ANTI-NICOTINE VACCINES: NEW PERSPECTIVE FOR SMOKERS AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

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Abstract: Smoking and Chronic Obstructive Pulmonary Disease (COPD) become a global problem in the world. *The increasing number of smokers in the world also led to significantly increased morbidity and mortality due to COPD. Many attempts were made, ranging from government policy that prohibits smoking in public places, to pharmacological therapy, and psychotherapy for smokers. However, often there is a failure to quit smoking. Dependence on nicotine is an important factor that causes someone failed to stop smoking. As for the pharmacological therapy is currently widely used to intervene in nicotine dependence, such as nicotine replacement therapy, bupropion, and varenicline. However, existing therapies have not given satisfactory results in reducing smoking rates and the number of COPD significantly. Therefore, the anti-nicotine vaccine that is currently in development and research, such as NicVAX, NIC002, TA-NIC, and SEL-068, become a new perspective for smokers to stop smoking and prevent long term recurrence.*

Keywords*: nicotine, anti-nicotine, smoking, COPD*

INTRODUCTION

Based on WHO data, found 3 million deaths from Chronic Obstructive Pulmonary Disease (COPD) in 2015 (5% of the number of deaths in the world). The main causes are exposure to second hand smoke in both active and passive smokers. More than 90% of deaths caused by COPD is found in poor countries and emerging economies. Many countries have made regulations about smoking bans in public places, but do not significantly reduce the number of smokers.[1] It has been shown that smoking increases the mortality by reducing the age of 10 years in women studied. It is associated with chronic lung disease and lung cancer. Quitting before age 40 reduces mortality by 90% in women and stops before the age of 30 reduces 97% mortality.[2]

The attempt to stop a person from smoking has an important impact and one that can be intervened to reduce the incidence of COPD. Many things are done to help a person quit smoking, both in terms of psychotherapy and from pharmacotherapy. Therapy is widely used today is nicotine replacement therapy in various forms such as *nicotine patches,* antidepressants such as bupropion and nortriptyline, and par pesky nicotine receptor agonist is varenicline.[3]

This varenicline has become the preferred therapy as a monotherapy for smoking cessation, which we often hear the brand name of Champix®.[3] However, in a study conducted by Robert MA et al, found any side effects of moderate to severe neuropsychiatric disorders on the use of varenicline, bupropion, and nicotine patches. The most common side effects are nausea, insomnia, nightmares, and headaches.[4] New -new products Champix / Chantix® add a warning in the description of the side effects of its products, in which the side effects that may arise in the form of changes in behaviour, prejudice, agitation, depressed mood, and the emergence of mind even suicidal action. These symptoms can occur when they start using this drug or therapy after a few weeks even after stopping therapy.[5] It was also found that nicotine replacement therapy indeed increases a smoker motivation to quit smoking but does not reduce the number of cigarettes that they used significantly due to the use of drugs long enough to affect someone motivation to smoke and prices spent too large.[6] Many of the latest findings are still in the research phase to stop smoking addictive. One of the interesting and still in the stage of clinical trials and promising is the discovery of an anti-nicotine vaccine. The workings of this vaccine are to stimulate the production of the antibody will bind nicotine from cigarettes and prevent them from passing through the blood-brain barrier.[3]

CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND SMOKING

Chronic Obstructive Pulmonary Disease (COPD) is a disease characterized by constriction of the airways symptoms are progressive and chronic lasts. Symptoms of the disease are often found is overcrowding, cough, and excess sputum production. COPD patients did diagnosis with spirometry examination by the acquisition of the first second forced expiratory volume (VEP1) / Forced Vital Capacity (KVP) <0.7 that showed the presence of persistent airflow limitation. COPD associated with a chronic inflammatory process, where the most risk factor is exposure to cigarette smoke.[7] air pollution indoors or outdoors and pollution in the workplace can also be a high-risk factor of COPD. The more numbers of smokers in the world, the higher morbidity of COPD patients. *World Health Organization (WHO)* states the prevalence of smokers in the world reached more than 1.1 billion people with the percentage of men more than women.[8] In the cigarette found in many substances harmful to the body and it is estimated there are approximately 400 substances contained in it. [9] For example, toxic and carcinogenic

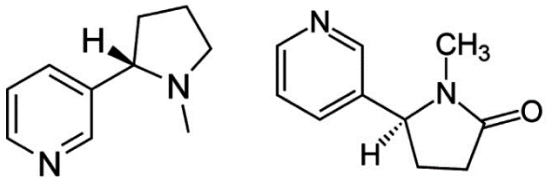
substances such as arsenic, *polycyclic aromatic hydrocarbons*, *N-nitrosamines*, nickel, cadmium, and so on. In addition, there is the content of toxins that contribute to the onset of smoking dependence is nicotine, *acetaldehyde*, ammonia, and so forth.[10]

In general, cigarette smoke causes symptoms of respiratory disorders in smokers such as reduced lung function, increased sputum production, and chronic cough.[11] Cigarette smoke contains many free radicals that directly affect human bronchial epithelium as the first defense of breathing. This causes an inflammatory reaction in which the bronchial epithelial cells have the ability to produce inflammatory mediators as well as a structural change of the respiratory tract. In addition, exposure to cigarette smoke also affects the function and size of ciliary epithelial cells and decreasing levels of glutathione that act as antioxidants.[12]

NICOTINE AS AN ADDICTIVE SUBSTANCE

Addiction / addictive defined as a condition caused by a drug or a substance that can control the behaviour of the wearer, often lead to a tolerance of the body, physical dependence, and the pleasant effects of the drug.[13] One of the substances that can cause this dependence is nicotine in cigarettes.

Nicotine was first discovered in 1828 and for many years studied the effects on the human nervous system to the 21st century found the effects of nicotine dependence to smoke.[14] The effect begins at smokers inhale cigarette smoke, nicotine into the blood and in a matter of ethics d pass the blood-brain barrier.[15] The accumulation of nicotine in the brain occur in just 7 seconds after inhaling cigarette smoke and the concentration of nicotine in the brain have a part-time over 33 seconds. In general, the half-life of nicotine is 2 hours and then be metabolized in the liver by the cytochrome P450 CYP2A6 isoenzyme into cotinine.[16]



(a) Nicotine **(b) Cotinine**

Figure 1. Chemical structure of (a) Nicotine dan (b) Cotinine[16]

Nicotine works on receptors in the brain that *nicotinic acetylcholine receptors (nAChRs).*[14] Receptors *nAChRs* is the most important things which were associated with nicotine dependence is α4 and β2 subunit, known as *α4β2 * nAChRs.* α4β2 * nAChRs become the target of current therapies in stopping nicotine dependence, as an example is the drug varenicline. In addition to α4 and β2 subunit also found that α5, α3 and β4 nAChR has the role of the addiction and lung cancer. β4 * nAChRs also play an important role in the regulation of appetite of smokers, where to hinder hunger in smokers.[17]

N AChRs active receptor also releases dopamine and epinephrine. These components play an important role in giving pleasure effects and reduce stress/anxiety. Therefore, if a person stops smoking, there will be a change in the feeling such as depression, irritable, anxiety, and restlessness.[16]

ANTI-NICOTINE VACCINE AS A NEW PERSPECTIVE FOR THE ADDICTION

Current therapy is still used to overcome smoking dependence, including nicotine replacement therapy, bupropion, and varenicline as the first line. For second-line therapy used clonidine and nortriptyline. However, therapy to overcome nicotine dependence is not very encouraging results. The smoking recurrence rate is still quite high. According to *the Centre for Disease Control and Prevention (CDC),* 75% of smokers who want to quit smoking, only <5% of

successful smoking of cigarettes after 1 t cope.[14]

In addition, the side effects of the drug were found in the form of moderate to severe neuropsychiatric disorders in using the drugs become contrary nowadays. [4] This led the effort to find the best therapy to stop nicotine dependence, starting from an electric cigarette, nicotine formulation of a new, *Cannabionoid* antagonist receptor, dopamine antagonists receptor, and anti-nicotine vaccine that seemed promising. [3]

Tabel 1. List of drugs in stopping the smoking addiction[3]

List of drugs stopping the smoking addiction	
Existing therapy	First line : - Nicotine replacing therapy - Bupropion - Varenicline (agonis parsial reseptor asetilkolin nikotinik α4β2)
Recent discovery	Second line : - Nortriptyline - Clonidine - Anti-nicotine vaccine : Nic VAX, SEL-068 - Electric cigarette - Nicotine with new formulas, i.e : *inhaled aerolized nicotine* (ARD-1600) - Partial agonist nicotine : *Cytisine* - Antagonis reseptor 1 Cannabinoid - Antagonis receptor D3 dopamin: GSK598809 - Inhibitor monoamine oxidase : Selegiline

The discovery of anti-nicotine vaccine gives a good breakthrough in the discovery of therapeutic nicotine dependence. The anti-nicotine vaccine works by stimulating the immune system that produces an antibody that will bind to nicotine and prevent it past the blood-brain barrier. This causes the effects of nicotine stimulants fail to go through the brain. Expected by this vaccine, could stop the unpleasant effects of d late dependence of smoke.[15]

There are challenges in itself, due to the very small size of the nicotine molecule to be recognized by the body's immune system. Therefore, a vaccine containing a recognizable component, for example, bacterial exoprotein in NicVAX (Prophet Biopharmaceuticals), virus-like particles with no genetic information in it such as NIC002 (Cytos and Novartis), recombinant cholera toxin such as TA-NIC (Celtic Pharma), and synthetic nano particles such as SEL-068 (Selecta Biosciences).[15,16] The nicotine vaccine developed has excellent advantages compared to other smoking cessation therapies, namely the effects of the body's immune system against nicotine can last for 6 to 12 months after vaccination.[15]

Antibodies generated does not cause symptoms off medication. The desire of smokers to get the fun effects of nicotine inhibited so as to make smokers do not get the fun effect again from smoking. The resulting antibody effect has a reversible ability between antibodies with nicotine in the blood where antibodies can repeatedly bind and release nicotine. Experiments on mice have also shown that in mice vaccinated had higher levels of nicotine in the blood that is high after 5 minutes of administration of nicotine into the body, compared with unvaccinated control.[13] It is

very important because of the high recurrence rate of smoking of therapies that already exists. However, there are disadvantages that may arise from the nicotine vaccine, such as some reinjection, the time before the immune response is reached, and the possibility of a given vaccine does not induce a maximal antibody response in the patient.[15]

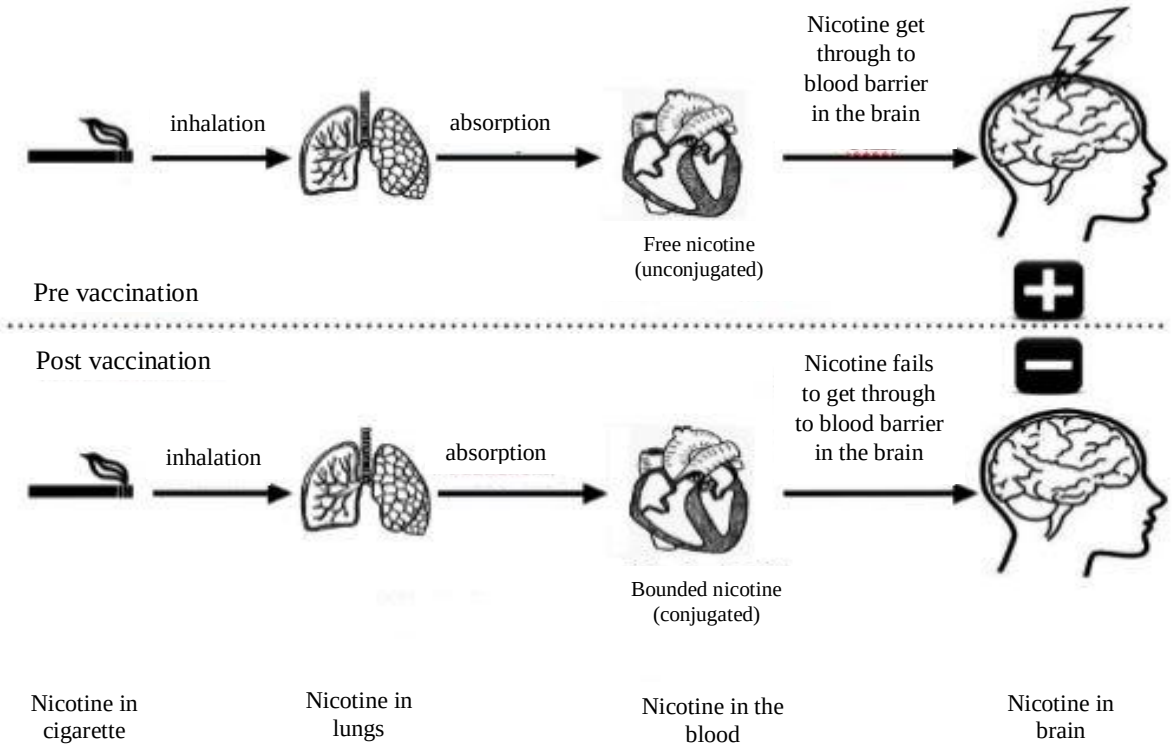


Figure 2. Mechanism of the anti-nicotine vaccine. The top image shows the effect of nicotine on the brain gives pleasure effect, while the bottom shows how nicotine vaccine that inhibits anti-nicotine get through to the brain.[16]

The development of anti-nicotine vaccine has shown results quite encouraging and safe for humans. Prophet Biopharmaceuticals has stated the positive results of the 2nd phase trial of the vaccine NicVAX where was found anti-nicotine antibody production in large quantities in patients vaccinated and there is correlation of antibody levels with long-term smoking cessation. Early developments of this vaccine are entering the 3rd phase clinical trials.[14] Although there is no research journal publishing the results of the 3rd phase of NicVAX vaccine, it has been announced from the NicVAX that there is no significant difference between study subjects with placebo.[18]

Another vaccine, NIC002 in 2005 revealed high levels of antibodies and was associated with smoking cessation. However, it was discovered the *flu-like symptoms* in 70% of subjects. This vaccine is in further development because it found the number of smoking recurrence in patients.[16]

TA-NIC vaccine is also entering the 2nd phase of clinical trials and has announced positive results, which found no serious side effects and antibody response in terms of the number and speed of onset is generated proportional to the doses of vaccine are given. In addition, it was also found in the 6th week of the trial, 19 of 44 subjects (43%) who received TA-NIC vaccine voluntarily quit smoking compared with placebo subjects.[19]

The above three vaccines are the NicVAX (Nabi Biopharmaceuticals) vaccine, NIC002 (Cytos and Novartis), TA-NIC (Celtic Pharma) has been declared safe

and well tolerated in stage I clinical trials. There are only mild local and systemic symptoms such as muscle aches, fever, headache, and nausea.[20] On the other hand, the vaccine SEL-068 (Selecta Biosciences), has not announced the results of its research.[16]

Table 2. List of companies and countries that are developing vaccine design and research to quit smoking.[13]

Companies	Countries
The main companies	
Cytos AGN	Switzerland
Nabi, Inc	USA
Celtic Pharma	United Kingdom
The other companies	
Chilka	British Virgin Islands
Scripps	San Diego, USA
Pharmaceutica AB	Stockholm, Swedia
Nebraska University	USA

If the anti-nicotine vaccine has been successful and can be applied globally, then this vaccine certainly has advantages over existing pharmacological therapies. These advantages are longer-lasting effects in months before the next booster is given and it takes less adherence from the smoker to affect the smaller recurrence rate compared with pharmacological therapy to be taken daily.[21]

CONCLUSIONS

Anti-nicotine vaccine that is under development and current research is NicVAX, NIC002, TA-NIC, and SEL-068. PT, other companies also are developing vaccine design and research on anti-nicotine like Chilka company in the British Virgin Islands, the company Scripps in San Diego, USA, the company Pharmaceutica AB in Stockholm-Sweden, and the University of Nebraska in the USA. Anti-nicotine vaccines that have been developed each of which has different components due to nicotine molecules are very small to recognize the body's immune system. The NIC-VAX vaccine developed by Prophet Biopharmaceuticals has a bacterial exoprotein component. The NIC002 vaccine developed by Cytos and Novartis has viral-like particle components with no genetic information in them. The TA-NIC vaccine developed by Celtic Pharma has a component of recombinant choline toxin. The SEL-068 vaccine developed by Selecta Biosciences has synthetic nanoparticles. Fourth vaccine stimulates the immune system works to produce antibodies that will bind to nicotine molecules and prevent past the blood-brain barrier.

Effects of this vaccine causing keingi n an smokers get unpleasant effects of smoking become obstructed and is expected to reduce the number of smokers in the world, and to prevent the recurrence rate of long term smoking. By discovering anti-nicotine vaccine, it has become a promising new perspective in the future to stop nicotine addiction so that morbidity and mortality of COPD that had a close relationship with the high smoking rates are expected to decline.

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