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Research progress on different nicotine administration routes and smoking cessation interventions: a narrative review

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Abstract

Nicotine, the core component of tobacco dependence, exhibits distinct variations in its absorption rate, bioavailability and health risk based on different administration routes. Rapid absorption routes (e.g., traditional combustible cigarettes, electronic cigarettes) are associated with high addictiveness and substantial health hazards, whereas nicotine replacement therapy (NRT) effectively alleviates withdrawal symptoms via sustained-release formulations. Novel smoking cessation interventions, including nanovaccines and gene delivery systems, have demonstrated promising potential but remain in need of further clinical validation. Future research should prioritize personalized administration strategies and long-term safety assessments of nicotine-based interventions. This article reviews the latest research progress on different nicotine administration routes and smoking cessation interventions, aiming to provide evidence for optimizing clinical tobacco cessation strategies.

Keywords: Nicotine, Administration route, Nicotine replacement therapy, Smoking cessation interventions

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Introduction

Nicotine is the primary driver of tobacco dependence[1] and is predominantly metabolized to cotinine (accounting for 70%–80% of total metabolites) in the liver via the cytochrome P450 2A6 (CYP2A6) enzyme[2]. The diversity of nicotine administration routes results in significant differences in terms of the pharmacological effects, addictiveness, and health risks. Traditional combustible cigarette smoking enables the rapid pulmonary absorption of nicotine, which induces strong addictive behavior and is accompanied by exposure to harmful substances such as tar and carbon monoxide (CO). In recent years, the emergence of novel nicotine delivery methods (e.g., electronic cigarettes [e-cigarettes], nicotine transdermal patches, chewing gum) has expanded the treatment options for smoking cessation. Advances in mental health therapies have extended beyond traditional pharmacological approaches. Cognitive behavioral therapy (CBT) remains a cornerstone of behavioral interventions for substance use disorders, including smoking cessation. Digital mental health tools—such as smartphone applications, artificial intelligence (AI)-driven behavioral interventions, and online platforms—have demonstrated feasibility and effectiveness in promoting smoking cessation[3]. This article reviews the pharmacokinetic characteristics, health risks, and addictiveness of nicotine delivered via different administration routes, and summarizes the research progress of novel smoking cessation interventions.

Traditional combustible cigarettes

Traditional combustible cigarettes release nicotine through tobacco combustion, which is rapidly absorbed into the systemic circulation via the pulmonary alveoli and reaches the central nervous system within a few seconds[2]. A pharmacokinetic study by Rostami et al.[4] demonstrated that approximately 20% of inhaled nicotine is deposited in the oral cavity, 25% in the upper respiratory tract, 50% in the lower respiratory tract, and only 5% is exhaled unabsorbed. The blood concentration of nicotine peaks at 15–20 ng/mL within 6 min of continuous smoking[5], and this rapid delivery is the key factor for its high addictiveness. These toxic substances are closely associated with the development of various chronic diseases, including cardiovascular diseases, lung cancer, chronic respiratory diseases, and digestive system tumors[6,7]. The 2020 Report on the Health Hazards of Smoking in China[8] stated that smoking is a direct cause of chronic obstructive pulmonary disease (COPD), respiratory infections, pulmonary tuberculosis, and interstitial lung diseases, and the risk of disease occurrence shows a significant dose–effect relationship with the amount and duration of smoking. As it is the most common nicotine administration route worldwide, the high nicotine delivery efficiency and severe health hazards of traditional smoking have become a major global public health challenge.

Electronic cigarettes

Principles and pharmacokinetics of e-cigarettes

E-cigarettes are battery-powered electronic devices that heat a liquid matrix (containing nicotine, propylene glycol, vegetable glycerin, and flavoring agents) to produce an aerosol for inhalation. Similar to traditional cigarettes, e-cigarette-derived nicotine is absorbed rapidly via the lungs, with an absorption rate second only to combustible cigarettes and a maximum plasma concentration (Cmax) of 10–15 ng/mL. The actual nicotine delivery efficiency of

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e-cigarettes is affected by multiple factors, including the device's power, the e-cigarette liquid's nicotine concentration, the form of nicotine salt, the propylene glycol/vegetable glycerin ratio, and individual users' behavior. Open-tank modifiable e-cigarettes, which allow adjustable power and liquid formulation, may deliver a higher nicotine dose per use than traditional combustible cigarettes.

Epidemiological trends

Epidemiological data show that the prevalence of e-cigarette use is increasing globally, especially among young people. In China, the adult e-cigarette use rate increased from 1.3% in 2015 to 1.6% in 2019[9]. In the United States, the adult use rate reached 4.5% in 2021, with the 18–24 age group having the highest rate at 11.0%[10,11]. A series of cohort studies and meta-analyses have confirmed that e-cigarette use is a significant risk factor for subsequent combustible cigarette smoking in adolescents and young adults: Those who have used electronic cigarettes are 3.5 times more likely to smoke traditional cigarettes than nonusers[12,13]. This is closely related to the appeal of various fruit, dessert, and beverage flavoring agents and the fancy packaging of e-cigarettes to minors.

Assessment of the evidence of health risks

Although e-cigarettes do not produce tar or carbon monoxide, their aerosol still contains toxic and harmful substances such as formaldehyde, acetaldehyde, acrolein, and heavy metals. Current research on the health risks of e-cigarettes remains at an exploratory stage, and existing evidence has the following limitations: (1) Insufficient evidence strength – most studies are short-term observational studies or case reports, lacking long-term prospective cohort studies; and (2) inconsistent study findings – although some studies suggest that the short-term cardiovascular risk of e-cigarettes is lower than that of traditional cigarettes[14], a growing number of studies have confirmed that e-cigarette use can cause adverse cardiac electrophysiological changes, including increased QT interval dispersion and abnormal ventricular repolarization, thereby increasing the risk of severe and even fatal arrhythmias[15]. Multiple case reports have also described new-onset atrial fibrillation in healthy young adults without prior heart disease after long-term e-cigarette use[16]. These discrepancies may arise from differences in device types, usage patterns, and study endpoints, and no definitive conclusions can be drawn at present.

Controversy surrounding e-cigarettes as a smoking cessation tool

Whether e-cigarettes should be recommended as a smoking cessation aid is the most controversial issue in this field. Proponents, citing several randomized controlled trials and the Cochrane review, argue that e-cigarettes may be more effective than nicotine patches for smoking cessation. However, the limitations in the evidence that warrant cautious interpretation include the following: (1) Most studies lack long-term abstinence data; (2) significant differences in the efficiency of nicotine delivery across device types lead to high study heterogeneity; (3) "dual use" (concurrent use of e-cigarettes and traditional cigarettes) is common; and (4) the population-level cessation benefits have not been confirmed. The WHO 2024 Clinical Treatment Guideline for Tobacco Cessation in Adults[17], citing the lack of long-term follow-up data and standardized research evidence, does not provide clear recommendations for e-cigarettes as a smoking cessation aid and only recommends five evidence-based pharmacological regimens (nicotine replacement therapy [NRT], bupropion, varenicline, cytisine, and their combinations). The current evidence does not support e-cigarettes as a first-line smoking cessation tool, and their cessation benefits require validation through more rigorous long-term studies.

Nicotine replacement therapy

NRT is a first-line pharmacological intervention for smoking cessation, which provides exogenous nicotine through nontobacco routes to alleviate nicotine withdrawal symptoms and reduce the urge to smoke, thereby improving the success rate of smoking cessation[18,19]. Its core mechanism is to replace tobacco-derived nicotine with a controlled and sustained supply of nicotine, maintain a stable low to moderate blood nicotine concentration in the body, and help tobacco-dependent individuals gradually reduce their nicotine dependence and achieve complete abstinence. Unlike traditional cigarettes and e-cigarettes, NRT avoids exposure to tobacco combustion products or aerosol toxic substances, which is the key to its high safety profile.

NRT currently has a variety of dosage forms approved for clinical use, with significant differences in their pharmacokinetic characteristics, which are mainly reflected in the absorption rate, time to maximum concentration (Tmax), and Cmax. (1) Transdermal patches: These are the only long-acting NRT dosage form. They release nicotine slowly through the skin, with a Tmax of 3–12 h and a Cmax of 11–23 ng/mL, and are capable of maintaining a stable basal blood nicotine concentration for 24 h[20]. (2) Nasal sprays: These are a fast-acting dosage form with the fastest absorption rate among NRT options, with a Tmax of 11–18 min and a Cmax of 5–8 ng/mL, but with obvious local irritation[20]. (3) Chewing gum: This is a fast-acting dosage form absorbed through the oral mucosa, with a Tmax of about 30 min and a Cmax of 6–17 ng/mL[18]. The absorption efficiency is affected by chewing frequency and duration. (4) Oral lozenges: These are also absorbed through the oral mucosa, with a Tmax of approximately 60 min and a Cmax of 4.4–10.8 ng/mL, with mild local side effects[20]. (5) Oral capsules: These are absorbed through the gastrointestinal tract, with a Tmax of 90 min and a Cmax of 6–8 ng/mL[20]. (6) Oral nicotine pouches: A novel NRT dosage form developed in recent years, these are absorbed through the oral mucosa, with a Tmax of about 60min and a Cmax of 11.9–18.4 ng/mL[21].

The Clinical Application Guidelines for Nicotine Replacement Therapy issued in China[22] recommends the combined use of long-acting and short-acting NRT as the first-line regimen for clinical smoking cessation, which can cover the basal nicotine demand and acute smoking cravings. Specifically, transdermal patches are used to maintain a stable basal blood nicotine concentration for 24 h, and fast-acting dosage forms are used on demand to cope with sudden smoking cravings, which can improve the smoking cessation success rate compared with the use of a single dosage form. For patients with a high degree of nicotine dependence, the combination of fast-acting and long-acting NRT is particularly important to avoid withdrawal symptoms[19].

NRT has an overall good safety profile and is well-tolerated in clinical use, with most side effects being mild local reactions that resolve spontaneously. However, rare adverse reaction case reports have emerged in recent years: Several clinical studies have found that the long-term use of tobacco-free nicotine pouches may cause hyperprolactinemia in individual users[23], which requires close attention in terms of clinical application and regular monitoring of related indicators. In addition, NRT should be avoided in

combination with combustible cigarettes or e-cigarettes, as this may lead to excessive nicotine intake and increase the cardiovascular burden, especially for patients with pre-existing cardiovascular diseases.

Novel smoking cessation intervention technologies

With the development of molecular biology, immunology, and nanotechnology, novel smoking cessation intervention technologies targeting nicotine dependence have been continuously developed, among which nicotine vaccines and gene delivery systems are the most studied and promising, providing a new direction for the treatment of severe tobacco dependence.

Nicotine vaccines

Nicotine vaccines are a novel immunotherapeutic strategy for smoking cessation which induce the body to produce specific antinicotine antibodies through active immunization. These antibodies bind to free nicotine in the blood to form macromolecular immune complexes, which cannot pass through the blood–brain barrier because of their large molecular weight, thereby blocking nicotine from reaching the central nervous system. Current evidence suggests that the antibodies are too large to cross the blood–brain barrier, so they do not directly interfere with the central nervous system's function[24]. However, their long-term neurological safety requires further validation.

Preclinical animal studies have confirmed the effectiveness of nicotine vaccines in reducing nicotine dependence: Immunization can significantly reduce the level of nicotine entering the brain tissue in mice and rats and inhibit nicotine-induced behavioral responses[25,26]. A novel mixed nanoparticle nicotine vaccine developed in recent years has improved immunogenicity and immune persistence compared with traditional protein conjugate vaccines: It induced an antibody titer 5.7 times higher than that of traditional vaccines in a mouse model and could effectively block nicotine from entering the brain for a long time[27]. Barbosa Méndez et al.[28] found that the NIC6-TT nicotine vaccine could induce a strong and specific immune response in rats, reduce nicotine-seeking behavior and nicotine-induced locomotor sensitization, and block the central rewarding effect of nicotine, thereby reducing its addictive potential.

The main limitation of traditional nicotine vaccines is insufficient immune persistence, which requires multiple booster immunizations to maintain effective antibody titers in the body, leading to poor patient compliance. The emergence of nanovaccine technology has solved this problem well: By using nanomaterial carriers, the vaccine can achieve slow release and targeted delivery in the body, realizing long-term efficacy with a single injection. At present, several nicotine vaccines are in the early clinical trial stage, and their safety, immunogenicity, and clinical efficacy in tobacco-dependent populations are still being further verified[29].

Gene delivery systems

Hicks et al.[30] conducted the first preclinical study on gene delivery systems for smoking cessation and found that an intramuscular injection of an adeno-associated virus vector carrying the antinicotine antibody gene could make mice secrete high levels of antinicotine antibodies in the body for a long time, reduce the nicotine concentration in the brain by up to 85%, and significantly reduce nicotine-induced reward behavior and addictive potential. Li et al. harnessed clustered regularly interspaced short palindromic repeats (CRISPR)-CRISPR-associated protein 9 (Cas9) gene editing and tailored expression control to engineer a probiotic strain of *Bacillus subtilis* that was capable of efficiently degrading nicotine, presenting a new avenue for smoking cessation therapy[31]. Compared with nicotine vaccines that require repeated inoculation, gene delivery systems have the advantage of a one-time administration and long-term efficacy, which is expected to become an effective adjuvant treatment for severe tobacco dependence that is difficult to quit via traditional methods. However, the clinical application of gene delivery systems for smoking cessation remains in the preclinical stage and faces challenges including the viral vector's safety, ethical concerns, and the need to precisely control antibody expression levels to avoid adverse reactions.

Addictiveness and health risks of different nicotine administration routes

Addictiveness

The addictive potential of different nicotine administration routes is mainly determined by the speed of nicotine delivery. Rapid absorption routes can make nicotine reach the brain within a few seconds and cause a rapid rise in the blood nicotine concentration, which strongly activates the mesolimbic dopamine reward pathway in the brain, producing a strong reward effect, and thus has very high addictive potential[32]. In contrast, sustained-release dosage forms release nicotine slowly, maintain a stable and low blood nicotine concentration, do not cause a sharp rise in dopamine levels, and thus have a low addictive risk, which is suitable for smoking cessation treatment. For fast-acting NRT dosage forms, although their absorption rate is faster than transdermal patches, their Cmax is significantly lower than that of traditional cigarettes and e-cigarettes, and the blood nicotine concentration rises slowly, so their addictive potential is moderate and controllable.

Health risks

There are significant differences in the health risks of different nicotine administration routes, which are mainly determined by whether there is exposure to toxic and harmful substances other than nicotine. (1) Traditional combustible cigarettes have the highest health risk, with tobacco combustion producing a large number of carcinogens and toxic substances, which are the direct cause of various chronic diseases such as lung cancer, COPD and cardiovascular diseases. (2) For e-cigarettes, the health risk is lower than that of traditional cigarettes but higher than NRT, with the aerosol containing formaldehyde, acetaldehyde, and other toxic substances. Exposure to e-cigarette aerosols may exert detrimental health effects via molecular mechanisms such as oxidative stress, mitochondrial dysfunction, and DNA damage[33]. Nevertheless, the long-term health effects (especially on the respiratory system and cardiovascular system) are still unclear and need further long-term follow-up research. (3) NRT has the lowest health risk among all nicotine administration routes, as it only provides pure nicotine and avoids exposure to other toxic and harmful substances, with mild and controllable side effects[18]. It should be noted that although nicotine itself has a certain effect on the cardiovascular system, the

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nicotine dose provided by NRT is low and the blood concentration is stable, so the cardiovascular risk is significantly lower than that of traditional cigarettes and e-cigarettes.

Clinical application strategies for smoking cessation

The precision of clinical intervention is the key to improving the success rate of smoking cessation. Smoking cessation strategies based on individual biological characteristics and clinical characteristics have been gradually applied in clinical practice, and significant clinical benefits have been achieved.

Individualized smoking cessation strategy based on the nicotine metabolite ratio

The nicotine metabolite ratio (NMR, the ratio of 3'-hydroxycotinine to cotinine in urine or plasma) is a reliable biomarker for evaluating individual nicotine metabolism rates, which are mainly determined by polymorphism in the *CYP2A6* gene[28]. Smokers can be divided into rapid metabolizers (high NMR, high CYP2A6 enzyme activity) and slow metabolizers (low NMR, low CYP2A6 enzyme activity) according to the NMR. A series of clinical studies and meta-analyses have confirmed that NMR-based individualized smoking cessation strategies can significantly improve the success rate of smoking cessation. For rapid metabolizers, varenicline has a higher smoking cessation success rate than NRT, because rapid metabolizers have a fast nicotine clearance rate, and NRT has difficulty maintaining an effective blood nicotine concentration, whereas varenicline, as a partial agonist of nicotine receptors, can directly activate the nicotine receptors and is not affected by the metabolism rate. For slow metabolizers, NRT has a better smoking cessation effect, because slow metabolizers have a slow nicotine clearance rate, and low-dose NRT can maintain a stable blood nicotine concentration, avoiding excessive nicotine intake and adverse reactions[34]. In addition to improving the smoking cessation success rate, NMR-based individualized strategies can also reduce the incidence of adverse reactions and improve treatment tolerance and medication compliance[34].

Stratified management of special populations

For special tobacco-dependent populations, stratified intervention and individualized management should be adopted according to their physiological characteristics and clinical status. (1) In adolescents and young adults, behavioral interventions and nonpharmacological therapy should be the first choice, because the brain development of adolescents is not yet mature, and the long-term effects of pharmacological smoking cessation on the central nervous system are unclear; if pharmacological intervention is necessary, NRT with high safety should be selected under the strict guidance of physicians, and e-cigarettes should be strictly prohibited[35]. (2) For pregnant women, as smoking during pregnancy is harmful to both the mother and the fetus, behavioral intervention is the first-line intervention measure; if a behavioral intervention is ineffective, NRT can be used under the rigorous assessment of physicians, and the risk of nicotine exposure is significantly lower than that of smoking[36]. (3) Regarding patients with pre-existing diseases, for patients with cardiovascular diseases, COPD, diabetes, and other chronic diseases, NRT is the preferred pharmacological regimen, and the combined use of long-acting and short-acting NRT is recommended, with close monitoring of vital signs during treatment; for patients with mental disorders, bupropion or a combination of bupropion and NRT can be selected, which can not only help smoking cessation but also improve mental symptoms[37].

Conclusions and future perspectives

The administration routes of nicotine are the core factor affecting its pharmacokinetic characteristics. NRT, as a first-line pharmacological smoking cessation measure, has the advantages of controllable nicotine delivery, low addictiveness, and high safety, and is the most evidence-based nicotine administration route for smoking cessation. In recent years, GLP-1 receptor agonists represent a promising novel avenue for smoking cessation, offering the dual benefits of reducing nicotine dependence and mitigating post-cessation cardiometabolic risks, particularly in smokers with underlying metabolic or psychiatric conditions[38]. Psychedelic-assisted therapy, particularly psilocybin, has shown preliminary antiaddictive effects on smoking behaviors[39]. Novel smoking cessation intervention technologies such as nicotine nanovaccines and gene delivery systems have demonstrated promising preclinical efficacy, providing a new direction for the treatment of severe tobacco dependence, but their clinical safety and effectiveness still need further verification through long-term clinical trials.

Future research in this field should focus on the following directions: (1) Strengthen long-term monitoring and research on e-cigarettes: Carry out large-sample, prospective cohort studies to clarify the long-term health effects of e-cigarettes on the respiratory system, cardiovascular system, and reproductive system and formulate targeted regulatory measures. (2) Promote the standardized clinical application of NRT: Further optimize the combination of dosage forms and dosage adjustment schemes of NRT, and improve the smoking cessation success rate by using personalized dosages. (3) Accelerate the clinical translation of novel smoking cessation technologies: Solve the technical problems of nicotine nanovaccines and gene delivery systems, and carry out clinical trials to verify their efficacy and safety. (4) Develop precision smoking cessation strategies: Based on multi-omics biomarkers, construct a personalized smoking cessation prediction model, and realize stratified intervention and precise treatment of tobacco-dependent populations. (5) Strengthen multidisciplinary cross-integration: Combine immunology, nanotechnology, gene therapy, clinical medicine, and public health to develop more safe, effective, and easy to use smoking cessation interventions, and form a comprehensive smoking cessation system integrating prevention, intervention, and treatment.

With the deepening of research and the development of technology, we expect to realize transformation of the model from general tobacco control to precision smoking cessation in the future and provide more effective strategies for reducing the harm of tobacco and improving the success rate of smoking cessation.

Ethical statements

Ethical approval was not required for this article, as it does not involve original research on human participants, animals, or sensitive data.

Author contributions

The authors confirm their contributions to the paper as follows: conceptualization and writing of the original draft: Zhu C, Zhou J; review, revision, and editing of the manuscript: Zhou JP, Shi G. All authors reviewed the results and approved the final version of the manuscript.

Data availability

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

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Conflict of interest

The authors confirm that they have no conflict of interest.

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