Nicotine constitutes the main addictive component of tobacco products. Unfortunately, this compound accounts for millions of deaths and diseases worldwide. Nicotine addiction is a complex phenomenon with multiple biological, psychological, and social factors. One of the challenges in treating nicotine addiction relates to its high rate of relapse, often triggered by exposure to nicotine or smoking cues. Nicotine vaccines, a novel immunological approach, serve to prevent or reduce nicotine addiction. They induce the production of antibodies that bind to nicotine and block its entry into the brain. Nicotine vaccines have shown promising results in preclinical studies but have failed to demonstrate sufficient efficacy and safety in human trials. Several factors may contribute to the limited success of nicotine vaccines: Different antibody responses, genetic and environmental factors, the complexity of nicotine pharmacokinetics and pharmacodynamics, and the heterogeneity of smoking behavior and motivation. This study reviews the rationale, mechanism, development, preclinical studies, and clinical trials of nicotine vaccines, as well as the challenges and future directions of this research field. We believe future research should focus on improving the design and delivery of nicotine vaccines, identifying biomarkers and predictors of antibody responses and treatment outcomes, exploring the combination of nicotine vaccines with other pharmacological and behavioral interventions, and evaluating nicotine vaccines’ long-term effects and cost-effectiveness.
Introduction

Tobacco use stands out as one of the leading causes of preventable death and diseases worldwide, accounting for more than 8 million deaths annually [1]. Tobacco products contain nicotine, a psychoactive alkaloid that induces addiction by activating nicotinic acetylcholine receptors (nAChRs) in the brain [2]. Multiple biological, psychological, and social aspects contribute to nicotine addiction, characterized by tolerance, withdrawal, craving, and loss of control over tobacco consumption [3]. One of the significant challenges in treating nicotine addiction relates to its high rate of relapse, often triggered by exposure to nicotine or cues associated with smoking [4].

Several pharmacological and behavioral interventions have been introduced to help smokers quit or reduce their tobacco use. Some interventions include nicotine replacement therapy, bupropion, varenicline, counseling, and cognitive-behavioral therapy [5]. However, these interventions have demonstrated limited efficacy and adherence, and many smokers fail to achieve or maintain abstinence. Therefore, novel and more effective strategies are required to prevent or treat nicotine addiction.

Nicotine vaccines demonstrate a new immunological approach aiming to block the effects of nicotine in the brain by inducing the production of antibodies that bind to nicotine and prevent its entry into the central nervous system (CNS) [6]. Nicotine vaccines act through active immunization: Introducing a foreign substance so the immune system makes specific antibodies against that substance. These antibodies can find and bind to nicotine molecules upon entering into the blood after smoking or using other types of tobacco. The nicotine-antibody complex is too big to pass through the blood-brain barrier. Consequently, the amount of nicotine that reaches the brain reduces, resulting in weakening the rewarding and reinforcing effects of nicotine [7].

The primary goal of nicotine vaccines is to reduce or eliminate the motivation to smoke by interfering with the pharmacological actions of nicotine in the brain. Nicotine vaccines may also reduce the severity of withdrawal symptoms and cravings by maintaining a low level of nicotine in the CNS [8]. Moreover, nicotine vaccines may prevent or delay the initiation of smoking among adolescents and young adults by reducing the likelihood of developing nicotine dependence. Nicotine vaccines may also play a role in harm reduction by switching from combustible cigarettes to less harmful forms of nicotine delivery, such as e-cigarettes or snus [9].

Accordingly, this review provides an overview of the rationale, mechanism, development, and preclinical and clinical trials of nicotine vaccines and the challenges and future directions of this research field. We will also highlight some ethical, social, and economic implications of nicotine vaccines for public health and tobacco control.

Materials and Methods

A narrative review of the English papers on nicotine vaccines was conducted, focusing on this immunological approach and its rationale, mechanism, development, preclinical studies, and clinical trials. The search was conducted in August 2023 with no date restrictions in electronic databases: PubMed, Scopus, and Web of Science. The keywords and their combinations used for the search included “nicotine” AND “vaccine” OR “immunotherapy” OR “antibody” AND “addiction” OR “smoking” AND “cessation” OR “relapse.” Preclinical and clinical studies on nicotine vaccines were included in our review.

Results

Rationale and mechanism of action

Nicotine vaccines use a new method based on immunology to stop nicotine from affecting the brain. Specific antibodies that attach to nicotine keep it out of the central nervous system [6]. Nicotine vaccines act through active immunization: Introducing a foreign substance so the immune system makes specific antibodies against that substance. These antibodies can find and bind to nicotine molecules upon entering into the blood after smoking or using other types of tobacco. The nicotine-antibody complex is too big to pass through the blood-brain barrier. Consequently, the amount of nicotine that reaches the brain reduces, resulting in weakening the rewarding and reinforcing effects of nicotine [7].

Development of nicotine vaccines

Several types of nicotine vaccines have been developed and tested in preclinical and clinical studies, with varying degrees of success and challenges. The most common types of nicotine vaccines are based on the conjugation of nicotine-like hapten to carrier proteins such
as keyhole limpet hemocyanin [10], tetanus toxoid [11], or diphtheria toxoid [12]. Some examples of nicotine vaccines are NicVAX [13], Niccine [11], TA-NIC [14], and SEL-068 [15]. These vaccines are administered by intramuscular injection, usually in multiple doses over several weeks or months, to induce and maintain a high level of anti-nicotine antibodies in the serum.

The efficacy and safety of nicotine vaccines have been evaluated in animal models and human trials, using various outcome measures, such as antibody titers [16], nicotine pharmacokinetics and pharmacodynamics [17], smoking behavior and biomarkers [18], smoking cessation and relapse rates [19], and adverse events [11]. The results of these studies are summarized below.

**Preclinical studies**

Preclinical studies have shown that nicotine vaccines can induce high and specific antibody responses against nicotine in rodents and non-human primates without adverse effects [12, 16, 20-22]. These antibodies can bind to nicotine and reduce its brain penetration and accumulation. This reaction can decrease the rewarding and reinforcing effects of nicotine, as measured by behavioral tests such as self-administration, conditioned place preference, and intracranial self-stimulation. Nicotine vaccines can also attenuate the withdrawal symptoms and reinstatement of nicotine-seeking behavior induced by nicotine or cues [23]. Moreover, nicotine vaccines can modulate the expression and function of nAChRs in the brain [24], which may affect the sensitivity and tolerance to nicotine.

**Clinical trials**

Clinical trials have tested the efficacy and safety of nicotine vaccines in smokers who wanted to quit or reduce their tobacco use. The results of these trials have been inconsistent and disappointing. Some trials have reported that nicotine vaccines can increase the antibody levels in smokers. Still, the antibody titers were highly variable among individuals and often insufficient to block the effects of nicotine [11, 17, 25, 26]. Other trials have found that nicotine vaccines can alter the pharmacokinetics and pharmacodynamics of nicotine, such as reducing the plasma concentration and decreasing the subjective effects of nicotine [20, 24]. However, these changes are not correlated with the antibody titers or the smoking outcomes [11]. Furthermore, none of the trials has demonstrated that nicotine vaccines can significantly improve smoking cessation or relapse rates compared with placebo or standard treatment. Nicotine vaccines are generally well tolerated by smokers, with mild to moderate local and systemic adverse events such as injection site reactions, headache, nausea, and fatigue [14, 18, 26].

**Challenges of nicotine vaccines**

One of the main challenges of nicotine vaccines is how to induce and maintain a high and consistent level of anti-nicotine antibodies in smokers. People respond differently to the antibody level induced by nicotine vaccines. The response depends on several factors, such as the type and dose of the vaccine, the number and frequency of injections, the genetic and immunological background of the subjects, and the smoking status and behavior of the subjects [18, 19]. Besides, the optimal antibody titer that can effectively block the effects of nicotine in the brain is not well established. Adding to this problem, the antibody titer may not reflect the antibodies’ actual binding capacity and affinity to nicotine, which may also affect their ability to block nicotine entry into the brain.

Nicotine vaccines should overcome the pharmacological and behavioral compensation mechanisms that smokers may adopt to counteract the reduced effects of nicotine in the brain. Smokers may increase their tobacco consumption or switch to more potent products to achieve the desired level of nicotine stimulation [27]. This tactic may increase exposure to harmful chemicals and risk adverse health consequences. Smokers may also experience more severe withdrawal symptoms and cravings due to the lower availability of nicotine in the brain [28]. These factors may reduce the motivation and adherence of smokers to quit or reduce their tobacco use. Therefore, it seems that nicotine vaccines should be complemented with other pharmacological and behavioral interventions that can help smokers cope with these challenges and enhance their chances of success [5].

Another challenge of nicotine vaccines relates to their long-term effects and cost-effectiveness for public health and tobacco control. Nicotine vaccines are expected to have a prolonged duration of action, which may be beneficial for preventing relapse or initiation of smoking. However, it may also pose some risks and limitations. For instance, nicotine vaccines may interfere with the therapeutic use of nicotine or other nicotinic agents for medical conditions such as Alzheimer disease, Parkinson disease, or schizophrenia [29].

Nicotine vaccines may also have ethical and social implications, such as the potential for coercion or discrimination of smokers or non-smokers by employers, insurers, or governments. Nicotine vaccines may also have
an economic impact, such as the cost of development, production, distribution, and administration of the vaccines, as well as the cost-effectiveness compared with other interventions for smoking cessation or prevention. These issues should be carefully addressed and balanced before society accepts and widely implements nicotine vaccines.

Future directions

Nicotine vaccines demonstrate a novel and promising strategy to prevent or treat nicotine addiction by blocking the effects of nicotine in the brain. However, more research is needed to optimize their development and application. Future research should focus on improving the design and delivery of nicotine vaccines, identifying biomarkers and predictors of antibody responses and treatment outcomes, exploring the combination of nicotine vaccines with other pharmacological and behavioral interventions, and evaluating nicotine vaccines’ long-term effects and cost-effectiveness.

Conclusion

In conclusion, nicotine vaccines may represent a promising tool to combat nicotine addiction. However, they are not a magic bullet. In fact, they should be considered part of a comprehensive and multidisciplinary tobacco control approach involving individual, interpersonal, community, environmental, and policy interventions.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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