

Anti-nicotine vaccine: current status**Vishal Prakash Giri^{1*}, Shubhra Kanodia², Om P. Giri³, K. Sumit¹**

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ABSTRACT

Tobacco abuse has an enormous impact on health. Nicotine is the main substance responsible for dependence on tobacco-containing products. The vast majority of cigarette smokers who try to quit ultimately fail because of high relapse rates. Clearly, novel approaches are needed for the treatment and prevention of nicotine addiction. Having an efficient vaccine that would generate antibodies to sequester the drug and prevent its access to the brain could go a long way toward helping a motivated addict quit an addiction.

Keywords: Anti-nicotine vaccine, Varenicline, Clinical trial

INTRODUCTION

Tobacco continues to be leading global cause of premature death and if the current trends continue by 2030 tobacco will kill more than 8 million people worldwide every year, the causes of mortality being cardiovascular, respiratory, and malignant diseases.¹

Nicotine is the main substance responsible for dependence on tobacco-containing products. Curbing the tobacco dependence necessitates effective management.

Drug addiction is considered as a lifelong, chronic, relapsing brain disorder in which physical dependence on a substance leads to its compulsive and repetitive use. Indicators include the following: (a) a strong desire to take the drug, (b) an impaired control over use, (c) a withdrawal syndrome after cessation or reduction of use, (d) tolerance to the effects of the substance, (e) the need for larger doses to achieve the desired psychological effect, (f) a disproportionate amount of time spent by the drug user to obtain, use, and recover from drug use, and (g) continuing to take the drug despite the problems that occur.^{2,3}

Pharmacokinetics of nicotine

The brain substrate corresponding to this “highway of pleasure” reaches from the nucleus accumbens where dopamine is secreted to the hippocampus, contextual information is stored to the cerebral cortex, and signals enter the awareness of the individual. Nicotine activates this circuit. Nicotine not only stimulates dopamine secretion but also inhibits an enzyme monoamine oxidase B, which is important for the catabolism of dopamine, leading to average dopamine concentrations in smokers well above those of nonsmokers.⁴

Nicotine binds in the brain to nicotinic cholinergic receptors. These are ion channels, which allow cations to enter the cell when an agonist docks to the gate on the outer side of the channel. The nicotinic cholinergic receptor complex itself is composed of five subunits. The most abundant subunits are the b2 and a4 subunit. Stimulation of the b2 subunit leads to dopamine release; the a4 subunit is closely linked with an individual’s sensitivity to nicotine, the a3 and b4 subtypes mediate cardiovascular effects of nicotine. An activation of the cholinergic receptors by nicotine leads, besides a secretion of dopamine, to a stimulation by other neurotransmitters such as norepinephrine (appetite reduction, arousal), glutamate (memory and sensory enhancement), acetylcholine (enhanced alertness), b-endorphin and gamma aminobutyric acid, lowering of anxiety.⁵

Smoking cessation eventually results in decreased dopamine levels and induces withdrawal symptoms such as irritability, weight gain, anxiety, learning deficiency and depression. Low doses of nicotine stimulate neural systems, whereas high doses produce a blockade. Tolerance to effects such as increase in heart rate develops rapidly in a time span as short as 1 day. The combination of rapid tolerance induction and appearance of unpleasant withdrawal symptoms on smoking cessation are at the root of the difficulties smokers confront when they want to quit.

The half-life of nicotine is about 2 hrs in man. Hepatic enzyme CAP2A6 transforms nicotine to its main metabolite cotinine, which has no significant pharmacological activity, a longer half-life than nicotine (16 hrs) (Figure 1).

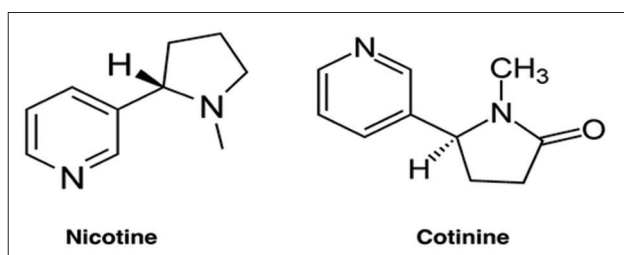


Figure 1: Chemical structures of nicotine (left) and its major metabolite cotinine (right).

Management of nicotine addiction

Over the years, various non-pharmacological methods such as counseling, hypnosis, magnet therapy, acupuncture, low-level laser therapy, and mind-body practices are being followed to combat tobacco addiction, but these conventional methods have low efficacy and high relapse rate.

Pharmacotherapy for smoking cessation focuses on minimizing the nicotine withdrawal effects by substitution of the nicotine reward effects or by attenuating the reinforcing effects of tobacco. Currently, available therapies such as nicotine replacement therapy, psychotropic drugs, and partial nicotine acetylcholine agonists, in combination with behavioral support, can increase abstinence rates to a maximum of 20-25% after 1 year.

Anti-nicotine vaccines are a novel, immunologic approach currently in the pipeline against tobacco dependence.

Basic principle of nicotine vaccination

Nicotine vaccination is based on active immunization against the, otherwise, non-immunogenic, nicotine molecule.

For this purpose, the small nicotine molecule is conjugated to a much larger carrier protein to induce and activate the immune system to produce highly specific nicotine antibodies. These antibodies sequester nicotine in the blood stream, after inhaling tobacco products, and the resulting antigen-antibody molecule becomes too large to cross the blood-brain barrier.

By preventing large amounts of nicotine reaching the central nervous system, nicotine vaccination is believed to attenuate the rewarding effect of nicotine (Figure 2).

ANTI-NICOTINIC VACCINES

Vaccines against nicotine are at an advanced stage of clinical evaluation and are not yet approved for treatment of individuals. These vaccines are NicVAX vaccine, NIC 002 vaccine, TA-NIC vaccine, Niccine vaccine, SEL-068 vaccine.

NICVAX VACCINE

3'-aminomethyl nicotine conjugated to *Pseudomonas aeruginosa* r-exoproteinA (3'-AmNic-rEPA) vaccine designed by Nabi Pharmaceuticals/GlaxoSmithKline, was initially developed as an aid in smoking cessation. For this purpose, multiple injections are administered prior to the planned quit date resulting in a gradual increase in anti-nicotine antibodies which helps smokers in gradually reducing the number of cigarettes and eventually achieve complete abstinence.

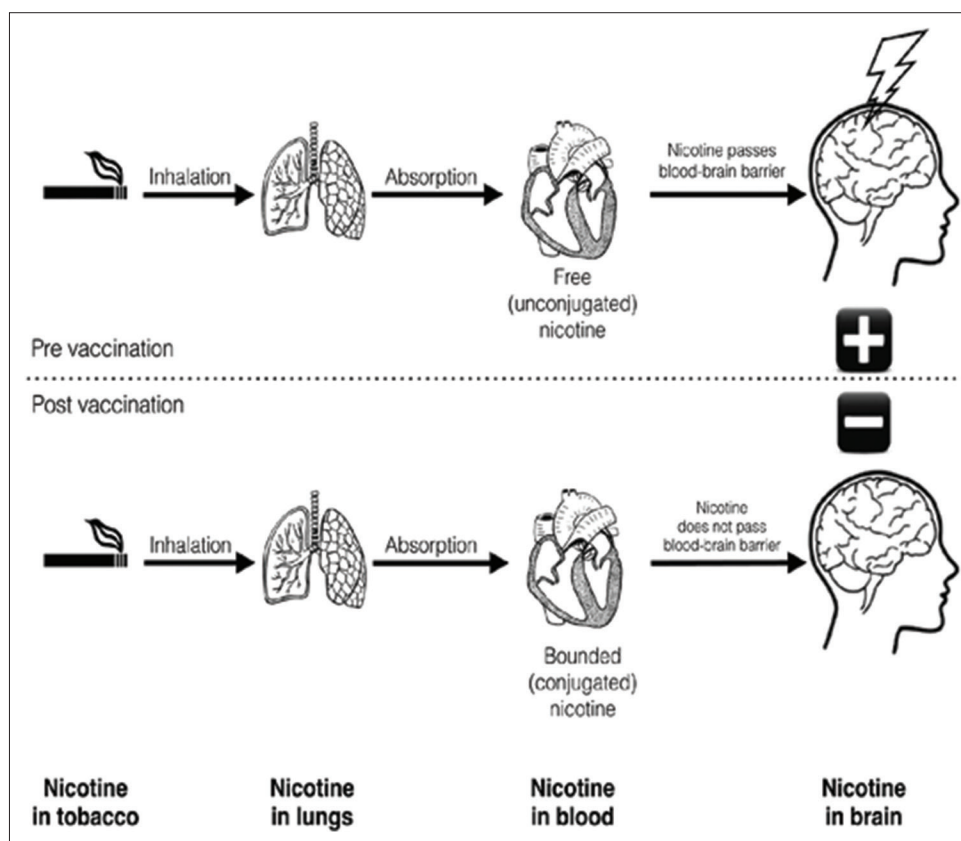


Figure 2: Mechanism of action of a vaccine against nicotine addiction. In the absence of vaccine (above), nicotine readily passes through the blood-brain barrier and causes reinforcement in brain. If a vaccine is administered (below), the antibodies bind to the drug and prevent nicotine from entering the brain (reproduced from human vaccines and immunotherapeutic. January 2013; ©2013 Landes Bioscience).

Nicotine vaccines could also be used to prevent relapse. Hence, vaccinated ex-smokers who lapse (i.e., take a puff of a cigarette, have a positive smoking status for 1-week after a period of abstinence) are expected to experience diminished reward from nicotine inhalation which could prevent a full-blown relapse (i.e., a positive smoking status for at least 2-week after a period of abstinence). The effects of a brief exposure to a positive stimulus such as second-hand smoke may also be blunted.

Three Phase I/II clinical trials with NicVAX have been published. Two of these studies were designed to evaluate the immunogenicity and safety while another study was specially designed to demonstrate the proof of concept to determine the relationship between immunogenicity and smoking cessation outcomes.⁶

Regarding the reported safety data, participants commonly reported local reactions at the injection site like “ache” and ‘tenderness. The reported systemic reactions were mostly mild to moderate of intensity and included symptoms of general discomfort/malaise, myalgia, and headache. There was no significant difference in local and systemic reactions between the placebo group and the NicVAX treatment group.

Of all reported safety data, there was only one serious adverse event (anaphylactic reaction) in a subject with a

history of allergic reactions that was considered by the investigator to be treatment-related.

Immunogenicity has been shown to be dose-related. Additional injections and higher vaccine doses have been shown to be related to stronger immune responses and higher antibody titers. These antibody titers typically peak following the final injection when 4 or 5 vaccinations are administered. The peak geometric mean antibody concentration reported in response to the nicotine conjugate vaccine NicVAX was 45 µg/ml in the subgroup who received 5 injections with 400 µg of NicVAX. Previous data reported no difference in antibody response between smokers and non-smokers.

Currently, only one study has been published to evaluate the relationship between smoking cessation outcomes and immunogenicity in smokers treated with 4 or 5 injections of NicVAX in different dose schedules.

A subgroup of the top 30% antibody responders were significantly more likely than the placebo group to achieve 8 weeks of continuous abstinence from weeks 19 through 26 (24.5% vs. 12.0%, odds ratio (OR)=2.69, 95% confidence interval (CI)=1.14-6.37) and weeks 19 through 52 (19.7% vs. 10.0%, OR=2.64, 95% CI=1.03-6.79). The target quit day was dependent on the dose regimen, which was either

week 5 (for 5 injections schedule) or week 7 (for 4 injections schedule).

Smokers who received the 5 injection schedule with 400 µg NicVAX dose elicited the highest antibody response, which resulted in significantly higher abstinence rates than placebo. In vaccinated smokers who failed to quit smoking, the authors observed a statistically significant reduction in daily cigarette consumption between the top 30% antibody responders and the placebo group in weeks 19-52; the median reduction in cigarette consumption between both groups was 4.6 cigarettes a day. There were no differences in withdrawal symptoms and no evidence for compensatory smoking in those smokers who received injections with NicVAX.

Nabi Biopharmaceutical conducted first two phases of Phase III and the second phase of Phase III trials of NicVAX. Primary end point was not met, and there was no statistical difference between NicVAX and placebo. At this point, there are no published results of secondary outcome measures of both Phase III trials.⁷

Despite the disappointing Phase III results of NicVAX, there is hope for a potential benefit for nicotine vaccination in future smoking cessation programs, particularly in view of observation in Phase II b study that high antibody response correlates with increased cessation outcome. This may be especially relevant if NicVAX is combined with varenicline.⁸

Phase III trial of NicVAX in combination with varenicline is in progress. The data and conclusion from the trial have not been published in peer-reviewed journal.

NIC 002 (FORMERLY CALLED CYT002-Nic QB) VACCINE

Recombinantly produced virus-like protein vaccine designed by Cytos Biotechnology/Novartis. Studies have been conducted to evaluate efficacy, safety, tolerability, and immunogenicity of NIC002 vaccine in cigarette smokers who were motivated to quit smoking.

Phase I trial, randomized, placebo-controlled, included 40 healthy, non-smoking volunteers; 10 subjects in each of four dose groups. Vaccine reported to be safe, good toleration and high immunogenicity. 93% adverse effects were mild, 7% as moderate and none as severe. The most frequent side effects were local reactions at injection site, headache and flu-like symptoms.⁹

In Phase II, randomized, double blinded, placebo-controlled trial, Nic 002 vaccine has been observed to be safe, well tolerated and highly immunogenic. Fever was noted in 40% and flu-like features in 70% cases.¹⁰

Phase II b, double blinded, placebo controlled, multi-centric trial reported Nic 002 vaccine to be safe and well tolerated,

but primary end point was not achieved because it failed to induce sufficient high antibody titers.¹¹

TA-NIC VACCINE

Nicotine butyric acid covalently linked to recombinant cholera toxin B vaccine, designed by CetlikPharma.

Phase II trial, double-blinded, randomized, placebo-controlled, was conducted to assess the efficacy and safety of the vaccine as an aid to smoking cessation. The study group included participants aged ≥18 years age, both sexes (male and female), regular smoker for ≥1 year and ≥10 cigarettes per day, motivated to quit smoking within 12 weeks. Total 522 participants were enrolled. TA-NIC vaccine was administered to each subject as 7 single doses, at weeks 0, 2, 4, 6, 8, 12, and 16. A booster dose was given at 32 weeks. No drug-related severe adverse events were noted. Minimal injection side effects were observed. Anti-nicotine antibody titer level was reported to be dose-dependent. At 6 weeks, 43% subjects gave up smoking and at 12 weeks, 95% gave up smoking.¹²

Phase II b, double-blinded, randomized, placebo-controlled, the multicentric trial showed TA-NIC vaccine efficacious with minor side effects. 420 patients were recruited for 10 weeks trial. Dropout rate noted was <10%.¹³

TA-NIC anti-nicotine vaccine is currently undergoing Phase III trial.¹⁴

NICCINE VACCINE

Niccine is a nicotine hapten tetanus toxoid conjugate vaccine, designed by independent Pharmaceuticals.

Phase II randomized, double blind, parallel group 1 year trial was conducted on 355 cigarette smokers (aged 25-50 years) to evaluate the clinical efficacy of Niccine for tobacco smoking relapse prevention.

Niccine 40 µg or placebo was administered on days 0, 28, 56, 90, 150, and 210. Between days 56 and 98, subjects were treated with varenicline to aid cessation.

Niccine vaccine was observed to be well tolerated but did not influence trajectories of relapse possibly because of insufficient antibodies level or lack of efficacy of vaccine concept of relapse prevention.¹⁵

SEL-068 VACCINE

SEL-068 is first synthetically engineered nanoparticle nicotine vaccine designed by Selecta Biosciences Inc. The greatest advantage of this vaccine is that immune response will focus on nicotine. Phase I double blinded, placebo-

controlled, ascending dose trial on healthy, non-smoking and smoking volunteers is in progress.¹⁶

CONCLUSION

Anti-nicotine vaccine efficacy depends on antibody specificity, affinity as well as antibody blood levels. These are influenced by vaccine conjugate, vaccine dose, vaccine adjuvant selection, and vaccinations frequencies. Further research is needed to improve anti-nicotine vaccine efficacy.

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Ethical approval: None required

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