

Advances in the Management of Psycho-Active Substance Dependence

R.C. Jiloha*, Soumiya Mudgal**

Director Professor & Head* Senior Resident**

Department of Psychiatry, G.B. Pant Hospital & Maulana Azad Medical College, New Delhi, India

Abstract: Over last 30 years majority of work has elucidated the role of mesolimbic dopamine system and related complex limbic circuits including amygdala, hippocampus, and medial prefrontal cortex in acute rewarding properties of psychoactive substances and also its role in craving and relapse. Recent studies have explained the role of mesolimbic – DA pathway as a reward predictor (omission or unexpected) than what was earlier considered as predictor of nature of reward. Specific brain areas have been known to be responsible for various addiction behaviours like nucleus accumbens for cue mediated drug seeking, amygdala for motivation and stress mediated relapse and anterior cingulate cortex for cue induced craving plus discrimination of reward stimuli from multiple stimuli. Neuro-adaptation by mechanism of long term potentiation and long term depression in mesolimbic area specially VTA due to impairment of astrocytic reuptake of glutamate leading to neuroplasticity is being implicated as core reason of compulsion to take substance, salience and continuous use. Latest pharmacotherapies for management of psychoactive substance like nicotine, alcohol, cocaine and cannabis have shown promising results though motivational enhancement and evidenced based psychosocial interventions are essential along with them to improve treatment results and prevent relapse. Understanding of neurobiology of addiction and mechanisms of persistent changes is critical for development of new pharmacotherapies and better utilisation of existing treatment modalities. Vulnerability to relapse and prevention of relapse is the challenge and need of further research.

Keywords: dependence, mesolimbic pathway, neuroplasticity, addiction treatment, relapse prevention.

INTRODUCTION

The contemporary drug situation in the world is a unique phenomenon unlike any experienced before. In fact, the use of psycho-active substances is a universal and traditional phenomenon which has long been a complex, often highly volatile social concern¹. An estimated 4,000 plants yield psycho-active substances, and about 60 of these drugs have been in constant use, somewhere in the world, throughout history – with cannabis, opium, cocaine, tea, coffee, tobacco and alcohol predominantly². The range of psycho-active substances continues to expand and their psycho-social antecedents change with time. Drug seeking and drug taking behaviour refers to compulsive drug use that is derived by strong, often irresistible urge. It can persist despite a desire to quit or even repeated attempts to quit. Addiction is a primary brain disease which is determined genetically, expressed biochemically and has psycho-social consequences. These consequences can and do occur in all aspects of addict's life, influencing the social, vocational, legal, family, spiritual, psychological and physical spheres. The disease is also characterized by its chronic, progressive, relapsing and lethal nature³. Four cardinal features generally seen in addiction are:

- Loss of control over the use of drug.
- Continuous use despite of adverse consequences.
- Compulsive use
- Craving when the drug is withheld.

International Classification of Diseases, 10th Revision (ICD-10)⁴ by World Health Organization (WHO) defines drug dependence as, "A state psychic and sometimes also physical, resulting from the interaction between a living organism and a drug, characterized by behavioural and other responses that always include a compulsion to take the drug on a continuous or periodic basis in order to experience its psychic effects, and sometimes to avoid discomfort of its absence." Tolerance may or may not be present⁵.

Drug dependence refers to the progressive adaptation of cells, circuits, and organ systems in response to excessive exposure to a drug. Thus, dependence represents a new equilibrium of physiological functions in response to the repeated, continuous exposure to a drug and the related organism's compensatory counter-mechanisms. Tolerance to the drug occurs if one observes either a decrease in the effect of the drug despite delivery of a constant dose or the need to increase the dose to maintain drug efficacy.

Over the last 30 years, a vast majority of work confirmed the role of the

mesolimbic dopamine (DA) system and related limbic circuits including the amygdala, hippocampus, and medial prefrontal cortex, in the acute rewarding properties of drugs of abuse and also in mechanisms of craving and relapse. Importantly, this work also revealed that most drugs of abuse are sharing common neural, molecular, and neuro-chemical substrates to produce acute reward and long-term neuro-adaptations, which ultimately lead to addiction. The understanding of those mechanisms responsible for persistent changes in the so called reward pathways is critical for the development of new pharmacotherapies for the treatment of drug dependence and addiction⁶.

NEUROBIOLOGICAL SUBSTRATES OF DRUG CRAVING AND ADDICTION

Most drugs of abuse have the following characteristics:

(1) they produce an effect that is sufficiently pleasant or rewarding to reinforce self-administration; (2) they produce an effect that the recipient can use to discriminate the drug from others; and (3) they elicit a sustained increase in extra-cellular DA in the mesolimbic system that originates in the ventral tegmental area (VTA) and projects towards limbic forebrain regions including the nucleus accumbens (NAc).

This increase in mesolimbic DA activity would then facilitate incentive learning or the attribution of positive incentive salience to cues. These cues include the discriminative cue properties of the drug itself, which are associated with its administration. Thus, any responses to the drug, which occur during the period of raised extracellular DA, may have the potential to acquire positive incentive salience and contribute to the progressive enhancement of the attention processing of drug-related cues. Such attention bias towards drug-related cues would elicit drug craving and contribute to compulsive drug use.

IS DOPAMINE A COMMON SUBSTRATE OF ADDICTIVE DRUGS' ACTION?

The DA hypothesis of addiction may hold true for psycho-stimulants, but the situation for drugs such as opiates⁷, nicotine⁸, and phencyclidine⁹ may be more complex than originally thought¹⁰.

Moreover, concept that the meso-limbic DA system simply encodes hedonic tone has been called into question. Enhanced dopaminergic activity in the NAc is not only elicited by reward-related stimuli, but can also be triggered

by aversive stimuli or exposure to a novel environment that has no obvious rewarding property¹¹. Furthermore, analysis of response patterns of single DA neurons to reward presentation has led to the suggestion that meso-limbic DA may be more involved in prediction of reward and the use of such information to strengthen behaviours and increase their future likelihood¹²⁻¹⁵.

Thus, the DA signal may constitute an alert message about reward prediction error, which rapidly informs postsynaptic structures about unexpected rewards or reward omissions, without detailed information about the nature of the reward *per se*. Such a reward alert signal would allow rapid behavioural reactions towards rewarding stimuli, while the exact nature of the reward would be evaluated by slower systems during the approach behaviour to the rewarding stimulus¹⁶. Third, rats with extensive neuro-toxic lesions of the DA neurons in the NAc show normal hedonic response patterns to sucrose¹⁶. Finally, a drug like cocaine is still rewarding in mutant mice lacking the DA transporter (DAT)¹⁷⁻¹⁸ suggesting that additional transporters and/or mechanisms contribute to the reinforcing properties of the drug.

Together these findings clearly support the idea that the mesoaccumbens DA system is involved in learning the *motivational significance* of a stimulus rather than mediating the hedonic value of the stimulus *per se*. These studies also highlight the need to direct investigations towards complex neurocircuits including brain regions such as the amygdala, hippocampus, and medial prefrontal cortex, which play an important role in the core feature of drug addiction that is the compulsive seeking and taking of the drug as well as risk of relapse.

BEYOND THE MESO-ACCUMBENS DA PATHWAY: NEURAL SUBSTRATES OF RELAPSE OR REINSTATEMENT OF DRUG SEEKING AND DRUG TAKING BEHAVIOUR

The circuitry that mediates reinstatement of drug seeking behavior remains largely unknown, but involves at least core regions such as the NAc, the amygdala and medial prefrontal cortex. The presentation of a drug-associated conditioned stimulus (CS) to animals can induce large conditioned increases in DA neurotransmission in the NAc^{19,20}, suggesting that DA in the NAc is involved in cue controlled drugseeking behaviour²¹. However, the amygdala has been shown to play an important role in drug enhanced stimulus-reward associations^{22,23} which may underlie drug craving and compulsive drug taking in humans^{24,25}. Enhanced monoaminergic tone in the basolateral subregion of the amygdala (BLA) appears to increase the motivational properties or salience of cocaine-associated cues during reinstatement of cocaine-seeking behaviour, whereas inactivation of the BLA produces the reverse effect²⁶. The central amygdala (CeA) may mediate conditioned increases in DA measured in the NAc following the non-contingent presentation of a CS²²⁻²³ perhaps *via* projections to the VTA²⁷ and seems to also play a key role in stress triggered relapse to cocaine-seeking behaviour^{28,29}. Finally, the anterior cingulate cortex (ACC) seems to serve as a common link in the neural circuitry underlying reinstatement of drug seeking behaviour³⁰⁻³³.

Functional magnetic resonance imaging (fMRI) and PET scan studies have shown that regions typically activated during drug craving partially overlap those activated during a working memory^{34,35} suggesting that both craving and attentional processes may involve similar neural circuits. The ACC is activated both in selective attention and response competition processes⁴¹⁻⁴³ as well as in cue induced cocaine craving⁴⁰⁻⁴². Importantly, the ACC has reciprocal connections with both the amygdala and NAc. Thus, one may suggest that the ACC, in concert with the NAc and the amygdala, contributes to discriminate between multiple stimuli on the basis of their association with reward. This notion further supports the idea of DA release in key terminal projection areas of the mesolimbic system as an error prediction signal to modify synaptic weights depending on the valence (better than-expected *vs.* worse-than-expected) of the environmental stimuli. Sustained increase of the DA signal following exposure to drugs of abuse or stress might result in an attentional narrowing towards reward-related stimuli, which would lead to craving and ultimately relapse^{43,44}.

DRUG ADDICTION, NEUROADAPTATIONS AND SYNAPTIC PLASTICITY

We have hypothesized that changes in the ACC-NAc amygdala pathway may only partly explain enhanced focusing towards drug-related stimuli and that alteration of the rheostatic role of DA in this circuit may lead to the inability to control the intake of the drug and the intense craving to seek for and take the drug. If this hypothesis has credence, then one must posit that neuro-adaptations progressively occurred in specific brain regions. These neuroadaptations may translate to mechanisms of synapse specific plasticity such as long-term potentiation (LTP) and long-term depression (LTD). Indeed, there is growing evidence suggesting that exposure to drugs of abuse including cocaine, morphine, nicotine and ethanol can elicit LTP at excitatory synapses in the meso-limbic DA system, in the VTA in particular^{46,47}. Importantly, stress can also trigger LTP at VTA synapses⁴⁵. The exact mechanisms by which most drugs of abuse and stress elicit LTP at VTA synapses are ill understood, but one may hypothesize that drug-or-stress-induced increase in extra-cellular glutamate levels in the VTA plays an important role in this process. In fact, exposure to psycho-stimulants produces an increase in glutamate efflux in the VTA, probably through an impairment of the astrocytic reuptake of glutamate^{48,49}. In addition, nicotinic acetylcholine receptors are localized on presynaptic glutamatergic nerve terminals in the VTA, and activation of these receptors by nicotine has been shown to increase glutamate release⁵⁰. Thus, enhanced glutamate efflux in the VTA may promote LTP at excitatory synapses on DA neurons. This LTP mechanism may be even more effective if one considers that several drugs of abuse also block LTD at VTA synapses^{51,52}.

Together, these findings support the idea that drugs of abuse produce persistent behavioural changes that are most probably mediated by long-lasting changes in synaptic weights in key brain pathways. In fact, recent studies have shown that the repeated administration of either amphetamine or cocaine produces an increase in dendritic spine density and an increase in the number of branched spines in the rat NAc and prefrontal cortex^{53,54}. The question of whether or not there is a causal relationship between altered synaptic weight in specific brain circuits and particular behavioural phenotypes remains to be demonstrated.

CURRENT PHARMACOTHERAPEUTIC STRATEGIES FOR THE MANAGEMENT OF DRUG ADDICTION CURRENT PHARMACOTHERAPIES FOR NICOTINE DEPENDENCE

Nicotine Replacement Therapies

Advances in nicotine dependence treatment show that till now, nicotine replacement therapies (NRTs) have shown superior efficacy in all placebo-controlled clinical trials at both short-term (end of trial) and long-term (6-12 months) assessments. NRTs are currently available in two main formulations, including the slow-acting transdermal nicotine patch (TNP) formulation, and faster-acting formulations such as the nicotine gum, nicotine nasal spray, nicotine vapour inhaler, and the nicotine lozenge. The rationale behind the use of NRTs is to provide relief from tobacco withdrawal by replacing sufficient levels of nicotine from an alternative source than smoking behaviour. NRTs seem to reduce the reinforcing effects of smoking cigarettes and to disrupt the usual pairing of nicotine with environmental cues.

The trans-dermal nicotine patch (TNP) delivers approximately 1 mg of nicotine per hour for up to 24 hours. TNP consisting of 15, 10 and 5 mg nicotine are worn successively over a period of 16 weeks^{55,56}. The efficacy of TNP treatment is further supported by a dose-response relationship between the nicotine content of the patch and smoking cessation success rates⁵⁷. Nasal sprays are capable of faster systemic nicotine delivery than gum or TNPs, and their use is recommended for rapid relief of craving symptoms. The efficacy of nasal sprays has been demonstrated in a randomized placebo controlled study, which showed that abstinence rates associated with spray

and placebo use were 32% and 12%, respectively, at 6 months, and 26% and 10%, respectively, at 1 year⁵⁷. Lozenges deliver nicotine through mucosal membranes, and their use is recommended for rapid relief of craving symptoms. Lozenges containing 1 mg nicotine can be administered every 1 or 2 hours up to a maximum of 25 mg per day.

Sublingual NRT spray preparations are also readily absorbed across mucosal membranes and up to one spray per hour can be used for prompt relief of withdrawal symptoms. NRT can also be delivered using inhaler devices, which consist of a mouthpiece and plastic cartridge containing 4 mg nicotine. A double-blind placebo-controlled trial found that 28% of subjects who received inhaled NRT therapy attained smoking abstinence at 1 year, compared with 18% in those who received placebo⁵⁸⁻⁶¹. The nicotine inhaler delivers 5 mg nicotine that is absorbed *via* the lining of the mouth rather than the lungs, typically providing 30% of the nicotine derived from cigarette smoking.

Sustained Release Bupropion (Bupropion SR)

Randomized studies have demonstrated efficacy and tolerability of bupropion SR^{62,63} with the most robust anti-smoking effects at a dose of 300 mg/day. Recent studies have extended its use to prevent relapse to nicotine-seeking behaviour after the initial achievement of smoking cessation⁶⁴. A double-blind, placebo-controlled study also examined the effects of bupropion SR, TNP, or combined treatment, and combination therapy was found to be superior to either alone.

Cessation rates at 1 year after attempted quitting were 16% for placebo, 16% for bupropion SR, 30% for NRT, and 36% for combined therapy.

Other Pharmacotherapeutic Strategies

Mecamylamine is a non-competitive nicotinic receptor antagonist, which has shown promise as an adjunct to TNPs^{65,66} although further studies must confirm these trends. The use of selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine alone⁶⁷ or in combination with NRT^{68,69} have yielded either equivocal or negative results. Similarly, the use of the 5-HT1A partial agonist Buspirone might be potentially interesting in anxious smokers although a placebo-controlled trial failed to support its efficacy in smoking cessation⁷⁰. Several clinical trials demonstrated that the alpha2- adrenoceptor agonist clonidine has modest efficacy in smoking cessation trials⁷¹⁻⁷⁴. However, significant side-effects, including orthostatic hypotension, might limit its use. Preliminary studies have also investigated the efficacy of naltrexone alone or when given in combination with TNPs⁷⁵, but the results gathered so far have been largely inconclusive. Finally, lobeline, which is a nicotine-like alkaloid, and silver acetate, which causes an aversive taste when combined with cigarette smoke have been suggested as smoking cessation aid^{76,77}.

CURRENT PHARMACO-THERAPIES FOR ALCOHOL DEPENDENCE

Alcohol dependence is a significant problem in India. In the National House Hold Survey 2004, 21% adult males and 5% adult females were found to be using alcohol and 50% of them satisfied the criteria for hazardous drinking. Alcohol users in India experience greater health events in their life course. Alcohol Detoxification means cleaning of alcohol from the body and readjusting all systems to function without alcohol.

Benzodiazepine pharmacotherapy is quite effective in detoxifying alcoholics. Alcohol dependence needs controlled detoxification with help of an attenuation therapy e.g. benzodiazepines to avoid withdrawal symptoms/ complications. It can be done on outdoor basis but in-patient care is recommended when: patient is at risk of suicide, without social support and patient has a history of severe withdrawal reactions. On the out-patient basis, daily supervision to detect complications should be done, multivitamin preparations be given to prevent Wernicke's encephalopathy, benzodiazepines to prevent withdrawal symptoms should be given. Benzodiazepines, longacting forms are used to reduce tremor and agitation e.g. diazepam or chlordiazepoxide. Short-acting benzodiazepines are used for seizures e.g. lorazepam intravenously. To avoid dependence on benzodiazepines - advise

short courses at lowest necessary dose. Vitamin B complex is given as IV for a couple of days and then patients are given oral thiamine and multivitamins. Intravenous therapy with vitamin B complex is used to treat Wernicke-Korsakoff syndrome. Beta blocker, can be used to reduce autonomic hyperactivity but are rarely used in practice as the long-acting benzodiazepines are usually sufficient.

For relapse prevention, disulfiram became the first drug approved by FDA for alcohol dependence treatment. There are currently four main pharmacological strategies used to treat alcohol dependence, which led to positive findings: aversive agents (disulfiram), acamprosate, naltrexone, and the treatment of co-morbid psychiatric disorders.

The great majority of studies assessing the efficacy of treatment with aversive drugs such as disulfiram have yielded some positive results compared with placebo only when distribution of the drug was supervised⁷⁸⁻⁸⁰. Disulfiram is used for more than 45 years. It inhibits alcohol dehydrogenase, which converts aldehyde to acetate in normal alcohol metabolism. Disulfiram administration in alcoholics increases acetaldehyde level 5 to 10 times more than without disulfiram treatment. Alcohol-disulfiram reaction is characterized by, flushing, weakness, nausea, tachycardia, hypotension and death. Standard dose of disulfiram is 250 mg per day⁸¹⁻⁸³.

Acamprosate has structural similarity with gamma-aminobutyric acid (GABA) and normalizes the dysregulated glutamatergic system during alcohol abstinence and thus prolongs abstinence from alcohol drinking. It is absorbed poorly with oral administration and higher dose of 2 gm per day in three divided doses is required. Studies suggested that acamprosate is efficacious in preventing relapse to alcohol drinking for up to 12 month post-treatment. Prevention of relapse to heavy drinking has been most consistently reported.

Naltrexone, an analogue of naloxone, is a relatively pure opioid antagonist with highest affinity for mu-opiate receptor type. It is better absorbed orally and has longer duration of action than naloxone.

Animal studies suggest that opioid receptors may participate in mediating the reinforcing effects of alcohol. Naltrexone 50 mg per day decreased alcohol consumption as adjunctive therapy in alcohol dependence. Naltrexone reduced alcohol craving, days of drinking per week, and rate of relapse. In contrast with acamprosate, the safety profile of naltrexone might be problematic and poorly tolerated side effects such as nausea, headache and hepatotoxicity may limit its therapeutic use.

The efficacy of acamprosate and naltrexone as pharmacotherapies for alcohol dependence has been assessed in several randomized, double-blind, placebo-controlled trials across countries. A recent finding suggests that co-administration of acamprosate and naltrexone significantly increases the rate and magnitude of absorption of acamprosate^{84,85}. Combination is said to be more effective than the individual therapy.

Topiramate is an antiseizure medication with multiple pharmacological effects in the brain including potentiation of GABAergic transmission, blockage of AMPA/kainite subtype of glutamate receptors, inhibition of sodium and calcium currents and inhibition of carbonic anhydrase. Based on these effects, topiramate is considered to be useful for the treatment of alcohol dependence by blocking the reward effect of alcohol. In a 12-week study, topiramate was found to decrease drinking in comparison to placebo.

Serotonergic agents such as fluoxetine and citalopram have demonstrated efficacy in reducing alcohol consumption in some studies, and 5-HT antagonist ondansetron, in a recent study was found to be effective in reducing craving in early onset alcoholics.

CURRENT PHARMACO-THERAPIES FOR COCAINE DEPENDENCE

The review of multiple clinical trials leads to one single conclusion: there are currently no efficacious pharmacological strategies for the treatment of cocaine dependence and addiction. Although some preliminary findings may have looked promising, most trials have demonstrated the lack of efficacy of compounds such as naltrexone^{86,87}, risperidone and pergolide^{88,89}, desipramine and carbamezapine⁹⁰, amantadine⁹¹, nootropic agents such as piracetam

and ginkgo biloba⁹², or olanzapine⁹³.

Dopaminergic Medications: amantadine is used for the treatment of Parkinson's disease and drug-induced extra-pyramidal reactions.

It increases dopaminergic transmission by augmenting the release and inhibiting the reuptake of dopamine. It also has antagonistic effect on cholinergic and N-methyl D-aspartate (NMDA) receptors.

Amantadine 100 mg twice daily showed modest efficacy at two weeks and one month follow-up.

Disulfiram; inhibits the acetaldehyde dehydrogenase enzyme, increasing acetaldehyde level after alcohol consumption. Disulfiram also inhibits dopamine-beta-hydroxylase which converts dopamine to norepinephrine and leads to increased dopamine and decreased norepinephrine levels in the brain, yielding some dopamine agonist like effect. In a 12-week trial, disulfiram (250 mg per day) treatment was associated with greater reduction in cocaine use.

Gamma-aminobutyric acidergic medication such as tiagabine which is an antiseizure medication increases the synaptic levels of GABA by inhibiting a GABA transporter. In a 10-week study 24 mg per day of tiagabine was found to have greater reduction in cocaine use than placebo. Baclofen, an antispasticity agent, is a non-selective GABAB agonist that activates pre- and post-synaptic GABAB receptors. In a 16-week double blind study baclofen 60 mg per day was found to have greater reduction in cocaine use as compared to placebo.

Cocaine activates the adrenergic system, mediating the physiological responses including heart rate, blood pressure and arousal. Studies show that alpha and beta adrenergic blockers, labetalol and carvedilol effectively attenuated smoked cocaine induced heart rate and blood pressure changes. Carvedilol which has a better CNS access, was more effective in attenuating the heart rate and blood pressure changes. At 25 mg daily dose, carvedilol also attenuated the cocaine self-administration suggesting that adrenergic blockers may attenuate the reinforcing effects of cocaine.

In summary, most of these clinical trials generated equivocal results and the efficacy of the compounds mentioned above remains uncertain mainly because their potential benefits have not been reproduced in well-designed placebo-controlled studies. An additional issue with regards to cocaine addiction is that cocaine addicts are most often poly-substance abusers who use different combinations of cocaine, opioids, alcohol and benzodiazepines. This fact has led several authors to suggest that treatment of poly-substance abusers with either methadone or buprenorphine may reduce both heroin and cocaine consumption⁹⁴⁻⁹⁹. This hypothesis, however, has not been confirmed by other studies¹⁰⁰⁻¹⁰² and there is a need for additional work to clarify.

CURRENT PHARMACO-THERAPIES FOR OPIATE DEPENDENCE

The modern era of opiate pharmacotherapy is often attributed to Dole and Nyswander's introduction of Methadone maintenance in 1964. It is a mu-opioid receptor agonist, a potent opiate analgesic with properties similar to morphine including euphoria, drowsiness, analgesia, respiratory depression, constipation, nausea, vomiting, itching and constriction of pupils, and has been used extensively for the treatment of pain. With continuous use tolerance develops to these effects. It is well absorbed orally and suppresses opiate withdrawal symptoms.

Because of long duration of action, once daily dose of methadone is sufficient to control heroin withdrawal symptoms. At higher doses (100 mg or more per day), methadone blocks the effect of other opioids by development of cross-tolerance. For maintenance treatment of opioid dependence, the usual starting dose is 20-30 mg, with 5 to 10 mg increase every alternate day. Higher dosage (80-100 mg per day) is more effective in reducing illicit opioid use. Once daily dosing required the patient's daily attendance to the clinic impeding vocational rehabilitation. This led to development of Levo-alpha-acetylmethadol (LAAM), a congener of methadone, which can be administered 3 times weekly because of the presence of active metabolite which combines to confer a long duration of action. Its long duration of

action allows dosing at 48- or 72 hours interval for opioid maintenance treatment. LAAM use has been associated with QT interval prolongation, ventricular tachycardia, angina pectoris, myocardial infarction and cardiac arrest. Therefore, it is not in use. The serendipitous observation that clonidine, an alpha agonist, can suppress symptoms of opiate withdrawal led to its adoption for opiate detoxification in 1980s and 1990s. Clonidine has considerable sideeffects, notably sedation and hypotension. An analogue of clonidine, lofexidine, is being used in some countries. Lofexidine is a potent vasodilator antihypertensive. In a double-blind, randomized, placebo controlled, subjects that remained on lofexidine + opiate antagonist regimen were more likely to remain opiate-free, were more compliant, had decreased cravings and lower perceived stress compared with patients receiving placebo. First synthesized in 1963, Buprenorphine is a potent analgesic, a derivative of thebaine and a partial mu-opioid agonist and a weak kappa opioid antagonist, it is used for moderate to severe pain. Since 1970s, buprenorphine is used as substitute for morphine to suppress opiate withdrawal having modest withdrawal of its own. The short-acting opioid receptor antagonist naloxone is effective in preventing nonfatal overdose among opioid addicts¹⁰³. To reduce abuse potential, a combination formulation of buprenorphine and naloxone was prepared in the ratio of 4:1.

However, the best strategy for detoxification still consists in substituting heroin with either the long acting opioid receptor agonist methadone¹⁰⁴ or the partial opioid receptor agonist buprenorphine¹⁰⁵.

An alternative strategy is to use alpha2-adrenoceptor agonists such as clonidine or lofexidine^{106,107} either alone or in combination with an opioid receptor antagonist such as naltrexone or naloxone¹⁰⁸. As with other drugs of abuse, prevention of relapse remains one of the main challenges for the long-term management of opiate dependence. The long-term prescription of naltrexone might be one option, but compliance to treatment makes the efficacy of such strategy rather unlikely^{109,110}, although the use of a 5-week depot formulation of naltrexone might improve treatment outcome¹¹¹. Finally, long-term maintenance programs currently include treatments with methadone, levo-alpha-acetylmethadol (LAAM), and buprenorphine¹¹²⁻¹¹⁴.

CURRENT PHARMACO-THERAPIES FOR CANNABIS DEPENDENCE

Cannabis is obtained from the plant *Cannabis sativa* and contains many psychoactive compounds that affect the endogenous cannabinoid receptor system, of which delta-9-tetrahydrocannabinol (THC) has been identified as the compound primarily responsible for the subjective "high" experienced by users¹¹⁵. The acute effects of cannabis include euphoria, relaxation, dream-like state, altered sensory perception, slowing of time, anxiety/paranoia, and increased appetite. Cannabis also increases heart rate and, in rare instances, can induce hallucinations or psychosis.

THC is a partial agonist of the CB1 receptor, a G-protein-coupled receptor that is expressed in the brain at the highest concentrations in the basal ganglia (motor control), cerebellum (sensorimotor coordination), hippocampus (memory), and cortex (higher-order cognition)¹¹⁶. Cannabinoids stimulates brain-reward areas inducing appetitive drug-seeking and drug-taking behaviors. Exposure to cannabis increased dopamine (DA) release in the mesolimbic dopamine reward pathway, enhanced electrical brain-stimulation reward, established conditioned place preference, and established drug self-administration¹¹⁷. Abrupt cessation of chronic cannabinoid exposure produces cellular changes in the brain reward pathway (increased corticotropin releasing factor, decreased DA) that have been linked to the dysphoric effects associated with withdrawal^{118,119}.

There are an estimated 160 million current cannabis users world wide, and the number of people who meet criteria for cannabis dependence exceeds that for dependence on any other illicit drug¹²⁰.

Treatment admissions for cannabis-use disorders in many areas have steadily increased in the past decade¹²¹⁻¹²³. Clinical trials have demonstrated that evidence-based psychosocial interventions (e.g. Motivational Enhancement, Contingency Management, Cognitive-Behavior Therapy) result in overall improved clinical outcomes compared with usual care or delayed-control

conditions^{124,125}. The majority relapse to use following therapeutic interventions¹²⁶⁻¹³⁵. Thus, there exists a clear need for the development and dissemination of interventions that improve clinical outcomes.

MANAGING WITHDRAWAL SYMPTOMS

Common symptoms of withdrawal include: anger and aggression, anxiety, depressed mood, irritability, restlessness, sleep difficulty and strange dreams, decreased appetite, and weight loss^{136,137}. Chills, headaches, physical tension, sweating, stomach pain, and general physical discomfort have also been observed, but are less common¹³⁶.

Most symptoms begin within the first 24 hours of cessation, peak within the first week, and last approximately 1-2 weeks¹³⁸⁻¹⁴⁰. Because there is evidence that cannabis withdrawal contributes to the high relapse rates among heavy cannabis users^{137,141-143}, amelioration of withdrawal symptoms may be an important target for the development of pharmacological treatment interventions for heavy cannabis users.

Medications tried in cannabis users have been bupropion, divalproex, nefazodone, lofexidine and dronabinol. Bupropion is used clinically as an antidepressant and for smoking cessation, and is thought to exert clinical effects by inhibiting reuptake of NE and DA, and possibly by acting as a nicotine receptor antagonist¹⁴⁴. Divalproex dissociates valproate ions in the GI tract, and, clinical effects are thought to be mediated by increased GABA concentrations in the CNS¹⁴⁵. Bupropion 300 mg/day for 17 days and divalproex 1500 mg/day for 29 days during periods of cannabis abstinence significantly worsened mood compared with placebo^{149,150}.

Nefazodone is an antidepressant and is believed to operate by blocking post-synaptic 5HT_{2a} receptors and, to a lesser extent, by inhibiting pre-synaptic 5HT and NE reuptake¹⁴⁶. Nefazodone 450 mg/day for 26 days significantly decreased ratings of anxiety and muscle pain during abstinence, but did not alter other essential features of cannabis withdrawal¹⁵¹. Lofexidine is used to treat symptoms of opiate withdrawal and acts as an agonist at the alpha₂-adrenergic receptor¹⁴⁷. Lofexidine 2.4 mg/day for 8 days significantly reduced ratings of chills, restlessness and upset stomach and improved sleep, but was associated with increased sedation during the day¹⁵¹⁻¹⁵³.

Dronabinol is used clinically as an antiemetic and appetite stimulant, and is a partial agonist of cannabinoid CB₁ receptor¹⁴⁸⁻¹⁴⁹. Dronabinol has demonstrated to be the most clinically potential drug in reducing cannabis withdrawal. Dronabinol is a synthetic formulation of THC, the primary psychoactive component in cannabis. Dronabinol 10 mg, 5 times/day for 6 days significantly decreased craving, anxiety, misery, chills, self-reported sleep disturbance, and reversed the anorexia and the weight loss associated with cannabis withdrawal¹⁵⁰.

MANAGEMENT OF CANNABIS DEPENDENCE

Cannabinoid (CB₁) receptor antagonist rimonabant significantly attenuated the physiological and subjective effects of smoked cannabis administered 2 hours later^{154,155}. Acute administration of 90 mg rimonabant reduced strength and liking of smoked cannabis by approximately 40% and reduced cannabis-induced tachycardia by 59%. Repeated daily doses of rimonabant (40 mg/day) administered for 15 consecutive days reduced cannabis-induced tachycardia.

Mu-opioid receptor antagonist naltrexone, which has been shown to decrease cannabinoid self-administration in non-humans¹⁵⁶⁻¹⁵⁸, but high dose of naltrexone (50-200 mg) failed to attenuate or enhanced the subjective effects of dronabinol^{159,160} and smoked cannabis¹⁶¹. A lower dose of naltrexone (12 mg) decreased the intoxicating effects of 20 mg but not 40 mg of dronabinol in a recent study¹⁶². These findings indicate that the influence of naltrexone on cannabinoid effects may vary as a function of naltrexone dose, but also that the effect of naltrexone can be overcome with higher doses of cannabis. The effect of dronabinol on the subjective and reinforcing effects of smoked cannabis has also been investigated¹⁶³. Participants received 10, or 20 mg dronabinol, 4 times per day, for three consecutive days. Dronabinol attenuated the subjective effects of smoked cannabis, but did not affect the choice to smoke cannabis (reinforcing effects).

RELAPSE PREVENTION

In one recent study¹⁵² effect of dronabinol (20 mg, 3 times/day) and lofexidine (2.4 mg/day) were evaluated both when administered alone and when administered together. The combination of the two drugs doubled the rate of complete abstinence (25% abstinent for each medication alone, 50% for the combination).

Repeated exposure to drugs of abuse produces long-term molecular and neurochemical changes, which may explain the core features of addiction, that is the compulsive seeking and taking of the drug and the drug-, cue-, or stress-dependent risk of relapse. A growing number of new molecular and cellular targets of addictive drugs have been identified. Furthermore, rapid advances are being made in relating those targets to specific behavioural phenotypes in animal models of addiction. As such, one hopes that current research efforts will lead to the discovery of new pharmacotherapeutic strategies that will help managing the life of those for whom drugs of abuse provided the illusion of control with the sad reality of degradation.

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