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Systematic Review

Recent advances in the development of Nicotine vaccine: A systematic review

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Abstract

Background: Nicotine is an important tobacco constituent that is responsible for addiction associated with the tobacco use. An efficient vaccine would generate antibodies that sequester nicotine in blood and prevent its access to the brain.

Objectives: The aim of this review was to assess the efficacy of nicotine vaccines for smoking cessation and for prevention of relapse, and to assess occurrence of any adverse events associated with their use.

Results: Three companies were in early clinical development of an anti-nicotine vaccine: Xenova (TA-NIC), Nabi (NicVAX) and Cytos (Nicotine-Qbeta). The carrier molecules are recombinant cholera toxin B (TA-NIC), an especially selected carrier protein (Nabi) and a virus-like particle VLP (Cytos). None of studies detected statistically significant difference in long-term cessation between participants receiving vaccine and placebo. But an increase in the smoking abstinence has been demonstrated for the individuals with a high titre of anti-nicotine antibody.

Conclusion: The studies on Nicotine vaccines have shown that these vaccines are effective in short term abstinence from smoking but effectiveness on a long term basis needs yet to be proven. No major side effects have been reported so far with minor side effects at times, limited in most cases to the site of injection and which are of short duration. No nicotine vaccines are currently licensed for use in any country but a number are under development.

INTRODUCTION

Tobacco is the single greatest preventable cause of death and only legal consumer product in the world today, killing up to half the people who use it [1] Generally, smoking has negative health effect and is the single largest preventable cause of morbidity and mortality all over the world [2]. World Health Organization (WHO) estimates that over 1 billion people addict to tobacco smoking, 5 million people die from tobacco-related diseases each year, and the toll will rise to over 8 million by 2030 if the current trends continue [3,4].

In a recent World Health Organization project report, [5] Tobacco-related deaths are projected to decline by 9% between 2002and 2030 in high-income countries, but to double from 3.4 million to 6.8 million in low- and middle-income countries.

Smokeless tobacco also contains substantial amounts of nicotine. With regular use throughout the day, this results in levels of nicotine in the blood similar to those observed in cigarette smokers [6,7] The time course of nicotine absorption from nasal snuff and oral snuff in packets has been reported [8,9].

Smokeless tobacco products cause addiction to nicotine that is characterized by intense craving, compelling urges to continue use despite recognized harm, inability to quit, and a withdrawal syndrome on abrupt discontinuation [10]. Absorption of nicotine across the buccal membrane appears to be related to the amount of nicotine present in the unionized “free base” form [11,12].

According to the World Health Organization, tobacco kills more than five million people in the world which is more than the mortality due to tuberculosis, HIV/AIDS, and malaria combined [9]. Nowadays, in the developed countries, smoking is the greatest cause of preventable death [13]. Health effects of particular concern include coronary artery and peripheral vascular disease, hypertension, peptic ulcer disease, and reproductive disorders [14].

Research over the past 3 decades has identified effective treatments for smoking, including counseling, social support, and several pharmacotherapies [15] six smoking cessation pharmacotherapies are currently approved by the US Food and Drug Administration. Five of these are nicotine replacement products (gum, patch, nasal spray, inhaler, and lozenge).

Each delivers nicotine, the agent that is responsible for the development of tobacco dependence, [16] in a way that allows an individual to reduce nicotine withdrawal symptoms and cravings for cigarettes when quitting smoking. Some other methods for tobacco use prevention include Non-nicotine treatments (Bupropion, Varenicline) and other medications (Clonidine, Nortryptiline) [17].

However, current pharmacological and non-pharmacological smoking cessation treatments have limited efficacy and are not widely disseminated to the general population of smokers [18,19]. Despite recent advances in behavioral and pharmacologic treatments, the vast majority of smokers who try to quit, they fail [20]. Quitting is not simply a matter of choice for most tobacco users, but involves a struggle. Tobacco use is typically woven into everyday life, and can be physiologically, psychologically, and socially reinforcing. Many factors, including media depictions and cultural and societal aspect of tobacco use, combine with tobacco's addictive capacity, making quitting difficult [21].

One of the new approaches for tobacco cessation in research is the nicotine vaccine which works by acting on the immune system to produce nicotine antibodies, which bind to nicotine and prevent it from crossing the blood brain barrier. Anti-drug vaccines are irreversible, provide protection over years and need booster injections far beyond the critical phase of acute withdrawal symptoms [20]. The aim of the present review is to update the information available on the nicotine vaccines being developed for smoking cessation and relapse prevention, and occurrence of any adverse events associated with their use.

LITERATURE SEARCH

The literature search was performed independently by 2 reviewers. The reviewers searched the electronic print media such as Medline and Pubmed, Google Scholar for literature, related to "Nicotine Vaccine" published either in English or with an English abstract in any other language publications from 2010 to April 2020.

The keywords for search were Nicotine vaccines, Anti-nicotinic vaccines, vaccines for smoking cessation, tobacco cessation vaccines. The relevant literature was searched thoroughly and the Cross references of the relevant articles were also retrieved.

There was limited literature on Nicotine vaccines. So, unpublished literature was also searched. A total of 8 articles were considered finally after the literature review which included 2 unpublished and 6 published articles. As the published literature on the nicotine vaccine was sparse, the unpublished literature was also included as a part of the systematic review.

How tobacco causes addiction?

The addiction, due to tobacco use, is caused by a component in tobacco called as Nicotine [22]. Nicotine increases the brain's responsiveness to rewarding stimuli, ultimately leading to addiction.

The dependence-producing properties of nicotine are believed to be mediated by the α4β2 subtype of the nicotinicacetylcholine receptor located in the ventral tegmental area of the brain [23]. Nicotine stimulates the mesolimbic reward system where dopamine is secreted from the nucleus accumbens to the hippocampus and then contextual information is stored to the cerebral cortex, and these signals give reward to the smoker, and positively reinforce the habitual use of tobacco. 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 non-smokers [24].

How does nicotine vaccine work?

The concept of vaccination against drugs of abuse has already been described by Boneseetal [22] who showed that immunisation with morphine conjugates reduced heroin self-administration in monkeys.

The mechanism of anti-nicotine vaccines is based on the binding of anti-nicotine antibodies to the nicotine molecule after it enters the body through the lungs. The molecular weight of a nicotine molecule is about a thousand times less than the weight of an IgG antibody. After binding to the nicotine molecule, the large antibody molecule covers the nicotine molecule so that the binding of the nicotine to its receptor is impaired or no longer possible (steric hindrance).For the smoker, the subjective impression is comparable to smoking a cigarette with no nicotine or very low nicotine content. The vaccine does not affect in any way directly the craving for the drug itself [24]

Anti-nicotinic antibodies, which do not cross the blood-brain barrier, bind the drug in the blood and thus reduce the amount and rate of drug entering the central nervous system. By lowering the rewards associated with nicotine use, the addicted individual could no longer be motivated to consume the tobacco.23This idea of using antibodies to bind a drug and thus disabling it from crossing the blood-brain barrier was first tested in an animal model of heroin addiction and subsequently extended to other species and other drugs of abuse, including morphine, methamphetamine, phencyclidine, cocaine and nicotine [25].

Immunological Mechanism of Action

The detailed immunological mechanism of action of nicotine vaccine is as follows. The minimum molecular weight for a molecule to elicit a specific immune response is 10kDa. Nicotine is too small (molecular weight 167 Da) to elicit an immune response (i.e., it is not immunogenic). Regular tobacco users do not have antibodies against it. Thus, Nicotine is rendered immunogenic by conjugating (linking) the drug itself or a structurally related compound (a hapten) to an immunogenic carrier protein to form a complete immunogen, referred to as a conjugate vaccine. Various types of carrier proteins have been employed, including keyhole limpet hemocyanin(KLH), [26-28] a 19-residue peptide, [29] recombinant cholera toxin B subunit, [30] and recombinant pseudomonas exoprotein A [31,32].

Current evidence related to nicotine vaccine

All anti-nicotine vaccines under research, are vaccine constructs made up of a conjugate, where nicotine is linked to a carrier protein to make it 'visible' to the immune system, and an adjuvant, which enhances antibody production against the

nicotine molecule. Various pharmacological companies and academic groups had developed nicotine vaccines based on different conjugates and coupling of different nicotine derivatives [16,32-34]. The conjugates used in the clinical trials vary widely and include virus-like particles (VLPs; Cytos AG) as well as bacterial toxin components (Nabi, Celtic Pharma). The different forms of adjuvant used so far in clinical trials are all widely used and approved adjuvant compounds such as Freund's in animals and alum in humans. The mode of application of the vaccines in the clinical trial reports has been limited to injection. There are three companies who have moved nicotine conjugates into clinical testing. The detail of the trials for testing the efficacy of the nicotine vaccines has been shown in the table 1.

TA-NIC (Celtic Pharma): TA-NIC, developed by Xenova and now in the portfolio of Celtic Pharma in the UK, was developed using a *recombinant cholera toxin-B subunit* as a carrier protein for the nicotine vaccine. The initial vaccine development goes back to Immulogic Pharmaceutical Co.'s development programme for an anti-nicotine vaccine in 1997. In 1999, this experimental vaccine programme was acquired by Cantab Pharmaceuticals which merged in 2001 with Xenova Group plc, which continued the vaccine development work. Celtic Pharma Holdings LP took over Xenova in 2005 [35].

No preclinical results have been published. Celtic obtained Investigational New Drug application (IND) approval for their anti-nicotine vaccine candidate TA-NIC. Xenova Group in the United Kingdom had already completed two Phase I/II studies with this vaccine candidate in 120 patients who were smokers. Prior trials showed efficacy of the vaccine and there were only minor side effects. It can be seen in the study protocol of Xenova's second Phase I trial that the company evaluated doses of 50 µg, 250 µg and 1000 µg. The last dose seems to be a lot of

Table 1: Showing the comparison of trials of various vaccines.

Researchers	Phase of trial	Vaccine used	Study population	Sample size	Dosages	Comparison group	Outcome measure & Results
Unpublished	I/II assessing safety and immunogenicity	TA-NIC	Smokers 18 yrs, male and female, regular smoker for 1 year	120	50µg, 250 µg, 1000 µg Intramuscular injection at weeks 0, 2, 4, 6, 8 and 12 with a booster at 32 weeks,	Not available	Anti-nicotine antibody responses were dose dependent.12 mo self-reported quit rates were substantially greater among those receiving TA-NIC than those receiving placebo; in the placebo group, 1 out of 12 participants (8%) reported being abstinent at their last visit or at 12 mo compared with 3 out of 16 (19%) and 6 out of 16 (38%) in the two groups receiving the higher doses of TA-NIC.
Unpublished	Phase II Multicentre placebo controlled double-blind study	TA-NIC	Smokers	200 per arm sample size was initially decided, but only 522 subjects were enrolled	100 or 250 µg of TA-NIC	Placebo group	Abstinence rate 6 months after the initial vaccination Results were not made public
Maurer et al (2005)	Phase I Safety and immunogenicity trial	Nic-Qb (NIC002) (Cytos- biotechnology)	healthy non-smokers	32	Not mention-ed	No comparison group was there	Nicotine specific IgM Antibodies at day 7 and nicotine specific IgG antibodies at day 14
Cornuz et al (2008)	Phase II Randomized Double-blind placebo controlled study	Nic-Qb	229 smokers Pts generally healthy, aged 18-70, smoking Fagerström score >=5. Randomized 2:1 to vaccine (229) or placebo (112);	229, 112	110 µg at 0,1,2,3,4months	112 smokers	Abstinence rate at 6 months Primary: Continuous Abstinence Rates for months 3-6, validated by CO<10ppm. Immunogenicity, safety and tolerability **Results**: Intervention did not significantly increase continuous abstinence rates in the intention to treat analysis Per-protocol analysis excluding all subjects with concomitant use of NRT revealed significantly higher abstinence rates in subjects with particularly high antibody titers

conjugate for a hapten vaccine. The 12 months self-reported quit rates were substantially higher among those receiving TA-NIC than compared to placebo; with 1 out of 12 participants (8%) in placebo group reporting to be abstinent at their last visit or at 12 months than 3 out of 16 (19%) and 6 out of 16 (38%) among 2 groups that received higher doses of TA-NIC. The proportion of participants who successfully made a quit attempt was 95% among those receiving TA-NIC and 73% among those receiving the placebo [36].

The new Phase IIB study, which Celtic started in the United States, was a placebo-controlled double-blind study. All treatment arms received professional counselling. The study was a multicenter trial that included different doses of the vaccine and enrolled up to 200 patients in each of the three treatment arms. The primary endpoint of the study was the abstinence rate 6 months after the initial vaccination.35The assessment was carried out at 4-weeks period with quit rate at Week 26 measured by self-reported abstinence in the 4 weeks immediately prior to the 26 week visit and supported by CO breath test data. The study was completed in 2009 and the results are not publically available [37].

Nic-Qb (Cytos Biotechnology): Cytos Biotechnology used virus-like particles (VLPs) in the Nic-Qb(synonym: NIC002) vaccine as a carrier protein in spite of cholera toxin. NicQb, utilized conjugation via the 3'-position on the pyrrolidine ring of nicotine to a virus-like particle of bacteriophage Qb.The coat protein of the bacteriophage Q β is recombinantly expressed in *Escherichia coli* and 180 subunits self-assemble into a highly ordered VLP with a diameter of 25-30 nm [38].

Both features- the repetitive antigen presentation on the VLP and the presence of T-helper cell epitopes-make the Q β -based vaccines highly immunogenic and enable a 100% responder rate in humans after only a single immunization. In the Nic-Qb vaccine, about 585 nicotine molecules are covalently coupled to one Q-β VLP [16].

In preclinical experiments of NicQb, mice were immunized and boosted on day 14. After a single immunization with 60 μg NicQb in the absence of adjuvants, high levels of nicotine-specific IgG titers were found in all vaccinated mice. Titers could be increased by a second immunization at day 14. Maximum titers were measured at about day 21 from which point anti-nicotine antibody levels slowly declined with a half-life of approximately 60 days. Addition of Alum increased the titers in mice about 6-fold and maximum titers after one boost (at day 14) were reached between day 40 and day 60. After intravenous nicotine challenge, vaccinated mice exhibited strongly reduced nicotine levels in the brain compared with control mice [16].

In a phase I study, 32 healthy non-smokers were immunized with NicQb. The vaccine was safe and well tolerated. All volunteers who received NicQb showed nicotine-specific IgM antibodies at day 7 and nicotine-specific IgG antibodies at day 14. Antibody levels could be boosted by a second injection or the addition of Alum as an adjuvant and the antibodies had a high affinity for nicotine [16].

Cornuz et al evaluated Nic-Qb (NIC002) in a 6-month randomized, double blind phase II smoking cessation study in 341smokers with a subsequent 6-month follow-up period. Two hundred and twenty-nine (229) participants randomized to active treatment received five injections of 100 gNIC002 at months 0, 1, 2, 3 and 4. One hundred and twelve participants were randomized to placebo received alum injections on the same schedule. The target quit date was set at one month and individual behavioural counselling was provided to all participants from week three to month four. Results showed that Nicotine-Qb did not significantly increase continuous abstinence rates in the intention-to-treat population. However, a per-protocol analysis excluding all subjects with concomitant use of nicotine replacement therapy revealed significantly higher abstinence rates in the upper third of responders (i.e. subjects with particularly high antibody titres) as compared with the placebo group (56.6%vs 31.3% with odds ratio of 2.9). This difference was maintained until 12 months (41.5%vs 21.3%; OR = 2.6) [39].

NicVax: This vaccine was developed by Nabi Pharmaceuticals, using Pseudomonas exoprotein A and is currently being further evaluated for clinical use by Glaxo-SmithKline. When administered to rats, this vaccine elicited high titers of nicotine-specific antibodies, reduced nicotine distribution to brain, and reduced some of the physiologic and behavioural effects of nicotine [31].

These data suggest that vaccination during concurrent nicotine administration is feasible, and that the ability of vaccination to reduce nicotine distribution to brain is preserved even after months of nicotine dosing at rates approximating cigarette smoking [31].

Wagena et al conducted a randomized, placebo-controlled phase 1/2 trial to evaluate the safety and immunogenicity of four doses of a nicotine vaccine in smokers and non-smokers. Study population was comprised of 21 smokers and 9 non-smokers in good physical and mental health. Each volunteer received four spaced intramuscular injections of 100 mg of purified 39-aminomethylnicotine conjugated to detoxified *Pseudomonas aeruginosar-exoprotein A* or placebo both adsorbed to 800 mg aluminium into the deltoid muscle of alternating arms. Clinical safety was determined by vital signs, reactogenicity, and adverse events, and immunogenicity was measured by enzyme-linked immunosorbent assay. Intensive follow-up for 266 days revealed the vaccine to be well tolerated. No significant differences were found in occurrence of adverse events between the vaccine and placebo groups. Significant increases in the Geometric Mean Titer (GMT) levels of nicotine-specific antibodies were observed from 7 days after the second vaccination (day 21) and third vaccination (day 49). A fourth dose administered at day 182 also significantly boosted waning antibody levels. The results showed that the immunogenicity of the vaccine was not impeded by the presence of nicotine [40].

Hatsukami et al assessed the safety and immunogenicity of NicVAX and its effects on smoking behaviour. Smokers (N=68) were recruited for a non-cessation treatment study and assigned to 1 of 3 doses of the nicotine vaccine (50, 100, or 200 μg) or placebo. They were injected on days 0, 28, 56, and 182 and monitored for a period of 38 weeks. Results showed that the nicotine vaccine was safe and well tolerated. Vaccine immunogenicity was dose-related (P <0.001), with the highest

dose eliciting antibody concentrations within the anticipated range of efficacy. The 30-day abstinence rate was significantly different across the 4 doses (P = 0.02), with the highest rate of abstinence occurring with 200 µg [41].

Hatsukami et alevaluated the results of 200- and 400-µg doses of NicVax administered four or five times in a 6-month randomized, double blind, multi-centre trial among 301 smokers with a subsequent 6-month follow-up period. Continuous abstinence rates at 12 months were significantly higher in the top 30% responders than in subjects receiving placebo (19.7%vs 6.0%; OR 4.41, 95% CI 1.53, 12.71; p = 0.006). In addition, continuous abstinence was enhanced in subjects receiving the most intensive vaccination regimen. Finally, among smokers who failed to quit, smoking reduction occurred more frequently in subjects with high antibody titres ('responders') compared with placebo [42].

Niccine: Niccine was developed by Independent PharmaceuticaABin Sweden, using tetanus toxoid. Niccine is a nicotine hapten tetanus-toxoid conjugate vaccine. Results of pre-clinical studies of this vaccine are not available for review [43].

Tonstad et al conducted a phase II trial to evaluate the clinical efficacy of Niccine for tobacco smoking relapse prevention. In this study, 355 smokers (cigarette) aged 25-50 years were enrolled in a randomized, double-blind, parallel group 1-year trial including 16 visits and 16 telephone calls. Niccine 40 µg or placebo was administered on days 0, 28, 56, 90, 150, and 210. Between days 56-98, subjects were also administered with Varenicline to aid cessation. Only individuals abstinent between days 90-98 (n = 265) were allowed to continue to 1 year (n = 219). At 1 year, no relapse was 43.3% in the Niccine versus 51.1% in the placebo groups (difference = -7.9%; 95% CI = -20.6% to 4.9%). There was no benefit of Niccine on smoking status at 6 or 9 months, exhaled carbon monoxide levels, time to relapse, abstinence and withdrawal symptoms did not differ between Niccine and placebo groups. Nicotine antibody levels increased (mean = 1.34 µg/ml; SD = 2.84 µg/ml) in the Niccine group, but were not related to relapse [43].

DISCUSSION

Nicotine vaccines are under development for tobacco dependence treatment and have shown some promising effects [41]. The exact mechanism of action of nicotine vaccines is still not clear. Most likely, the inhibition of the passage of nicotine from the blood to the brain during a lapse is crucial for the efficacy of nicotine vaccines. This inhibition can be achieved by a more or less complete peripheral block of nicotine or just by a delay in time to peak nicotine concentrations in the brain. Anti-nicotine antibodies in the serum would thus serve as a buffer for nicotine dampening or delaying the peak nicotine concentrations and thus interfering with reinforcement.44The fact that the vaccine efficiency is directly related to the level of specific antibodies is encouraging, because it shows how to maximize the efficiency of existing vaccines [35].

In the case of vaccination, due to the type of application, the compliance is good and easy to control. Improved patient compliance led to a lack of major side effects and relatively minimal dosing requirements. Moreover, the mechanism of action allows simultaneous combination of other pharmacotherapies.

Nicotine vaccines can be used both for relapse prevention and as preparation for aquit attempt. Results from a few clinical trials are available so far. The majority of those trials were designed as smoking-cessation studies with target quit days rather than relapse prevention trials.

The results from Phase II clinical trials published so far indicated only modest efficacy of the nicotine vaccine for smoking cessation. The abstinence rates among vaccinated smokers do not surpass those in the placebocontrol groups. Abstinence rates were significantly higher than placebo only in those smokers who achieved higher therapeutic antibody levels. Two Phase III clinical trials of the NicVAX have not been published in peer-reviewed journals yet. However, according to press releases, both trials failed to show efficacy of the vaccine *vs.* control, despite success in Phase I and II trials.

The study by Hatsukami et al showed that smokers who achieved higher anti-nicotine Ab concentrations after the delivery of NicVAX, nicotine vaccine were more likely to quit and remain abstinent from smoking. The higher Ab group demonstrated the highest abstinence rates independent of the time period of ascertainment of status. A sufficient level of antibodies has to be achieved for nicotine vaccine to be useful in making the patients quit smoking [41].

Chronic nicotine-dependent smokers seeking help to quit or not to relapse are the primary target for immunotherapy. In theory, vaccination should not have an effect on withdrawal and craving, in contrast to presently available therapies, which attenuate withdrawal and craving by affecting neuronal receptor signalling in the brain [44].

CONCLUSION

All clinical studies except one reported encouraging data indicating that the vaccines enhance the smoking cessation rates of already existing therapies and are complementary to them. As such no side effects have been reported such as nausea, insomnia and abnormal dreams, as seen for drugs binding to receptors in the brain. The tendency to increase the intake of nicotine in the form of increased smoking to compensate for the reduced availability in the brain has not yet been reported. None of the vaccines tested has received regulatory approval and the clinical trials have not yet been completed. So, concrete evidence needs yet to be established through Phase III trials with improved dose, regimen and formulation.

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