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Dr. Nagma Bansal
Tutor Department of Pharmacology, GGS Medical College and Hospital Faridkot, Punjab, India

Dr. Kamalpreet Kaur
Assistant Professor, Department of Pharmacology, GGS Medical College and Hospital, Faridkot, Punjab, India

Dr. Amita Jindal
Senior Tutor, Department of Pharmacology, GGS Medical College and Hospital, Faridkot, Punjab, India

Correspondence
Dr. Nagma Bansal
Tutor Department of Pharmacology, GGS Medical College and Hospital Faridkot, Punjab, India

Vaccines against drugs of abuse: An area to explore

Dr. Nagma Bansal, Dr. Kamalpreet Kaur and Dr. Amita Jindal

Abstract
Drug Addiction and substance abuse is a chronic, relapsing disease wherein the recent years have seen a rise in the number of abusers. The drug user compulsively spends time looking for and using an illegal drug. This form of addiction is characterized by neurochemical and molecular changes in the brain. The present pharmacotherapy is not paving the way to complete solution of the problem, therefore Immunotherapy is looked upon as a great potential to treat this evil. But still a lot of work needs to be done in this field.

Keywords: Drug abuse, addiction, vaccine

1. Introduction
Substance misuse disorder is a major health challenge seen in adults and now even in the younger age groups owing to life styles and work pressures. Drug abuse is a complex phenomenon, which has various social, cultural, biological, geographical, historical and economic aspects. A meta-analysis by Reddy and Chandrashekhar revealed an overall substance use prevalence of 6.9/1000 for India with urban and rural rates of 5.8 and 7.3/1000 population [1].

Treating adolescents for substance abuse requires special consideration of the adolescent's individual experience and how it affects the nature and severity of his or her alcohol or drug use. First treatment goal is "*harm reduction*" by reducing or eliminating (a very gradual process) the non-prescribed drug use [2]. Apart from all established therapies, based on results of preclinical and clinical studies *Immunotherapy* is looked upon as great potential of becoming a *new therapeutic strategy* in the treatment of addiction to psychoactive drugs. It may be used to treat addiction as well as to prevent complications of drug overdose, which may be neurotoxic too [3].

In preclinical studies two immunological methods have been tested first is the *active immunization*, which relies on the administration of vaccines and secondly *passive immunization*, in which directly monoclonal antibodies are given. With successful preclinical studies, researchers have been able to develop vaccines and/or antibodies against addiction of substances like cocaine, methamphetamine, heroin, nicotine and phencyclidine with variable success rates pragmatically [3].

2. How do these vaccines work?
These drugs of abuse on reaching the systemic circulation and undergoing appropriate metabolism usually generates the active metabolite. This active chemical must cross the blood-brain barrier in order to exert psychoactive effects by binding to its specific receptor in the brain. Repeated injections/ingestion of these drugs of abuse have varying degrees of psychological and sometimes physical reinforcing effects that often lead to compulsive drug seeking and use, despite harmful consequences and the person is called addicted to that particular substance. The *rationale* behind creating a therapeutic vaccine to an offending drug is the induction of high levels of specific antibodies that bind the drug in the blood itself and hence prevent it from crossing the blood-brain barrier, thus blocking the reinforcing effect. Speed of infusion is another important factor behind reinforcing actions of intravenously administered drugs of abuse. A beneficial effect will be produced if antibodies to the drug could help retarding the rate of transport of the drug from the blood to the brain. Therefore, an effective vaccine can work by two ways - either by complete sequestration of the drug in the blood or by serving as a "pharmacokinetic antagonist" to slow the speed of entry of the drug into the brain, either of which will result in a diminished psychoactive effect [4, 5]

3. Nicotine Addiction

Tobacco smoking is a commonly seen addiction in almost every strata of Indian society and is also the best known factor of many diseases. Not only males but females are falling prey to this habit [6]. The diseases which can occur after long term smoking are diseases of circulation system, chronic obstructive pulmonary disease, hypertension, atherosclerosis and tumors. Another big issue is passive smoking, which results in increased risk of lung cancer and ischemic heart disease [7]. The treatment of tobacco use usually involves some form of counselling or pharmacotherapy; ideally, both approaches should be combined. Currently available pharmacotherapy for tobacco dependence include nicotine replacement medications in the form of gum, transdermal patch, lozenge, sublingual tablet, nasal spray, and vapor inhaler formulations. The only non-nicotine medication that has been approved by is bupropion. Further, new medications such as Varenicline and Rimonabant are likely to reach tobacco users who are refractory to current treatments [8]. These drugs acts by reducing craving or providing relief from withdrawal symptoms.

An intriguing novel concept is nicotine vaccination [9]. Four conjugate vaccines have been tested in humans:

- NIC002, developed by Cytos, using a virus-like particle;
- Niccine, developed by Independent Pharmaceutica AB, using a tetanus taxoid;
- NicVAX®, developed by Nabi Biopharmaceuticals, using *Pseudomonas aeruginosa* exoprotein A; and
- TA-NIC, developed by Xenova, using a recombinant cholera toxin B subunit.

A Cochrane review reported that in four trials, with a combined total of 2642 smokers, both NicVAX® and NIC002 had no detectable effect on long-term smoking cessation. *Post-hoc* analyses conducted on two studies detected higher cessation rates in participants with higher levels of nicotine antibodies, but these findings are not readily generalizable. However, Niccine has also failed to demonstrate an effect on relapse prevention (defined as preventing smokers who have successfully quit from relapsing to smoking). [10]

Several other nicotine vaccine candidates are in pipeline, yet been tested in humans. These are different from above mentioned vaccines as they are being developed for linking nicotine to a synthetic carrier as opposed to the four above-mentioned biological carriers. Despite disappointing results thus far, new attempts have been proposed to treat nicotine addiction in conjunction with non-nicotine medicines and behavioural interventions [11].

4. Therapeutic Vaccines for Cocaine

Addiction to cocaine is a major problem around the world. According to the World Drug Report, of 81,802 treatment seekers in India in 2004-2005, 61.3% reported use of opioids, 15.5% cannabis, 4.1% sedatives, 1.5% cocaine, 0.2% amphetamines and 0.9% solvents [12]. Currently available options for combating this particular abuse are cysteine pro-drug i.e *N-acetylcysteine* which acts by restoring the inhibitory tone on presynaptic glutamate receptors and has been effective in reducing cue-induced craving and cocaine use in humans. Some newer antiepileptics, such as topiramate or lamotrigine, have shown efficacy in treating cocaine dependence or reducing relapse in humans [13].

Lack of safe and effective, non-addictive therapeutics has instigated efforts to develop alternative approaches for treatment, including anticocaine vaccines [14] The first cocaine vaccine was designed in conjugation with inactivated cholera toxin B resulting in the creation of a molecule capable of stimulating an antibody response [15] These antibodies are cocaine specific; ingestion of the substance by any means (intranasal, inhalational, intravenous) results in its binding and the creation of immune complexes unable to cross the blood brain-barrier due to their relatively larger size [16]. It was estimated that to be successful, the vaccine needed to generate concentrations of anti-cocaine antibodies exceeding 280 nM in order to block peak plasma cocaine concentrations of 500 nM, a concentration previously observed following typical recreational cocaine use. In the Phase IIA study, most but not all of the patients who attained that level of anti-cocaine antibody had more cocaine free urines when these high levels of antibody were present in circulation. However, only one third of the patients produced the levels of anti-cocaine antibody required for this effect. Thus, there is an unmet need to reengineer the existing vaccine formulation for increased immunogenicity and improved cocaine binding in order to treat cocaine addiction using immunotherapy [17].

5. Vaccines against Amphetamine

Methamphetamine (METH) abuse and addiction is a serious public health concern for which successful treatment remains elusive. Behavioural therapy as well as pharmacotherapy's have limited efficacy for treating METH addiction. Recently, Immuno-pharmacotherapy has shown promise as a treatment for drug addiction in recent years [18] It has been seen in studies that active immuno-pharmacotherapy attenuated the rate of the *acquisition* of *d*-methamphetamine (METH) intravenous self-administration in rats by using the MH6-KLH conjugate vaccine previously shown to attenuate locomotor and thermoregulatory effects of METH, as well as to reduce METH entry to the brain [18]. Because of the promising results in animal studies these vaccines may proceed to further clinical development [19].

6. Vaccines against Opioids

Opioid dependence is a serious health problem world-wide. The approved pharmacological treatments like Methadone and LAAM (LevoAlpha-AcetylMethadol) stimulate the cells much as the illicit opioids do, but they have different effects because of their different durations of action. Naltrexone and buprenorphine stimulate the cells in ways quite distinct from the addictive opioids. Each medication can play a role in comprehensive treatment for opioid addiction [20]. Despite the medical treatment for this disorder the relapse rates remain high the reason being high cost, limited availability, problems with compliance. Anti-opioid vaccine can be a hopeful alternative strategy for developing a treatment of this highly prevalent addiction [21]. The immunogenicity and efficacy of such a candidate heroin hapten-carrier conjugate vaccine will depend on many factors, including hapten design, choice of the carrier protein,1,carrier coupling strategy, hapten density (the hapten: carrier molar ratio), and an effective adjuvant formulation that is suitable for human use. [22] Studies have shown that the vaccine inhibited the expression of morphine induced locomotor sensitization, suggesting that it is able to attenuate the psychoactive effects of morphine and heroin. But to maintain a sustained antibody level repeated booster injections of the vaccine are required as the antibodies gradually decrease after the last vaccine injection, this being the one major limitation of drug vaccines is that therefore [23]

Synthetic opioid drug abuse is posing another hindrance in the development of opioid vaccines, as different vaccine was needed for each synthetic drug [24]

7. Vaccine against Alcohol Abuse

Alcoholism is a major problem which affects the society in every aspect. There has been a rapid change in patterns and trends of alcohol use in India. Chief among them is people are beginning to drink at ever-younger ages with an "average age of initiation" dropping from 19 years to 13 years in the past two decades. The percentage of the drinking population aged less than 21 years has increased from 2% to more than 14% in the past 15 years [25]

There are currently three US FDA approved medications for the relapse prevention of alcohol dependence. These are Disulfiram, Naltrexone and Acamprosate. Newer agents like Topiramate and Selective Serotonin Reuptake Inhibitors [26] 5HT-3 receptor antagonist Ondansetron [27] are being investigated for their role in alcohol dependence.

To further improve the results of alcohol de-addiction, a therapeutic vaccine against alcohol was developed in University of Chile, Santiago, in 2013. Animal studies have shown 50% decrease in addiction on genetically induced alcoholism in rats. Soon, clinical trials will be underway. Similar studies on therapeutic vaccine are being done in North Carolina, USA. The mechanism by which these vaccines act is by causing genetic mutation of aldehyde dehydrogenase enzyme, which is the one of the most important enzyme involved in alcohol metabolism leading to accumulation of acetaldehyde which leads to feeling of uneasiness, nausea, and increased heart rate which is also known as medically induced hangover. One injection will have its effect for 6 months, and this effect is not reversible for at least these 6 months [28]

8. Conclusion

From the above discussion we can conclude that addiction is a chronic medical illness and current therapies are not sufficient. Cure for drug addiction is plodding with frequent recurrences which can be reason foe therapy and effort failure but long-term treatment can limit the disease's adverse effects and improve the patient's day-to-day functioning. Vaccines though in the nascent phase of development can prove a reward in conjunction with existing pharmacotherapy in this field but still lot of work needs to be done.

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