ISSN: 2306-6091

International Journal of Pharmaceuticals and Health care Research (IJPHR)

IJPHR |Vol.13 | Issue 2 | Apr - Jun -2025

www.ijphr.com

DOI : https://doi.org/10.61096/ijphr.v13.(SPL 1).2025.203-212

Review

A Short Review On Nicotine Replacement Therapy

[1]Abhilash Bisht, [2]Gagandeep Singh*

[1]Research Scholar, Maya College of Pharmacy, Dehradun
[2]Assistant Professor, School of Pharmacy, Maya College of Pharmacy, Dehradun

*Corresponding Author: Gagandeep Singh
Email: gagandeep.singh@maya.edu.in

Published on: 31 May 2025

Published by:
DrSriram Publications

Abstract

Nicotine replacement therapy (NRT) remains the most widely accessible and evidence-based pharmacological intervention for smoking cessation. This review summarizes the mechanisms, formulations, efficacy, and safety profiles of FDA-approved NRT products, including transdermal patches, gum, lozenges, inhalers, and nasal sprays. While all NRTs alleviate withdrawal symptoms by delivering nicotine without tobacco toxins, their pharmacokinetic differences influence user adherence and success rates. Fast-acting forms (gum, spray) provide rapid craving relief but require behavioral compliance, whereas patches offer steady dosing with lower misuse potential. Emerging approaches like nicotine vaccines and monoclonal antibodies show theoretical promise but lack clinical efficacy in trials. Despite limitations including variable individual response and compensatory smoking behaviors NRT doubles quit rates when combined with behavioral support. The review highlights the importance of personalized NRT selection based on dependence severity, side effect profiles, and patient preferences, while underscoring the need for novel agents to address treatment-resistant addiction.

Keywords: Nicotine replacement therapy (NRT), smoking cessation, nicotine dependence, transdermal patch, nicotine gum, nicotine lozeng.

INTRODUCTION

Nicotine is a naturally occurring alkaloid found primarily in the leaves of the tobacco plant (*Nicotiana tabacum*), though it is also present in smaller quantities in other plants of the Solanaceae family, such as tomatoes, potatoes, and eggplants.[1-4] As the primary psychoactive component in tobacco, nicotine is responsible for the addictive properties of cigarettes, cigars, e-cigarettes, and other tobacco products. Chemically, nicotine is composed of a pyridine and a pyrrolidine ring, and it acts as a potent stimulant in low doses and a sedative in high doses. Its effects on the human body are mediated through its interaction with nicotinic acetylcholine receptors (nAChRs) in the central and peripheral nervous systems, leading to the release of neurotransmitters such as

dopamine, norepinephrine, serotonin, and endorphins. This release creates the pleasurable sensations associated with smoking, reinforcing repeated use and contributing to dependence.[5-12]

The history of nicotine use dates back thousands of years, with indigenous peoples in the Americas using tobacco for ceremonial, medicinal, and recreational purposes long before European colonization. Following the arrival of Europeans in the New World, tobacco was introduced to Europe and quickly became a global commodity. [13-18] By the 19th century, advancements in cigarette manufacturing and mass marketing led to widespread nicotine consumption, despite growing awareness of its health risks. In the 20th century, scientific research established the link between smoking and diseases such as lung cancer, cardiovascular disease, and chronic obstructive pulmonary disease (COPD), prompting public health campaigns to reduce tobacco use. Despite these efforts, nicotine remains one of the most widely used addictive substances worldwide, with millions of people dependent on tobacco products.[19,20]

Nicotine exerts its effects primarily through its action on the brain's reward system. When inhaled or absorbed, it rapidly crosses the blood-brain barrier, binding to nAChRs and triggering the release of dopamine in the nucleus accumbens,[21][22] a key region associated with pleasure and reinforcement. This dopaminergic activity underlies nicotine's addictive potential, as users repeatedly seek to recreate the rewarding sensation. Additionally, nicotine enhances cognitive functions such as attention, memory, and reaction time in the short term, which contributes to its perceived benefits among users. However, chronic use leads to neuroadaptations, including receptor desensitization and upregulation, resulting in tolerance and withdrawal symptoms upon cessation. Withdrawal symptoms such as irritability, anxiety, difficulty concentrating, increased appetite, and intense cravings make quitting challenging and often lead to relapse.[23] [24][25]

Beyond its neurological effects, nicotine has significant cardiovascular and metabolic impacts. It stimulates the adrenal glands to release epinephrine (adrenaline), increasing heart rate, blood pressure, and cardiac output. These effects raise the risk of hypertension, arrhythmias, and atherosclerosis, particularly in long-term smokers.[26] Nicotine also influences insulin sensitivity, contributing to an increased risk of type 2 diabetes among tobacco users. While nicotine itself is not the primary carcinogen in tobacco smoke most cancers are caused by tar and other combustion byproducts it promotes tumor growth by stimulating angiogenesis and cell proliferation. This has raised concerns about the safety of long-term nicotine use, even in non-combustible forms like e-cigarettes and nicotine replacement therapies (NRTs).[27] [28][29]

In recent years, the rise of electronic nicotine delivery systems (ENDS), such as e-cigarettes and vapes, has transformed the landscape of nicotine consumption. Marketed as a less harmful alternative to traditional smoking, these devices heat a nicotine-containing liquid into an aerosol, which users inhale.[30][31] While they eliminate many of the toxic combustion products found in cigarette smoke, concerns remain about their long-term health effects, particularly regarding lung health and cardiovascular risk. Additionally, the popularity of flavored e-liquids and sleek, discreet designs has led to a surge in nicotine use among adolescents, sparking public health debates over regulation and youth prevention strategies. Some studies suggest that e-cigarettes may serve as effective smoking cessation tools for adult smokers, while others warn that they may act as a gateway to traditional smoking or sustain nicotine addiction indefinitely.[32]

Nicotine replacement therapies (NRTs), including patches, gums, lozenges, inhalers, and nasal sprays, provide controlled doses of nicotine to help smokers quit by reducing withdrawal symptoms and cravings.[33][34][35] These products are designed to wean users off nicotine gradually while avoiding the harmful toxins in tobacco smoke. Clinical studies have demonstrated their efficacy when combined with behavioral support, though success rates vary depending on individual factors such as dependence level and motivation. Other pharmacological treatments for nicotine dependence include bupropion, an antidepressant that reduces cravings, and varenicline, a partial agonist at nAChRs that blocks nicotine's rewarding effects.[36] Despite these options, relapse rates remain high, underscoring the complexity of nicotine addiction and the need for personalized treatment approaches.

Public health policies aimed at reducing nicotine addiction have included measures such as smoking bans in public places, graphic warning labels on tobacco products, and taxation to deter consumption. The World Health Organization's Framework Convention on Tobacco Control (FCTC) has been instrumental in coordinating global efforts to curb tobacco use, though disparities persist in policy implementation between high-income and low-income countries.[36] In some regions, harm reduction strategies such as promoting smokeless tobacco or vaping as alternatives have been adopted, while others maintain strict prohibitions on all nicotine products. The debate over how to balance individual choice, public health, and corporate interests continues to evolve, particularly as new nicotine products enter the market.[38][39][40]

The societal and economic costs of nicotine addiction are substantial. [41][42] Tobacco-related illnesses place a heavy burden on healthcare systems, with billions spent annually on treating diseases caused by smoking. Lost productivity due to illness and premature death further exacerbates the economic impact. On the other hand, the tobacco industry remains a powerful economic force, generating significant revenue and employment in many countries. [43][44] This tension between public health objectives and economic interests complicates efforts to implement stricter regulations. Meanwhile, the rise of corporate social responsibility initiatives within the tobacco

industry, such as funding smoking cessation programs, has been met with skepticism by critics who view these efforts as attempts to offset liability and maintain consumer dependence.[42][45][46][47]

Looking ahead, research into nicotine's effects and addiction mechanisms continues to advance, with emerging studies exploring genetic predispositions to dependence, novel pharmacological treatments, and the potential cognitive benefits of nicotine in neurodegenerative disorders like Parkinson's and Alzheimer's disease. [48][49][50] While nicotine's role in these conditions remains controversial, such investigations highlight the compound's complex and multifaceted nature. Ultimately, nicotine's dual identity as both a highly addictive substance and a potential therapeutic agent underscores the need for balanced, evidence-based approaches to regulation, treatment, and public education. As technology and science progress, the challenge will be to mitigate the harms of nicotine addiction while exploring its possible benefits in a controlled and ethical manner.[51][52]

METHODS

To explore the latest advancements in nicotine replacement therapy (NRT), a systematic literature search was performed using PubMed, focusing on studies published between December 2024 and May 2025. The search term "nicotine replacement therapy" was employed to identify relevant articles, supplemented by reference tracking and the pearl-growing method to expand the selection. The review included clinical trials, comparative studies, systematic reviews, narrative reviews, and guidelines from international health organizations. Only English-language publications were considered for analysis. This approach ensured a comprehensive evaluation of recent NRT developments, including efficacy, safety, and emerging formulations. The findings highlight innovations such as personalized NRT dosing, combination therapies, and digital health interventions to improve smoking cessation outcomes. Additionally, the review assessed real-world effectiveness, adherence challenges, and comparisons between traditional NRT (patches, gums) and newer alternatives like oral strips and inhalers. By synthesizing current evidence, this analysis provides insights into evolving NRT strategies and their implications for public health and clinical practice.

Mechanism of action of nicotine

In the brain's ventral tegmental region, nicotine functions via activating neuronal nicotinic acetylcholine receptors (NAChRs). In the nucleus accumbens, this results in the release of dopamine. may cause frequent smokers to experience fewer symptoms of nicotine withdrawal. Don't smoke. (19) By reducing the reward of tobacco products, NRT may also serve as a coping method. Since none of the current nicotine delivery methods can replicate the quick and high levels of arterial nicotine attained when cigarette smoke is breathed, it does not totally alleviate the withdrawal symptoms. (22) Since systemic venous absorption is the basis for all currently available medicinal nicotine medications, they are unable to achieve such rapid systemic arterial delivery. (23) High nicotine dosages from cigarettes take a few seconds to reach the brain, (fig,1) whereas medications release lesser levels over the course of minutes for nasal sprays and hours for transdermal patches and oral items like gum, inhalators, sublingual tablets, or lozenges. (13)

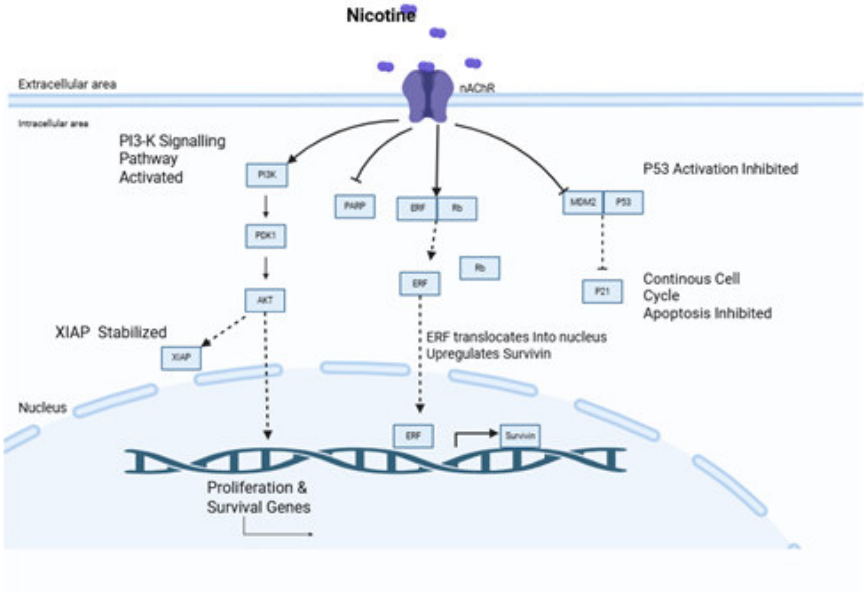

Fig 1: Mechanism of action of nicotine

FORMS OF NICOTINE REPLACEMENT THERAPY

Nicotine replacement therapy (NRT) is the most extensively studied and widely used pharmacological approach for managing nicotine dependence and withdrawal symptoms. NRT products are available in multiple forms, including transdermal patches, chewing gum, lozenges, nasal sprays, and oral inhalers, each designed to deliver nicotine in different ways.[47][48] Transdermal patches provide a slow, steady release of nicotine through the skin, helping to maintain baseline nicotine levels and reduce general cravings. In contrast, fast-acting forms such as gum, lozenges, nasal sprays, and inhalers offer rapid nicotine absorption, which helps alleviate acute cravings and withdrawal symptoms as they arise. The effectiveness of these products varies based on their nicotine absorption rates and individual user preferences.[49][51] While NRT is most successful when combined with behavioral counseling, studies show that it can still be beneficial even without additional therapy. The availability of multiple NRT formulations allows for personalized treatment plans, increasing the likelihood of successful smoking cessation.

Transdermal patch

The transdermal nicotine patch is a widely used form of nicotine replacement therapy (NRT) designed to help individuals quit smoking by delivering a controlled dose of nicotine through the skin. Unlike fast-acting NRT products such as gum or lozenges, the patch provides a steady release of nicotine over 16 to 24 hours, helping to stabilize blood nicotine levels and reduce withdrawal symptoms.[52][53] Available in varying strengths, the patch allows users to gradually taper their nicotine intake, typically starting with a higher dose and stepping down over several weeks. Its ease of use applied once daily to a clean, hairless area of the skin makes it a convenient option for many smokers. Clinical studies have shown that the patch, when used as directed, can double the chances of successful smoking cessation, especially when combined with behavioral support.[54] However, some users may experience mild side effects such as skin irritation, sleep disturbances, or vivid dreams. Despite these drawbacks, the transdermal patch remains a first-line treatment for nicotine dependence due to its consistent dosing, low maintenance, and proven efficacy in reducing cravings and relapse rates.[55]

Acute Dosing Nicotine Product

A key advantage of fast-acting nicotine replacement therapy (NRT) products is their flexible dosing, allowing users to adjust both the amount and timing of nicotine intake based on their individual needs. Smokers experiencing mild side effects can reduce their dosage, while those with higher nicotine dependence can increase it to manage cravings effectively. This self-titration feature makes acute-dosing NRT products particularly useful as "rescue medications" during sudden, intense cravings or high-risk situations that threaten abstinence. [56] Such breakthrough cravings are a major challenge for smokers trying to quit and are strongly associated with relapse. Fast-acting NRT options including nicotine gum, lozenges, sublingual tablets, inhalers, and nasal sprays provide rapid nicotine absorption, closely mimicking the quick relief offered by cigarettes. Unlike transdermal patches, which deliver a steady nicotine release, these on-demand products empower users to take immediate control over withdrawal symptoms, improving adherence and cessation success. Studies suggest that combining long-acting patches with fast-acting NRT can further enhance outcomes by addressing both baseline withdrawal and acute cravings. By offering personalized nicotine delivery, these acute-dosing formulations play a critical role in smoking cessation strategies, particularly for individuals with strong situational triggers or fluctuating nicotine needs.[57][58]

Nicotine Gum

Nicotine polacrilex, commonly known as nicotine gum, was the first nicotine replacement therapy (NRT) product made available to the public. Unlike regular chewing gum, it is used transmucosally kept in the mouth for about 30 minutes and chewed intermittently to release nicotine gradually. [59][60] Available in 2 mg and 4 mg doses, the gum's strength is selected based on the user's level of nicotine dependence, with studies showing that heavily dependent smokers benefit more from the 4 mg formulation. The treatment involves gradually reducing daily usage over weeks or months until nicotine intake is no longer needed. However, proper administration is crucial for effectiveness: acidic beverages like soda, coffee, or beer should be avoided 15 minutes before and during gum use, as they can interfere with buccal nicotine absorption. By providing controlled, on-demand nicotine delivery, nicotine gum helps manage cravings and withdrawal symptoms, making it a widely used and effective tool in smoking cessation programs.[61]

Nicotine Lozenge

Nicotine lozenges offer an alternative to nicotine gum, providing similar benefits through a different delivery method. Available in 2 mg and 4 mg strengths, the lozenge is designed to dissolve slowly in the mouth over approximately 30 minutes, allowing nicotine to be absorbed through the buccal mucosa much like nicotine gum. While the dosing guidelines mirror those of gum (with heavier smokers typically requiring the 4 mg option), lozenges are particularly useful for individuals who prefer not to chew or who need a more discreet form of nicotine replacement. Studies suggest that lozenges may deliver slightly higher nicotine absorption per dose compared to gum, potentially enhancing their effectiveness for some users. As with gum, acidic beverages should

be avoided before and during use to maximize nicotine uptake. This controlled-release format provides flexible, on-demand craving relief, making it a valuable option in smoking cessation strategies.[62]

Nicotine Sublingual Tablet

Nicotine sublingual tablets provide another convenient option for nicotine replacement therapy (NRT). Designed to dissolve under the tongue, these 2 mg tablets deliver nicotine through sublingual absorption, offering comparable nicotine levels to a 2 mg lozenge. Like lozenges, they eliminate the need for chewing, making [63]them ideal for users who prefer a discreet and straightforward method. Clinical guidelines recommend using these tablets for at least 12 weeks to stabilize smoking cessation, after which the dosage should be gradually tapered to wean the body off nicotine dependence. Their rapid absorption and ease of use make sublingual tablets a practical choice for individuals seeking flexible, on-demand craving relief while avoiding the chewing motion required by gum. This method ensures steady nicotine delivery while minimizing behavioral triggers associated with smoking.[64]

Nicotine Oral Inhaler

The nicotine inhaler offers a unique approach to nicotine replacement therapy (NRT) by addressing both physiological dependence and behavioral aspects of smoking. Designed to mimic the hand-to-mouth ritual of cigarette use, the device consists of a mouthpiece and replaceable plastic cartridges containing 10 mg of nicotine each. While called an "inhaler," it primarily delivers nicotine to the oral cavity (36%) and gastrointestinal tract (36%), with only about 4% reaching the lungs. This means absorption occurs mainly through the oral mucosa, resulting in a nicotine uptake rate similar to nicotine gum. With regular use, each cartridge delivers approximately 2-4 mg of absorbable nicotine through repeated puffing. By satisfying both the physical need for nicotine and the habitual motions of smoking, the inhaler may improve adherence for some users. However, its effectiveness depends on proper technique and frequent use, as the nicotine delivery is gradual and requires active participation compared to other NRT forms. This makes it particularly suitable for smokers who miss the behavioral components of their smoking routine during cessation attempts.[61][62]

Nicotine Nasal Spray

The nicotine nasal spray is designed for rapid nicotine delivery, offering the fastest absorption among all nicotine replacement therapy (NRT) formulations. Each metered-dose pump delivers 0.5 mg of nicotine per 50-µL spray, with a standard dose consisting of two sprays (one in each nostril, totaling 1 mg). Unlike other NRTs, which rely on slower mucosal absorption, the nasal spray allows nicotine to enter the bloodstream quickly, helping to alleviate intense cravings more effectively.[63] Patients typically start with 1-2 doses per hour, with a maximum of 40 doses per day to prevent overuse. A single 1 mg dose maintains an average plasma nicotine concentration of 8 ng/mL for up to 10 hours, making it particularly useful for heavy smokers or those with strong withdrawal symptoms. However, its rapid delivery can cause nasal irritation, sneezing, or throat discomfort, which may limit its acceptability for some users. Despite these side effects, the nasal spray remains a valuable option for smokers needing immediate craving relief, especially when transitioning away from cigarettes. Its fast-acting nature makes it a strong alternative for individuals who do not respond well to slower-release NRTs like patches or gum.

Table 1: Nicotine Replacement Therapy Formulation(11,14,24)

Product	Nicotine Dose	Absorption Time	Key Features	Advantages	Limitations
Nicotine Gum	2 mg or 4 mg per piece	20-30 minutes	Chewed intermittently; buccal absorption	Portable, controls cravings	Requires proper technique; jaw fatigue
Nicotine Lozenge	2 mg or 4 mg per unit	20-30 minutes	Dissolves in mouth; buccal absorption	No chewing; discreet	Slower than spray; GI irritation
Sublingual Tablet	2 mg per tablet	10-15 minutes	Dissolves under tongue; rapid sublingual absorption	Fast onset; no chewing	Limited dose options
Nicotine Inhaler	10 mg/cartridge (2-4 mg absorbed)	5-10 minutes	Mimics hand-to-mouth ritual; oral/GI absorption	Behavioral replacement	Requires frequent puffing; throat irritation
Nasal Spray	0.5 mg/spray (1 mg/dose)	5-10 minutes	Rapid nasal absorption; highest bioavailability	Fastest craving relief	Nasal irritation; harsh for some users

Transdermal Patch	7-21 mg/day (step-down)	2-4 hours (steady)	Continuous delivery via skin	Easy to use; once-daily	Skin irritation; no acute craving relief

Improving Delivery

Electronic nicotine delivery systems (ENDS) or Electronic cigarettes

Electronic Nicotine Delivery Systems (ENDS), commonly known as e-cigarettes or vapes, are battery-powered devices that heat a liquid solution into an inhalable aerosol. These solutions typically contain nicotine, propylene glycol, glycerol, flavorings, and water, with nicotine concentrations varying widely from 0 to 34 mg/mL though studies have found discrepancies between labeled and actual nicotine levels. Unlike traditional cigarettes, ENDS do not burn tobacco, eliminating combustion-related toxins, but they still deliver nicotine to the upper and lower respiratory tracts, mimicking the sensory experience of smoking. Many smokers prefer e-cigarettes because they replicate the look, feel, and taste of conventional cigarettes, potentially aiding cessation. However, concerns persist over safety and regulation. The FDA has raised alarms about hazardous ingredients in some e-liquids and advocates for restrictions, citing risks such as youth initiation fearing ENDS may act as a gateway to nicotine addiction for non-smokers. While some evidence supports their effectiveness in smoking cessation, long-term safety and efficacy remain unclear, necessitating further research. Current debates balance their harm reduction potential for adult smokers against public health risks, particularly for younger users. [63]

High-dose nicotine patches

While standard 22 mg/day nicotine patches typically replace only ~50% of a smoker's baseline nicotine levels, clinical investigations have evaluated higher-dose transdermal formulations (e.g., 42 mg/day) to better address the needs of heavily dependent smokers. Emerging evidence suggests these elevated doses may yield significantly improved abstinence rates, likely through more complete suppression of withdrawal symptoms and cravings in high-tolerance individuals. However, a 2023 Cochrane systematic review highlighted critical gaps in the evidence base, finding insufficient high-quality data to definitively establish the safety profile and long-term efficacy of these intensified regimens.[64]

The potential benefits of high-dose monotherapy must be carefully balanced against dose-dependent adverse effects, including nausea (reported in 15-20% of users), dermatologic reactions, and theoretical cardiovascular risks from prolonged supratherapeutic nicotine exposure. Current clinical practice favors a stepped-care approach: initiating therapy with standard-dose patches (21-22 mg/day) and reserving higher doses for treatment-resistant cases with documented heavy dependence (≥25 cigarettes/day). Notably, combination NRT strategies (e.g., patch + PRN oral formulations) demonstrate superior efficacy to monotherapy in most comparative studies, achieving abstinence rates of 25-35% at 6 months versus 15-20% with single-modality approaches.

Rapid release gum

This technological advancement addresses a critical gap in nicotine replacement therapy - the delayed onset of action that often leads to treatment failure during sudden, intense cravings. By more closely mimicking the nicotine delivery profile of cigarettes while maintaining built-in overdose protection, rapid-release gum may improve adherence and success rates among highly dependent smokers attempting cessation.

Nicotine

Nicotine preloading also known as pre-cessation NRT involves the use of nicotine replacement therapy (NRT) before a smoker's designated quit date. This method, typically implemented 2–4 weeks prior to cessation, Reduce smoking satisfaction by saturating nicotinic receptors, thereby weakening the reinforcing effects of cigarettes. Disrupt conditioned smoking cues by decoupling nicotine intake from smoking behavior. Familiarize users with NRT, easing the transition to complete abstinence.

True pulmonary inhaler

Unlike the nicotine inhalers that are already on the market, a real pulmonary inhaler would deliver nicotine to the lung more like smoking cigarettes. (14) It is anticipated that this will provide enough nicotine to lessen withdrawal symptoms and background cravings while enabling prompt alleviation of morning cravings and acute cravings. A smoker may completely stop using tobacco and then gradually reduce their nicotine intake to lessen their reliance on it since direct nicotine delivery to the lung would successfully replicate the physiological consequences of cigarette smoking. Even though creating a lung inhaler that is both effective and palatable presents significant scientific problems, the biggest obstacle to advancement may be the possibility of abuse and the consequences for regulations. (14) The problem is that in order to allow inhalation into the pulmonary alveoli, nicotine molecules must be suitably condensed onto particles with a median diameter of about 1 micron. Additionally, the nicotine particles must be made in a way that avoids producing unpleasant sensory effects. (14)

Nicotine Vaccine

Nicotine vaccines represent an innovative but still experimental strategy for treating tobacco dependence. Unlike traditional nicotine replacement therapies (NRTs), these vaccines aim to induce an immune response against nicotine itself. Because nicotine is too small to trigger immunity on its own, it is conjugated with a carrier protein (e.g., bacterial toxoid) to stimulate antibody production. The resulting antibodies bind nicotine in the bloodstream, preventing it from crossing the blood-brain barrier and reducing its reinforcing effects.

Table 2: Novel Biological or Vaccine Agents in Clinical Testing for Smoking Cessation (53,55)

Agent Name	Type	Mechanism of Action	Development Stage	Key Findings	Challenges
NicVAX (Nabi Biopharms)	Nicotine-protein conjugate vaccine	Induces anti-nicotine antibodies to block brain entry	Phase III (discontinued)	Failed primary endpoints; insufficient antibody titers in 60% of subjects	Low immunogenicity; compensatory smoking
SIgN-3C (Cytos)	Nicotine-like hapten vaccine	Triggers IgG antibodies to sequester nicotine	Phase II (halted)	Modest reduction in smoking pleasure; no significant abstinence improvement	Short antibody persistence (≤3 months)
TA-NIC (Celtic Pharma)	T-cell stimulating vaccine	Targets nicotine via carrier protein	Phase II (inactive)	Mixed results; some subjects showed reduced cigarette consumption	Variable immune response
Anti-nicotine mAbs (e.g., NIC7B1)	Monoclonal antibody	Binds nicotine in serum with high affinity	Preclinical/Phase I	Rapid nicotine neutralization in animal models	High production cost; frequent dosing needed
rAd5-nicotine vaccine (Vector-based)	Viral vector vaccine	Enhances immune memory against nicotine	Phase I (ongoing)	Preliminary data show durable antibody production	Safety concerns with adenovirus vectors
Nanoparticle vaccines (e.g., SEL-068)	Synthetic nanoparticle	Multivalent nicotine-peptide presentation	Preclinical	Potent antibody response in rodents	Unproven human efficacy

Nicotine safety and toxicity

Nicotine exhibits biphasic effects stimulating neuronal activity at moderate doses but inhibiting it at very high concentrations. While 40–60 mg constitutes an acute lethal dose (causing respiratory paralysis at 500 mg), nicotine replacement therapy (NRT) at recommended doses does not pose life-threatening risks. Overdose symptoms nausea, vomiting, headaches, and weakness are typically mild and reversible.[62]

For pregnant smokers, NRT presents a safer alternative to cigarettes, with no evidence of adverse birth outcomes in major trials like the SNAP study. However, long-term developmental effects require further investigation. NRT is considered safe for stable cardiovascular patients, though caution is advised for those with acute heart disease, adolescents, or breastfeeding mothers, where risks and benefits must be carefully weighed. [63]

Overall, NRT's controlled dosing minimizes toxicity risks, making it a viable cessation tool under medical supervision. While high-dose nicotine is dangerous, therapeutic NRT use does not share the same hazards as tobacco consumption.

Patient Compliance with NRT

The majority of NRT users stop their therapy too soon. Poor compliance is frequently caused by misinformation about NRT. (65) A number of reasons for low NRT compliance were found; worries regarding security, (66,67) NRT's addictive nature, (67) Lack of faith in its effectiveness, (66,67) Relapse, Cost, and Side Effects

(68, 69) and "I ought to be able to stop on my own." The effectiveness of NRT was found to be one of the most frequent causes of low compliance. Patients may falsely believe that treatment is no longer required once cravings and withdrawal are effectively managed with medication. (70) These ideas compromise the efficacy of NRT. The main way to address this is for medical practitioners to give individuals undergoing NRT scientific knowledge. (71)

CONCLUSION

The main obstacle to long-term sobriety and smoking cessation is nicotine addiction. Many nicotine treatments are now available in a variety of forms, dosages, and tastes, and it is advised that all tobacco users utilize them. are not contraindicated by medicine. The patient's preferences should typically serve as the basis for the NRT product selection.

According to published data, their odds of successfully quitting smoking are increased by all commercially available types of NRT, including gum, transdermal patches, nasal sprays, inhalers, and sublingual tablets/lozenges. NRTs result in a 50–70% increase in the rate of quitting. (50) NRT raised the possibility of lowering the size of the habit among smokers who are unwilling to quit smoking entirely, according to another meta-analysis. (71) Research has recently focused more on immunological and fast administration methods to increase the effectiveness of NRT. To get these new modalities from the bench to the bedside, additional high-caliber research is needed. Given the potential of NRT, health practitioners must learn about all of its variations in order to respond to the demands and inquiries of tobacco users who seem to be becoming more and more interested in quitting.

REFERENCES

1. Foulds J, Burke M, Steinberg M, Williams JM, Ziedonis DM. Advancesin pharmacotherapy for tobacco dependence. Expert OpinEmerg Drugs. 2004;9(1):39
2. Kotlyar M, Hatsukami DK. Managing nicotine addiction. J Dent Educ. 2002 Sep;66(9):1061-73.
3. Scherer G. Smoking behavior and compensation: a review of the literature. Psychopharmacology (Berl)1999;145(1):1
4. Balfour DJ. The neurobiology of tobacco dependence: a preclinical perspective on the role of the dopamine projections to the nucleus accumbens. Nicotine Tob Res. 2004;6(6):899–912.
5. Garret BE, Rose CA, Hennigfield JE. Tobacco addiction and pharmacological interventions. Expert OpinPharmacother. 2001;2(10):1545–1555
6. Benowitz NL. Pharmacology of nicotine: addiction, smoking-induced disease, and therapeutics. Annu Rev PharmacolToxicol. 2009;49:57-71.
7. Balfour DJ. The neurobiology of tobacco dependence: a preclinical perspective on the role of the dopamine projections to the 432 Umesh Wadgave and Nagesh L nucleus accumbens. Nicotine Tob Res. 2004;6(6):899–912.
8. Centers for Disease Control and Prevention (US), National Center for Chronic Disease Prevention and Health Promotion (US), Office on Smoking and Health (US). How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General. Atlanta (GA): Centers for Disease Control and Prevention (US); 2010. Available from: http://www.ncbi.nlm.nih.gov/books/NBK53 018/
9. Silagy C, Lancaster T, Stead L, Mant D, Fowler G. Nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev. 2004;(3):CD000146. Review. Update in: Cochrane Database Syst Rev. 2008;(1):CD000146.
10. Le Foll B, Melihan-Cheinin P, Rostoker G, Lagrue G. Smoking cessation guidelines: evidence-based recommendations of the French Health Products Safety Agency. European Psychiatry 2005; 20:431–4.
11. Yildiz D. Nicotine, its metabolism and an overview of its biological effects. Toxicon. 2004;43(6):619–632.
12. Molyneux A, Králíková E, Himmerová V. ABC of smoking cessation. Nicotine replacement therapy. CasLekCesk. 2004;143(11):781-3.
13. A clinical practice guideline for treating tobacco use and dependence: A US Public Health Service report. The Tobacco Use and Dependence Clinical Practice Guideline Panel, Staff, and Consortium Representatives. JAMA. 2000 Jun 28;283(24):3244-54. Review.
14. Henningfield JE, Fant RV, Buchhalter AR, Stitzer ML. Pharmacotherapy for nicotine dependence. CA Cancer J Clin. 2005 SepOct;55(5):281-99.
15. Sweeney CT, Fant RV, Fagerstrom KO, McGovern JF, Henningfield JE. Combination nicotine replacement therapy for smoking cessation: rationale, efficacy and tolerability. CNS Drugs 2001;15:453–
16. Fagerstrom KO. Combined use of nicotine replacement products. Health Values 1994;18:15–20.
17. Prochaska JJ. Nicotine Replacement Therapy as a Maintenance Treatment. JAMA.2015 Aug;314(7):718-9.

18. Hajek P, Stead LF. Aversive smoking for smoking cessation. Cochrane Database Syst Rev. 2000;(2):CD000546.
19. D'Souza MS, Markou A. Neuronal mechanisms underlying development of nicotine dependence: implications for novel smoking-cessation treatments. Addict SciClinPract. 2011 Jul;6(1):4-16.
20. Shiffman S, Rolf CN, HellebuschSJ,Gorsline J, Gorodetzky CW, Chiang YK,et al. Real-world efficacy of prescription and over-the counter nicotine replacement therapy. Addiction 2002;97:505–16
21. Henningfield JE. Nicotine medications for smoking cessation. N Engl J Med.1995 Nov 2;333(18):1196-203.
22. Molander L, Lunell E. Pharmacokinetic investigation of a nicotine sublingual tablet. Eur J ClinPharmacol. 2001 JanFeb;56(11):813-19.
23. Choi JH, Dresler CM, Norton MR, Strahs KR. Pharmacokinetics of a nicotine polacrilex lozenge. Nicotine Tob Res. 2003 Oct;5(5):635-44.
24. Clinical Practice Guideline Treating Tobacco Use and Dependence 2008 Update Panel, Liaisons, and Staff. A clinical practice guideline for treating tobacco use and dependence: 2008 update. A U.S. Public Health Service report. Am J Prev Med. 2008 Aug;35(2):158-76.
25. Henningfield JE. Nicotine medications for smoking cessation. N Engl J Med.1995 Nov 2;333(18):1196-203.
26. Hajek P, Etter JF, Benowitz N, Eissenberg T, McRobbie H. Electronic cigarettes: review of use, content, safety, effects on smokers and potential for harm and benefit. Addiction. 2014 Nov;109(11):1801-
27. Cantrell FL. Adverse effects of e-cigarette exposures. Journal of community health. 2014-Jun 2014;39(3):614-16.
28. Brokowski L, Chen J, Tanner S. High-dose transdermal nicotine replacement for tobacco cessation. Am J Health Syst Pharm. 2014 Apr 15;71(8):634-8.
29. Recommendations for Use of Combination Therapy in Tobacco Use Cessation [cited 433 Nicotine Replacement Therapy: An Overview 2016 Januray 03]. Available from:http://www.healthquality.va.gov/guidel ines/CD/mtu/tuc_combination_therapy.pdf
30. U.S.Department of Veteran affairs [cited 2015 october 15] Available from: https://www.myhealth.va.gov/mhvportalweb/anonymous.portal?_nfpb=trueC_nfto=falseC_pageLabel=spotlightArchive CcontentPage=spotlight/November%2020 11/spotlight_nov2011_smoking.html
31. Seigel MB, Tanwar KL, Wood KS. Electronic cigarettes as a smokingcessation tool: results from an online survey. Am J Prev Med2011;40:472–5.
32. International Union against Tuberculosis and Lung diseases [cited 2016 January 04] Available from: file:///C:/Users/Client/Downloads/Ecigarette_statement_FULL.pdf
33. Goniewicz ML, Kuma T, GawronM,Knysak J, Kosmider L.. Nicotine levels in electronic cigarettes. Nicotine Tob Res2013;15:158–
34. Palazzolo DL. Electronic cigarettes and vaping: a new challenge in clinical medicine and public health. A literature review. Front Public Health. 2013 Nov 18;1:56.
35. Jerry JM, Collins GB, Streem D. Ecigarettes: Safe to recommend to patients? Cleve Clin J Med.2015 Aug;82(8):521-6.
36. Lam C, West A. Are electronic nicotine delivery systems an effective smoking cessation tool? Can J RespirTher. 2015 Fall;51(4):93-8.
37. McRobbie H, Bullen C, Hartmann-Boyce J, Hajek P. Electronic cigarettes for smoking cessation and reduction. Cochrane Database Syst Rev. 2014;12:CD010216.
38. Hurt RD, Dale LC, Offord KP, Lauger GG, Baskin LB, Lawson GM, et al. Serum nicotine and cotinine levels during nicotinepatch therapy. ClinPharmacolTher. 1993; 54:98-106.
39. Schnoll RA, Wileyto EP, Leone FT, Tyndale RF, Benowitz NL. High dose transdermal nicotine for fast metabolizers of nicotine: a proof of concept placebocontrolled trial. Nicotine Tob Res. 2013; 15:348-54.
40. Hughes JR, Lesmes GR, Hatsukami DK, Richmond RL, Lichtenstein E, Jorenby DE et al. Are higher doses of nicotine replacement more effective for smoking cessation? Nicotine Tob Res.
41. Ebbert JO, Dale LC, Patten CA. Croghan IT, Schroeder DR, Moyer TP, et al. Effect of high-dose nicotine patch therapy on tobacco withdrawal symptoms among smokeless tobacco users. Nicotine Tob Res. 2007; 9:43-52.
42. Shiffman S, Cone EJ, Buchhalter AR, Henningfield JE, Rohay JM, Gitchell JG et al. Rapid absorption of nicotine from new nicotine gum formulations. PharmacolBiochemBehav. 2009 Jan;91(3):380-4.
43. Niaura R, Sayette M, Shiffman S, Glover ED, Nides M, Shelanski M, et al. Comparative efficacy of rapid-release nicotine gum versus nicotine polacrilex gum in relieving smoking cue-provoked craving. Addiction. 2005 Nov;100(11):1720-30.
44. Fagerstrom KO, Schneider NG, Lunell E. Effectiveness of nicotine patch and nicotine gum as individual versus combined treatments for tobacco withdrawal symptoms. Psychopharmacology 1993;111:271–277.
45. Kornitzer M, Boutsen M, Dramaix M, Thijs J, Gustavsson G.. Combined use of nicotine patch and gum

in smoking cessation: a placebo-controlled clinical trial. Prev Med 1995;24:41–47.
46. Puska P, Korhonen H, Vartiainen E, E. L. Urjanheimo, G. Gustavsson, A. Westin. Combined use of nicotine patch and gum compared with gum alone in smoking cessation: a clinical trial in North Karelia. Tob Control 1995;4:231 –235.
47. Shah SD, Wilken lA, Winkler SR, lin S-J. Systematic review and meta-analysis of combination therapy for smoking cessation. J Am Pharm Assoc 2008;48:659 – 65.
48. Fagerström K., Hughes J. Nicotine concentrations with concurrent use of cigarettes and nicotine replacement. Nicotine Tob Res2002;4: 73–9.
49. Rose J. E., Behm F. M., Westman E. C. Nicotine– mecamylamine treatment for smoking cessation: the role of precessation therapy.ExpClin Psychopharmacol1998;6: 331–43
50. Stead L. F., Perera R., Bullen C., Mant D., Lancaster T. Nicotine replacement therapy 434 Umesh Wadgave and Nagesh L for smoking cessation. Cochrane Database Syst Rev2008;1: CD000146.
51. Bullen C, Howe C, Lin RB, Grigg M, Laugesen M, McRobbie H, et al. Precessation nicotine replacement therapy: pragmatic randomized trial. Addiction. 2010 Aug;105(8):1474-83.
52. Carrera, M. R., Ashley, J. A., Hoffman, T. Z., Isomura, S., Wirsching, P., Koob, G. F.et al. Investigations using immunization to attenuate the psychoactive effects of nicotine. Bioorganic C Medicinal Chemistry, 2004;12(3): 563–70.
53. Harmey D, Griffin PR, Kenny PJ. Development of novel pharmacotherapeutics for tobacco dependence: progress and future directions. Nicotine Tob Res. 2012 Nov;14(11):1300-18.
54. Scherer, G. Smoking behaviour and compensation: a review of the literature. Psychopharmacology, 1999;145(1):1–20.
55. Hartmann-Boyce J, Cahill K, Hatsukami D, Cornuz J. Nicotine vaccines forsmoking cessation. Cochrane Database Syst Rev. 2012 Aug 15;8:CD007072.
56. Nabi Biopharmaceuticals Announces Results of Second NicVAX(R) Phase III Clinical Trial. Available From: http://globenewswire.com/newsrelease/2011/11/07/460749/237357/en/Na
57. Shen XY, Orson FM, Kosten TR. Vaccines against drug abuse. ClinPharmacolTher. 2012 Jan;91(1):60-70.
58. Shen X, Orson FM, Kosten TR. Antiaddiction vaccines. F1000 Med Rep. 2011;3:20.
59. Meyer, B. How much nicotine kills a human? Tracing back the generally accepted lethal dose to dubious self experiments in the nineteenth century. Arch Toxicol. 2014 Jan;88(1):5-7.
60. Karl Fagerström . Nicotine: Pharmacology, Toxicity and Therapeutic use. J SmokCessat. 2014;9: 53-59
61. Lavelle C, Birek C, Scott DA. Are nicotine replacement strategies to facilitate smoking cessation safe? J Can Dent Assoc. 2003 Oct;69(9):592-7.
62. Moore D, Aveyard P, Connock M, Wang D, Fry-Smith A, Barton P. Effectiveness andsafety of nicotine replacement therapy assisted reduction to stop smoking: systematic review and meta-analysis. BMJ. 2009 Apr 2;338:b1024.
63. Osadchy A, Kazmin A, Koren G. Nicotine replacement therapy during pregnancy: recommended or not recommended? J ObstetGynaecol Can. 2009 Aug;31(8):744- 7
64. Cooper S, Lewis S, Thornton JG, Marlow N, Watts K, Britton J, et al. Smoking, Nicotine and Pregnancy Trial Team. The SNAP trial: a randomized placebocontrolled trial of nicotine replacement therapy in pregnancy-clinical effectiveness and safety until 2 years after delivery, with economic evaluation. Health Technol Assess. 2014 Aug;18(54):1-128.
65. Mendelsohn C. Optimising nicotine replacement therapy in clinical practice. AustFam Physician. 2013 May;42(5):305
66. Shiffman S, Ferguson SG, Rohay J, Gitchell JG. Perceived safety and efficacy of nicotine replacement therapies among uS smokers and ex-smokers: relationship with use and compliance. Addiction 2008;103:1371–8.
67. Ferguson SG, Gitchell JG, Shiffman S, Sembower MA, Rohay JM, Allen J. Providing accurate safety information may increase a smoker's willingness to use nicotine replacement therapy as part of a quit attempt. Addict Behav 2011;36:713 –6.
68. Yingst JM, Veldheer S, Hrabovsky S, Sciamanna C, Foulds J. Reasons for nonadherence to nicotine patch therapy during the first month of a quit attempt. Int J ClinPract. 2015 Aug;69(8):883-8.
69. Hughes JR. Use of nicotine replacement after a smoking lapse. Nicotine Tob Res 2012;14:751–4.
70. Balmford J, Borland R, Hammond D, Cummings KM. Adherence to and reasons for premature discontinuation from stopsmoking medications: data from the ITC four- country survey. Nicotine Tob Res 2011;13:94–102.
71. K.O. Fagerstrom and C.A. Jimenez-Ruiz. Pharmacological treatments for tobacco dependence. European Respiratory 2008;17(110):192–8.