study has shown that patients who are receiving acupuncture treatment are more likely to produce cocaine negative urine samples with significant improvement and negligible side effect compare to that of the control patients[49].

Acupuncture has also supported for smoking cessation and report shown that patients remained abstinence during treatment and quit smoking after three acupuncture treatments[50].

Aroma therapy

Aromatherapy is a is a holistic therapy that uses aromatic ingredients or essential oils to help people feel better either physically, mentally, spiritually and emotionally. it is also used in religious spiritual purposes. Aromatherapy is named because essential oils are consumed through inhalation[51]. In addiction, the physical and mental health of an individual is altered hence, essential oil can be used

as an alternative treatment to normalize the health issue related to addiction (Table-1)[52].

Aromatherapy is beneficial in many ways to overcome addiction including- controlling cravings, gaining mental clarity, staying present, enabling physical ailments and regulating emotions[53].

Yoga therapy

Yoga therapy is effective in rehabilitation of drug addicts. Breathing exercise (*Anulom- Vilom Pranayam*) helps to balance and calm the mind, increasing mental clarity and alertness. Relaxation (*Savasana*) are useful in reducing mental tension and anxiety. Meditation usually transcendental meditation that focus the mind on some mantra sound are done to achieve transcendental state of consciousness[54].

Table 1: Essential oils used traditionally for various addiction treatment.

For opiate and opioid withdrawals	For alcoholism	For stimulant addiction
Lavender oil- calming	Black pepper oil- reduce craving	Orange oil- uplift mode and increase focus
Ylang ylang oil- reduce fear and agitation	Roman chamomile oil	Peppermint oil- provide energy boost
Eucalyptus oil- stimulate mind & body and reduce lethargy	Lemon oil- support a recovering immune system.	Jasmine oil- soothes and relax
Cinnamon oil- decrease confusion, stress, fear and doubt	Peppermint oil- reduce pains during withdrawal symptoms	
Peppermint oil- mental clarity	Grapefruit oil- reduces hangover	
Rosemary oil- improve memory and concentration	Ginger oil- hepatoprotective	
Bergamot oil-- relieve tension		

Nutritional therapy

It is well known that substance or drug abuse can successively impair an individual ability to consume a balanced diet and also reduces many essential vitamins and minerals in the body. Which further aggravate sleep disturbance, poor digestion and compromised nervous system. Hence, adequate nutrition and hydration are vigorous to substance use treatment for reinstating physical and mental well-being and for endorsing long term recovery[55].

Horticulture therapy

Horticulture therapy is comparatively new therapy when compared to traditional forms of therapy. This therapy involves connecting of affected human with nature via gardening. Dr Benjamin Rush found that engaging gardening improved the patient's mental health. There are many potential benefits that can be gain from horticulture therapy such as – reduces stress, improves mood, strengthen memory and cognitive function, improve physical coordination and balance, increase muscle tones through movement and decrease the sense of isolation[56].

CONCLUSION

Major advances in understanding of neurobiological effect of addictive substances and their short- and long-term consequences in the brain can be provided by using a refined preclinical model such as CPP, drug self-administration and cue induced paradigm or models etc. Numerous plants and/or active principles have verified with varied mechanism of action in treatment of addiction which may be effective when used alone or in combination with other approaches such as nutrition's, body work out, acupuncture, Yoga, aromatherapy, relaxation and exercise that support the entire health of the patients.

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