Are therapeutic vaccines an answer to the global problem of drug and alcohol abuse?

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Abstract:
Drug Abuse has become a major challenging problem for the society. It affects people of all countries economical strata’s and all ages. According. Monetary loss all over the world regarding drug abuse is in million dollars, it not only has an impact on human productivity and healthcare cost but also on cost of crimes conducted by these drugs and alcohol abuse. Therapeutic vaccine has come as new approach to deal with this problem, after failures in search for a pharmaceutical agent to deal with drug of abuse and alcohol. Research in field of nicotine abuse has gone a way ahead with number of vaccines being tried clinically followed by cocaine, opioids, methamphetamine, phencyclidine and alcohol. All of them have a common mechanism of action by antibody production whereas alcohol acts by genetic intervention. None have being approved yet due to poor results in phase II trials, possibly due to not able to trigger an adequate immunological response. But still quest is on for cracking the ice by developing first successful vaccine against drug of abuse, that would follow for other drugs too. It would be great step in field of therapeutic vaccines for drug abuse after similar successful vaccines being approved for other diseases like cancer.

Key words:
Alcohol, drug abuse, therapeutic vaccines

Drug abuse has become a major challenging problem for the society. It affects people from all countries and economical status. Drug dependence of one person may affect others who are associated with him or her, like family and friends. According to the National Institute of Drug Abuse, monetary loss only in the USA regarding drug abuse was in millions of dollars; it not only has an impact on human productivity and health-care cost but also on cost of crimes conducted by these drugs and alcohol abuse. There has been huge research in finding new medications preventing drug dependence, but success was there only in the field of nicotine dependence, whereas opioid antagonists are known, but exploring novel options become an important need for the day. Therapeutic vaccines are being explored exhaustively for many drugs of abuse and even alcohol.

Therapeutic Vaccines have Common Mechanism of Action

All drugs of abuse have to act on the brain to show its effects, for this, it has to cross the blood brain. If somehow a drug is prevented from entering the blood–brain barrier, it would prevent it from showing its psychological effects. This would help motivated addicts, who first quit a drug and after brief period of abstinence, start abusing it again. If at this point of abstinence a drug can be prevented from showing its psychological effects, it would prevent relapse. From here came the theory of stopping the drugs into the circulation before it can enter the blood–brain barrier by antibody binding. If a drug is conjugated with a large particle and vaccinated, it is capable of producing immunological response producing IgG antibodies against the drug. IgG will bind the drug and prevents its entry into the blood–brain barrier as overall size of a molecule increase. For this, vaccine should be capable enough to produce high titer of antibodies and their high levels should be maintained for substantial amount of time or else a booster dose would be needed, mainly to prevent a relapse during abstinence. Most of the therapeutic vaccines for drug abuse have this common basis of action. On

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the other hand, mechanism for vaccines against alcohol acts by gene intervention.[8]

**Therapeutic Vaccines for Nicotine**

Nicotine abuse is one of the most common problems, affecting millions of people worldwide. Nicotine industry contributes in millions as taxes to the governments all over the globe.[2] Nicotine is abused both by inhalation and orally, affecting all types of population from low to high socioeconomic strata of the society.[2] Millions of dollars are being spent to rehabilitate patients from nicotine abuse and treating diseases due to consequence of nicotine abuse. Nicotine is the only drug of abuse against which considerable drug development has taken place in last few decades.[2] Many types of drug forms have been developed, some of which have been withdrawn too, due to their adverse effects.[5] Success rate of all of them have being not being promising due to high relapse rate. This makes nicotine an important target for developing therapeutic vaccines against it, especially during abstinence phase.[7] Nicotine is the only drug of abuse in which substantial work has been done to find a therapeutic vaccines. NicVax, NicQb, Niccine, and TANIC are four vaccines presently undergoing clinical trials.[9] After successful animal studies and phase I studies, it was found to be well tolerated without any action on other endogenous molecules.[7] NicQb is a viruses like vaccines developed by Cytos Biotechnology.[7] In phase II trials, upper one-third of participants who were high responders with high antibodies titers showed high rates of abstinence at follow-up at 6 and 12 months, but unfortunately, they also showed a higher number of side effects.[7] Whereas medium and low responders (2/3 of the test population) showed no difference in results as compared to placebo.[7] Subsequently, in 2008, Novartis conducted fresh trials after reformulation of the vaccine to decrease side effect, which also failed to keep participants in continuous abstinence at 8–12 weeks after treatment was started.[10] TANIC was developed by Celts pharmaceuticals.[8] In 2009, phase II trials were conducted with dose range from 100 to 250 mcg. Abstinence rate was only 25% with the highest dose of vaccine, as compared to 9% with placebo.[7] Nicvax vaccine was developed by Nabi Biopharmaceutical and GlaxoSmithKline. Phase II trials conducted in 2007 did not show any positive results, as it could not prove its superiority over placebo.[9]

Further, in 2008, phase III trials were conducted in 1000 patients with primary end point being abstinence rate for 16 weeks.[8] Overall results showed abstinence rate of vaccinated population being significantly superior to that of the placebo.[9] Possible drawback with all these vaccines were that they all showed inconsistency in degree of immunological response, leading to low titers of antibodies in some population.[9] Niccine is a tetanus-toxoid conjugate vaccine developed in Sweden.[10] Its phase II trials were done with those patients who were treated with varenicline to stop smoking and were used to prevent relapse.[10] It was a 1-year trial, in which 40 µg of this vaccine was administered on 0, 28, 56, 90, 150, and 210 days.[10] Between 58th and 98th day, patients were treated with a nicotine receptor partial agonist varenicline to quit smoking.[10] Nonrelapse was 43.3% compared to placebo which was 51.1%. Again a new vaccine was a failure, due to lack of its ability to produce adequate antibodies.[10]

Advantages of a successful therapeutic vaccine against nicotine over other drugs used for nicotine addiction would overcome the problem of patient adherence to the drugs which have to be used daily.[9] Second, seeing large number of population into nicotine abuse, therapeutic vaccine is an inexpensive option with relatively low cost of development, which would be economically feasible to treat a large population as compared to the costly drugs available as present option.[9]

**Therapeutic Vaccines for Cocaine**

Cocaine abuse is prevalent all over the world specially affecting people of middle and high economic strata, due to its high cost. Moreover, there is no Food and Drug Administration-approved drug available for treating cocaine abuse, so developing a therapeutic vaccine is a need of the hour.[11,12] First vaccine was developed by attaching cocaine with Cholera Toxin B (TA-CD). After successful phase I trials, phase II trials were conducted in 2005, 67% showed high antibody titer at 4 weeks, whereas, on other hand, 33% showed low levels of IgG titers for unknown reasons. However, these patients had high titer of IgM antibodies.[13]

**Therapeutic Vaccines for Methamphetamine**

Methamphetamine is a stimulant drug, abused by all sections of the population. It increases alertness, concentration, decreases sleep and appetite.[14] It acts by blocking N-methyl-D-aspartate receptor.[4] Phencyclidine is a bit different from other drugs of abuse as it does not produce any dependence but can be fatal during overdose, due to acute toxicity.[4] Therapeutic vaccine against phencyclidine can be developed as a tool to treat acute toxicity by reversing its toxic effects.[4] Animal studies on phencyclidine conjugate vaccines which were conducted in rats have shown promising results in producing high levels of antibodies against phencyclidine and reversing the behavioral effects that are induced by its high dose.[4]

**Therapeutic Vaccines for Phencyclidine**

It is one of the famous designer drugs being abused, specially for party goers. It acts by blocking N-methyl-D-aspartate receptor.[4] Phencyclidine is a bit different from other drugs of abuse as it does not produce any dependence but can be fatal during overdose, due to acute toxicity.[4] Therapeutic vaccine against phencyclidine can be developed as a tool to treat acute toxicity by reversing its toxic effects.[4] Animal studies on phencyclidine conjugate vaccines which were conducted in rats have shown promising results in producing high levels of antibodies against phencyclidine and reversing the behavioral effects that are induced by its high dose.[4]

**Therapeutic Vaccines against Opioids**

Opioids are highly addictive group of drugs with very low rate of abstinence due to high rate of relapse.[14] It was estimated that millions of people are facing the problem with opioid addiction.[15] Therapeutic vaccine against opioids were one of the first therapeutic vaccines developed against any of the drugs of abuse.[14] In 1972, morphine was linked with bovine serum albumin and tested in rats which showed production of high
titers of morphine antibodies. Subsequently, in 1974, a similar type of conjugated vaccines was tried in rhesus monkeys which also showed positive results. Many morphine vaccines have being developed by linking hapten through 6 hydroxyl group of morphine to a carrier protein. Problems arose due to the development of synthetic opioid drugs which are now abused commonly in Western world as compared to morphine and heroin. This created hindrance in the development of opioid vaccines, as different vaccine was needed for each synthetic drug. In western countries, prescription drugs such as oxycodone and hydroxycodone are being misused in large scale, recently a therapeutic vaccine against oxycodone was tried in rats, which reduced the number of rats undertaking self-administration of the drug and also showed altered mRNA expression in the reward pathway. However, on the other hand, in developing countries, heroin and morphine are still being abused more commonly as compared to other synthetic opioid drugs. Hence, a therapeutic vaccine against heroin or morphine would be worthwhile in these developing countries. After decades of gap, these vaccines are being explored again.

**Therapeutic Vaccine against Alcohol Abuse**

Alcoholism is a major problem affecting the society adversely. The World Health Organization estimated alcohol as the third largest risk factor for various diseases and estimated 2.5 million deaths annually. In 2013, a therapeutic vaccine against alcoholism was developed in University of Chile, Santiago, for the first time. 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. These vaccines act by causing genetic mutation of aldehyde dehydrogenase enzyme, which is the second most important enzyme involved in alcohol metabolism. This leads to accumulation of acetaldehyde which is not metabolized due to lack of the enzyme involved. This 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.

**Conclusions**

As we are all aware of the magnitude of problem, this world is facing with issue of drug and alcohol abuse. It has become one of the largest pandemic affecting communities all over the world. Millions are being spent to find a drug to cope up with these problems, but with very less success, especially in the field of nicotine abuse. Main issues in treating the patients are motivation to quit, overcoming withdrawal symptoms, adherence to daily medications, and maintaining continuous abstinence. Relapse rate is very high for all drugs of abuse including alcohol. Therapeutic vaccines have become a new approach to deal with this problem. It is worth a chance to be taken into consideration, especially where pharmacotherapy has failed. Only obstacles that are being faced are inability to produce high titer of antibodies in all subjects and maintenance of the levels of antibodies for a sustained period. If one of such conjugate vaccines is successful, it will open the gates for development of other vaccines. Furthermore, the option of genetic alteration can be explored as in the case of vaccine against alcohol abuse. Still, a substantial amount of research has to be done to achieve these targets which can help to wipe out these problems for the current and future generations.

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**Conflicts of Interest**

There are no conflicts of interest.

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