

# Nicotine Vaccine : Might Be Boon for Smokers

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## Abstract

**T**obacco is the single most preventable cause of the death worldwide. Despite its known ill effects it has 1 billion consumers in the world. About 90% of the users try to quit, but only 1% of them succeeds in their attempt. This is mainly because of the addictive properties of the nicotine. As the rate of absorption of the nicotine by the brain is high, it immediately shows pleasurable effect ever since we take a first puff of smoking tobacco. In order to bring out a remedy for this several pharmaceuticals companies are trying to develop a Vaccine on the basis of the above principle. There are three such kind of the vaccines which are under phase III clinical trial right now and which holds a lots of promises in bringing out smoking cessation. These are namely NicVAX (Nabi Biopharmaceuticals), NicQb (Cytos Biotechnology), and TA-NIC (Celtic Pharma). A lot of hope has been laid on these vaccines as globally the burden of smoking is increasing day by day. The current review focuses mainly on the use of nicotine vaccines for smoking cessation.

**Key Words :** Tobacco, Nicotine, Nicotine Vaccine.

## Introduction

Nicotiana Tabacum, or cultivated tobacco, which used in any of its form, ultimately leads to slow and painful death. Humans came across this plant about 18000 years ago when they migrated from Asian continent to America. Later Christopher Columbus, an Italian explorer discovered and introduced this crop to rest of the world. In 16<sup>th</sup> century tobacco plant got famous as a medicinal herb and very ironically it is claimed as it helps in curing and preventing cancer.<sup>1</sup>

Harmful effects of tobacco existed for more than 200 years. In 1950 following the publication of 5 case-control studies relating smoking to lung cancer the ill effects of tobacco came into limelight. Ultimate impact was made by US Surgeon General Report which was published in 1964.<sup>2</sup> Smoking rate increased dramatically during the 20th century in developed countries until recently and rate of consumption are still increasing in underdeveloped countries. An epidemic of smoking-related diseases has followed the prevalence of smoking. Today tobacco is the most threatening problem worldwide. It kills more than half of its users and also its ill effects are seen in passive smokers and tobacco workers.<sup>3</sup> Among these majority of smokers wish to quit, but find it difficult to do so because of the addictive effects of nicotine. Nicotine is at least as addictive as cocaine, amphetamines or opiates.<sup>4</sup>

“To cease smoking is the easiest thing I ever did. I ought to know because I’ve done it a thousand times.”

This popular quote, attributed to Mark Twain, mockingly captures the difficulties of long-term abstinence for nicotine-dependent individuals. Although there are many pharmacological methods available as nicotine replacement, antidepressants, and behavioral therapies but the relapse rate is quite higher.<sup>5</sup>

## Available Pharmacological Methods

A variety of pharmacological methods are available for cessation now a day. These include.

- NRT (Nicotine Replacement Therapy)
- Antidepressants
- A variety of other pharmacological therapies

## Nicotine Replacement Therapy

The aim of nicotine replacement therapy (NRT) is to provide some of the nicotine from cigarettes minus the harmful constituents contained in tobacco smoke. NRT reduces withdrawal symptoms associated with smoking cessation and makes it easier to avoid smoking by replacing some of the nicotine obtained from smoking.<sup>6</sup> Nicotine replacement therapy (NRT) achieves quit rates of 18% to 31% in clinical trials but only 5% to 15% among general-population smokers who use NRT for cessation assistance. This discrepancy may be partly explained by non-adherence to NRT regimens outside clinical trials. Compliance with recommended length of treatment occurs among 50% or fewer NRT users.<sup>7</sup>

## Types of NRT

There are several different forms of nicotine replacement therapy-

- Chewing gum (2 mg and 4 mg doses);
- Transdermal patches (16 hour and 24 hour in varying doses);
- Nasal spray;
- Inhalers;
- Sublingual tablets and
- Lozenges.

## Nicotine Gum

The U.S. Food and Drug Administration (FDA) approved nicotine polacrilex gum in 1984.

**Dosage:** The gum comes in 2-mg and 4-mg doses and can be chewed every 1 to 2 hours for a maximum daily dose of 60 mg. The typical daily dose is 10 pieces, and the recommended duration of therapy is 1 to 3 months. The gum should be chewed slowly and then “parked” between the cheek and gum to facilitate nicotine absorption. The gum should be “chewed and parked” for about 30 minutes.

**Adverse Effect:** Common adverse effects include jaw ache and dyspepsia.<sup>7</sup>

## Transdermal Patches

The nicotine patch was introduced in 1992.

**Dosage:** Patches are available in 21-mg, 14-mg, and 7-mg doses. The recommended taper is 21 mg for 4 weeks, then 14 mg for 2 weeks, followed by 7 mg for 2 weeks. The patch is available as a 15-mg dose. The recommended duration of treatment is 6 weeks.

**Adverse Effect:** Skin irritation, a common adverse effect of nicotine patches, can be reduced by rotating the patch site.<sup>8</sup>

## Nicotine Nasal Spray

The nicotine nasal spray was introduced in 1996. Spray is available by prescription in a quantity of 10 ml. Each 0.05-ml spray delivers 0.5 mg of nicotine.

**Dosage:** The daily dose may be titrated to a maximum of 40 mg. The recommended dosage is 1 to 2 sprays every hour for 6 to 8 weeks. The minimum recommended treatment is 8 doses per day for 3 to 6 months. Tapering of doses in the subsequent 4 to 6 week period is optimal to prevent withdrawal symptoms.

**Adverse Effect:** Common adverse effects include nasal irritation, rhinorrhea, sneezing, throat irritation, and coughing.

## Nicotine Inhaler

The nicotine inhaler was introduced in 1998.

**Dosage:** The recommended dose is 6 to 16 cartridges per day for 6 to 12 weeks, with tapering over the subsequent 3 months.

**Adverse Effect:** Common adverse effects include throat irritation and coughing.<sup>7</sup>

## Antidepressants

After the era of NRT it has been came to notice that few antidepressants are also equally effective in the treatment of the smoking cessation. One of the drug Bupropion was developed and initially introduced in the United States as an antidepressant but was subsequently noted to reduce the desire to smoke cigarettes.<sup>9</sup>

## Bupropion SR

Bupropion was developed and first marketed as an antidepressant. The suggested mechanism of action is inhibition of neural reuptake of dopamine or noradrenaline, but this may be simplistic.<sup>10</sup> When used for smoking cessation bupropion is initiated 12 weeks before the target quit date and is generally continued for three months. Bupropion is contra-indicated in people with seizure disorders, a current or prior diagnosis of anorexia nervosa or bulimia, use of a monoamine oxidase (MAO) inhibitor within the previous 14 days or using other medications that contain bupropion.<sup>6</sup>

### Nortriptyline

Nortriptyline is an efficacious smoking cessation treatment. It may be used under a doctor's supervision as a second line agent to treat tobacco dependence. When used for smoking cessation treatment it is initiated 24 weeks before the quit date and continued for approximately 12 weeks.

### Varenicline

Varenicline is the most recently FDA-approved agent for smoking cessation and has been included in the DHHS guidelines for the treatment of tobacco dependence. It is formulated as 0.5-mg and 1-mg tablets. The recommended dosage is 1 mg twice daily following a 1-week titration: 0.5 mg once daily on days 1 to 3 and 0.5 mg twice daily on days 4 to 7.

### Safety and Tolerability

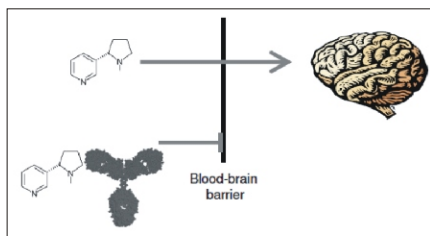
Varenicline is generally well tolerated, with the most common adverse events being nausea, insomnia, and headache.<sup>6</sup>

### Other Pharmacological Aids

Other pharmacological methods such as Clonidine, Mecamylamine, Naltrexone, Anxiolytics, Silver acetate can also be used for cessation.

### Rationale for Nicotine Vaccines

Nicotine is the addictive substance present in the cigarettes. Its pleasurable effect is seen immediately after smoking as absorption rate of the nicotine by brain is higher. Nicotine is a small molecule and easily crosses Blood Brain Barrier. Rationale behind the nicotine vaccine is to either to slow down this rate of absorption or to reduce it. Conjugating this nicotine with a larger molecule can help in preventing it to cross blood brain barrier.<sup>11</sup>



Source: Bachmann *et al.*, Science, 262, 1448-1451 (1993)

### Nicotine conjugated Vaccines

Nicotine must be conjugated with the larger molecule to elicit an immune response that forms Anti-Nicotine antibodies. Nicotine vaccine has a unique mechanism that antibodies bind to the drug itself and not to the nicotine receptor in brain. Some of the receptors remain unbound depending on several other parameters. Currently, three

nicotine conjugate vaccines are being studied in clinical trials: NicVAX (Nabi Biopharmaceuticals), NicQb (Cytos Biotechnology), and TA-NIC (Celtic Pharma).<sup>12</sup>

### NicVax

In 2006, the manufacturer of NicVAX was given fast-track designation by FDA and awarded several million dollars in grants from the National Institute on Drug Abuse to fund further clinical trials. NicVAX then was moved into two pivotal Phase III trials in hopes of becoming the first vaccine brought to market. The unfavorable results of these trials were recently announced by Nabi Biopharmaceuticals on July 18, 2011 and November 7, 2011.<sup>12</sup>

Hoogsteder PH et al in 2012 controlled trial to assess the efficacy of the nicotine vaccine NicVAXW co-administered with Varenicline (ChampixW). The study concluded that Although NicVAXW is primarily designed as an aid to smoking cessation, our study is designed to explore its potential to maintain abstinence and prevent relapse. The results of this trial will give a unique insight in the potential of nicotine vaccination for relapse prevention.<sup>13</sup>

### NicQb

There are generally two kinds of vaccine one is active and another is passive. Active vaccine is a one which activates a lifetime immune response against the intruder. Passive is the one which delivers readymade antibodies to elicit an immune response. The Weill Cornell research team developed a new, third kind, a genetic vaccine that they initially tested in mice to treat certain eye diseases and tumor types. The NicQb vaccine is based on this model.<sup>14</sup>

Cytos biotechnology developed a virus like particle based vaccine against nicotine addiction. Vaccination with NicQb leads to the induction of nicotine-specific antibodies. The antibodies bind nicotine (from inhaled tobacco smoke) in the blood and inhibit its passage to the brain, as antibodies normally cannot pass the bloodbrain barrier. Phase II clinical trials with NicQb have shown that this vaccine is efficacious for smoking cessation in humans when antinicotine antibody levels are sufficiently high.<sup>15</sup> It has also proven that NicQb is safe and well tolerated.

### TA-NIC

The initial vaccine development of Celtic Pharma's vaccine goes back to Immulogic Pharmaceutical Company's development program for a nicotine vaccine in 1997. In

April 2007 they had obtained IND approval for their nicotine vaccine candidate TA-NIC. The vaccine already done with phase I and phase II trials and testing is undergoing in phase III trial.<sup>16</sup>

### Summary

Today globally more than 5 million peoples worldwide die by the use of tobacco and around 1 billion consume it in various forms. Many of the non-pharmacological and pharmacological treatments have been tried but the addictive property of nicotine always creates the barrier for cessation. Currently researchers are working on nicotine vaccine and there are three nicotine vaccines which are under Phase III trial. If in future a nicotine vaccine comes out and shows effectiveness in helping out smokers for cessation, definitely it will be a biggest boon for mankind.

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