

Anti-Nicotine Vaccine: An Insight

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ABSTRACT

Tobacco dependence is the most common form of drug abuse. Chronic use of tobacco has been associated with various diseases. Worldwide tobacco usage is the leading cause of preventable death. According to the World Health Organisation, there are 1.2 billion smokers and 5 million tobacco-related deaths annually by causing cardiovascular, respiratory, malignancy diseases, which accounts for 10% global mortality. Nicotine is the major component in tobacco that causes addiction. Over the years, various pharmacological and non-pharmacological methods like nicotine replacement therapy, antidepressants, counseling are commonly followed. These conventional methods have low efficacy and have high relapse rate. Anti-nicotine vaccines that are a novel immunologic approach in smoking cessation are currently in the pipeline. The concept of the anti-nicotine vaccine was introduced by E.H Cerny in 1990, based on active immunization against the nicotine molecule. Nicotine vaccines are a novel therapeutic approach to treating nicotine addiction by preventing the entry of nicotine into the brain. The primary role of such interventions will be in preventing relapse in smokers who are motivated to quit. Currently, nicotine vaccines are in Phase II and Phase III trials and if successful will be a boon against tobacco addiction. Some of the vaccines against nicotine that are under clinical trials are Nic VAX, NIC002, TA-NIC, CYT002-NicQb. The present article discusses the various vaccines that are available and the advantage of them over the routine conventional treatment modalities against nicotine addiction.

Keywords: Addiction, Anti nicotine vaccine, Nicotine, Tobacco, Vaccine

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INTRODUCTION

Tobacco dependence is the most common form of drug abuse.¹ Nicotine is the major component in tobacco that causes addiction and its other components like tar, volatile oxidant gases, carbon monoxide cause damage to health.^{2,3} Chronic use of tobacco have been associated with serious diseases like coronary heart disease, chronic obstructive pulmonary disease, stroke, vascular disease, chronic lung disease and cancer.⁴ Smoking is a global healthcare problem. Worldwide tobacco usage is the leading cause of preventable death.^{1,5} According to the World Health Organisation, there are 1.2 billion smokers and 5 million tobacco-related deaths annually by causing cardiovascular, respiratory, malignancy diseases, which accounts for 10% global mortality.⁶ Smoking increases the risk of cancer in men by 23 times and in females by 13 times.⁷ The life span of a smoker is seen to be reduced by 10 years.⁸ If the current trend continues, it has been estimated that smoking will cause 10 million death by 2020.⁹ Stopping smoking is

among the key medical interventions to lower the global burden of tobacco-related disorders and death.

Nicotine invokes addiction in smokers due to its pharmacokinetic properties. Among the majority of smokers who are motivated to quit without intervention, 95% relapse within a year.¹ Curbing the tobacco dependence necessitates effective long-term treatment for both economy and public health.⁶ Over the years various pharmacological and non-pharmacological methods such as counseling, drug therapy, hypnosis, magnet therapy, acupuncture, low-level laser therapy, mind-body practices are being followed to combat tobacco addiction. Since these conventional methods have low efficacy and high relapse rate, anti-nicotine vaccines are a novel, immunologic approach currently in the pipeline against tobacco dependence.^{6,10}

An anti-nicotine vaccine produces antibodies for nicotine, which are too large to cross the blood-brain

barrier. Thus, less nicotine enters the central nervous system and decreases the addictive effect of nicotine.¹ Some of the vaccines against nicotine that are under clinical trials are Nic VAX, NIC002, TA-NIC, CYT002-NicQb. Currently, nicotine vaccines are in Phase II and Phase III trials and if successful will be a boon against tobacco addiction. Moreover, the unique mechanism of action of immunotherapy makes it suitable for combining with other modalities against nicotine addiction.⁵ The primary role of such interventions will be in preventing relapse in smokers who are motivated to quit. This article provides an insight into tobacco dependence, various anti-nicotine vaccines and its efficiency against nicotine addiction when compared to conventionally followed methods and summarizes the current status of research.

NICOTINE ADDICTION

Nicotine has a wide variety of effects on the central nervous system and produces its addictive effect by altering neuropharmacological effect in the brain.⁵ Nicotine is very similar to signaling molecule acetylcholine. After nicotine enters the body, it binds with acetylcholine and stimulates the heterogenic group of nicotinic receptors of the adrenal gland, neuromuscular gaps and the brain.^{8,11} Thus, it increases the level of intracellular dopamine in the nucleus accumbens in the brain.⁵ This further inhibits the enzymatic catabolism of dopamine (Figure 1).¹¹ The continued stimulation leads to tobacco dependence. Withdrawal from nicotine creates a decreased functional state in the body and lowers brain activity and produces symptoms like irritability, dizziness, insomnia, restlessness, altered mood and fatigue.¹²

The average nicotine content of the cigarette is 10-14 mg of that 10% enters systemic circulation resulting in plasma concentration of 300-500 nM. Nicotine intake from one cigarette is approximately 0.015 mg per kg.¹³ As nicotine enters the body, it crosses the blood-brain barrier within 10-20 s after a puff. Plasma half-life of nicotine is approximately 2 h. In the brain distributional $t_{1/2}$ of nicotine is 10 min.³ The concentration of nicotine in the brain is 5 times than that of serum.¹⁴ Nicotine in the cigarette is present as negative enantiomer that upon combustion gets transformed into the positive enantiomer thus leading to high sustained rates of smoking.^{5,11}

TREATMENT OF NICOTINE ADDICTION

Among 90% of tobacco users who try to quit only 1% of them succeed in their attempt.¹⁵ Withdrawal from nicotine addiction leads to decrease in dopamine

level that induces craving and dependence. It also leads to a decreased functional state in the body and leads to symptoms like irritability, insomnia, restlessness, fatigue, dizziness.¹² There are various pharmacological and non-pharmacological modalities against nicotine addiction. Nicotine replacement therapy (NRT), antidepressants are the commonly followed pharmacological methods (Figure 2). The long-term tobacco abstinence rates are <30% even when behavioral treatment was combined with pharmacological methods.²

NRT reduces withdrawal symptoms from smoking cessation, and it avoids smoking by replacing some amount of nicotine obtained from nicotine. It includes nicotine gum, nicotine patch, nicotine lozenge, nicotine

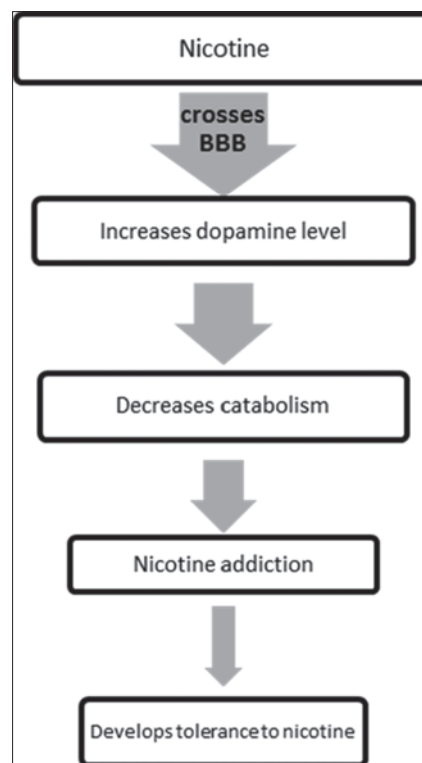


Figure 1: Nicotine addiction

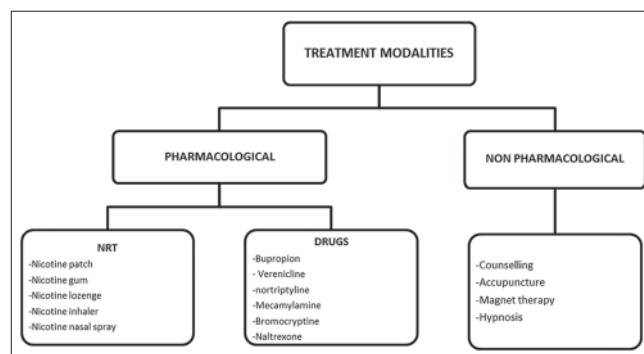


Figure 2: Treatment modalities for nicotine addiction

inhaler, nicotine nasal spray. These improve cessation efforts through any of the following mechanisms.

- Reduces severity of cravings
- Reduces severity of withdrawal symptoms
- During the time of cravings, provides an alternating coping strategy
- Reduces the reinforcing effects of tobacco-induced nicotine.

Antidepressant drugs against nicotine dependence include bupropion, varenicline, nortriptyline, mecamylamine, bromocriptine, naltrexone, silver acetate.^{2,15} These medications help patients especially to relieve withdrawal symptoms.¹⁶

Among the non-pharmacological methods, counseling is the most commonly accepted one. Other methods include hypnosis, magnet therapy, acupuncture, low-level laser therapy, mind-body practices. These conventional methods have low efficacy and have high relapse rate.

Anti-nicotine vaccines that are a novel immunologic approach in smoking cessation are currently in the pipeline.⁵

CONCEPT OF ANTI NICOTINE VACCINE

The history of anti-addiction vaccines dates back to 1972 when Berkovitz *et al.* at the University of Chicago immunized a rhesus monkey against morphine. The animal showed protection against heroin and thus they concluded "That this blockade has been shown to be dose-dependent, and it could be overcome by high doses of drugs."^{9,11} This idea of using antibodies to bind a drug and thus disabling it from crossing the blood-brain barrier was subsequently extended to other species. Later the concept of immunization was extended to drugs of abuse like morphine, methamphetamine, cocaine and nicotine.¹³ The concept of the anti-nicotine vaccine was introduced by E.H Cerny in 1990, based on active immunization against the nicotine molecule. The mechanism is this immunization will elicit the immune system to produce nicotine specific antibodies that sequester nicotine in the blood stream. The resulting antigen-antibody is too large to cross the blood-brain barrier.¹⁷ Since enough nicotine is not reaching the brain, it would prevent the nicotine's psychoactive effects. By reducing the rewarding effects of smoking, this would reduce the drive for further consumption (Figure 3).²

The nicotine molecule is too small to be recognized by the immune system and is therefore not immunogenic. Therefore, vaccines are developed which contain components that are recognized by the immune system,

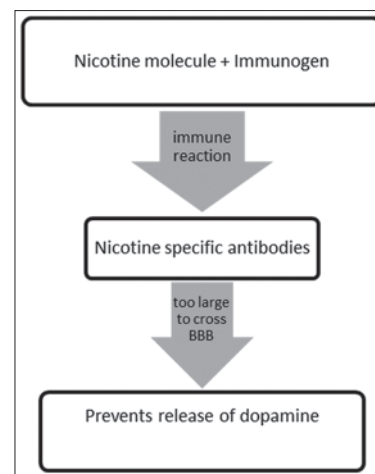


Figure 3: Principle of anti nicotine vaccine

e.g., bacterial exoprotein, virus-like particle, recombinant cholera toxin.¹⁰ This promising immunological technology for improving the success of smoking cessation is currently in trials.¹⁸

NICOTINE VACCINES

Initial studies have shown that there is statistically an initial increase in the rate of abstinence among smokers; still long-term efficacy has to be determined. Based on current immunologic studies, nicotine vaccines hold a promising future.¹⁹ Immunization against nicotine is achieved by two methods: Active immunization and passive immunization. Former involves repeated administration of an immunogen to the subjects, thus stimulating the immune system to produce antibodies. Latter involves the production of antibodies via *in vivo* or *in vitro* that are then administered to the subjects.⁶ Vaccines can be administered either by subcutaneous, intramuscular, intranasal routes. Some of the vaccines against nicotine that are under clinical trials are Nic VAX, NIC002, TA-NIC, CYT002-NicQb.

NICVAX

This most advanced proprietary vaccine is developed by Nabi Biopharmaceuticals and consists of the hapten 3-aminomethylnicotine, which is conjugated with *Pseudomonas aeruginosa* exoprotein A. NicVax is administered by injection into the arm. The antibody binds to the nicotine molecules, thus causing the nicotine-antibody complexes to be too large to enter the brain. Because not enough nicotine enters the brain, addiction relevant neural pathways are not generated. So, no pleasure is derived from tobacco cigarette, and the vaccinated subject does not relapse and begin smoking again. This vaccine is currently in Phase III clinical trials and demonstrated that it was well tolerated, highly immunogenic, and subjects remained abstinent from smoking up to 12 months.^{9,20}

CYT002-NICQB

The CYT002-NicQb a virus-like particle vaccine developed by Cytos Biotechnology and Novartis obtained by recombination of bacteriophage Qb mantle protein and is in Phase II clinical trials. This vaccine has shown promising results when antibody levels are sufficiently high. Clinical trials have shown that the CYT002-NicQb vaccine is safe and well tolerated.^{15,16} In 2007, Cytos Biotechnology entered into a license agreement with Novartis and in 2008 Novartis began Phase II trials with a reformulated vaccine with fewer side effects. However, continuous abstinence from smoking was not achieved because NIC002 failed to induce sufficiently high antibody titres.⁹

TA-NIC

TA-NIC is developed by Celtic Pharma and is currently undergoing Phase III trials. This anti-nicotine vaccine uses bacterial toxin component (inactivated cholera toxin). After the initial dose, the vaccine has shown abstinence of 6 months. Phase II trials showed efficacy and minor side effects and the dropout rate was <10% among 520 patients in 10 weeks. Phase III study results are not yet published for TA-NIC vaccine.^{6,8}

ADVANTAGES

The immunologic approach has certain advantages over other modalities against nicotine addiction.

- Good specificity
- Low cross-reactivity
- Fewer side effects
- Does not patient compliance, vaccines immunologic approach requires initial dose followed by booster doses^{1,4}
- Unique mechanism of action
- Have long-lasting effects
- Well suited for combination with other pharmacotherapies⁵
- Vaccination prevents addiction among those who do not smoke currently and thus would prevent drug dependence.³

POTENTIAL CONCERNS

Anti-nicotine vaccine has certain limitations:

- Lack of control over antibody levels
- Large variability between the subjects⁵
- Anti-nicotine vaccination can increase accumulation of nicotine in brain and can lead to disparity in natural immune response⁷
- Slow development of antibody levels and the onset of effects could discourage the tobacco users who are motivated and eager to quit

- Safety in immunizing pregnant ladies has to be confirmed through clinical studies
- Vaccination could even precipitate withdrawal
- Lead to side effects like an allergic reaction.⁶

CONCLUSION

Currently, the anti-nicotine vaccine is considered as a novel therapeutic approach in curbing the tobacco dependence. Nicotine vaccines act by preventing the entry of nicotine into the brain. The primary role of such interventions will be in preventing relapse in smokers who are motivated to quit. These interventions do not target the non-pharmacological factors that cause and maintain tobacco dependence. The anti-nicotine vaccine can be combined with other behavioral interventions to yield maximum beneficial effect. Currently, nicotine vaccines are in Phase II and Phase III trials and if successful will be a boon against tobacco addiction. Further studies and safety interventions have to be carried out before the anti-nicotine vaccine is used widely to curb tobacco dependence.

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