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NICOTINE REPLACEMENT THERAPY: A COMPREHENSIVE REVIEW OF ITS ROLE IN SMOKING CESSATION

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ABSTRACT

Cigarette smoking remains the leading preventable cause of morbidity and mortality worldwide, contributing to millions of deaths annually due to the presence of carcinogenic and toxic compounds in tobacco smoke. Nicotine, the principal addictive component of tobacco, exerts complex pharmacological effects that sustain dependence, making cessation challenging. Nicotine Replacement Therapy (NRT) offers a safer and effective means of overcoming withdrawal symptoms by delivering controlled doses of nicotine through formulations such as gums, lozenges, patches, inhalers, nasal sprays, and emerging modalities like electronic nicotine delivery systems. Evidence suggests that NRT increases quit rates by 50–70% when combined with behavioural support, with combination therapies proving more effective in managing severe withdrawal. Despite advantages, NRT carries limitations, including adverse effects, potential misuse, drug–drug interactions, and the risk of prolonged nicotine dependence, highlighting the need for medical supervision. In India, where tobacco consumption remains among the highest globally, widespread use of NRT could significantly reduce smoking-related health burdens. Future research into rapid delivery systems and novel approaches, such as nicotine vaccines, holds promise for enhancing treatment efficacy. Overall, NRT represents a crucial intervention in global tobacco control strategies, warranting careful management, monitoring, and integration with behavioural support to achieve long-term smoking cessation.

KEYWORDS: Nicotine Replacement Therapy (NRT), Smoking cessation, Tobacco dependence, Nicotine gum.

INTRODUCTION

Cigarette smoking is the foremost preventable cause of death globally; it claims close to 4 million lives annually. The World Health Organization projects that 10 million smokers will perish per year by 2030. Cigarette smoke contains over 4000 chemicals, including 43 cancer-causing agents and 400 other toxic substances.[1]

Nicotine replacement therapy (NRT) is a treatment employed to help smokers quit the habit. In this approach, the nicotine found in cigarettes is substituted by providing nicotine in reliable forms, such as nicotine gums, nicotine lozenges, and nicotine patches.[2]

The countries of the world can be categorized into different 'tobacco dependence stages' based on the rate of

lung cancer deaths in their populations. The United States and Western Europe are regarded as developed tobacco dependence markets. In these regions, the percentage of men who smoke has already reached its peak, which is then followed by a peak in lung cancer deaths approximately 20 years later, as the proportion of male smokers begins to decline. Regrettably, the lung cancer death rates for women in these areas have not yet started to decrease, even though the rate of increase has slowed down.[3]

India is the second largest producer and the third largest consumer of tobacco globally. India has more than 100 million adult smokers, which is the second highest number of smokers in the world, after China.[4]

Review of literature

1. Cigarette Smoking

In 2017, an estimated 34.3 million adults aged 18 and older in the United States, representing 14.0% of the adult population, were smokers (Centres for Disease Control and Prevention, 2018). The smoking prevalence was higher among men compared to women (15.8% vs 12.2%). That same year, 7.4 million adults in the United Kingdom, or 15.1% of the adult population, smoked (17.0% of men and 13.3% of women) (Office for National Statistics, 2018a). In Canada, approximately 5 million individuals aged 12 and older, or 16.2% of that population, were smokers, with a higher rate among men at 19.1% compared to 13.4% for women (Statistics Canada, 2019). The majority of current smokers, defined as those who report themselves as non-daily or daily smokers, smoke on a daily basis. Other forms of tobacco use, such as cigars and cigarillos, are less common than cigarettes, with 4% of Americans and 3% of Canadians reporting such usage (Centres for Disease Control and Prevention, 2018; Reid et al., 2017).[5]

Table 01: Health Risks of Smoking.[6]

Cause of Death / Complication	Benefit of Stopping Smoking
Coronary Heart Disease	The risk is preventable if cessation occurs in early adulthood. The damage is at least partially reversible if you quit later in life.
Stroke	The risk is preventable if cessation occurs in early adulthood. Quitting at any point prevents a further increase in risk.
Cancers of the Lung and Upper Airways	The risk is preventable if cessation occurs in early adulthood. Quitting at any point prevents a further increase in risk compared to continuing to smoke.
Chronic Obstructive Pulmonary Disease (COPD)	The risk is preventable if cessation occurs in early adulthood. If quit later, the decline in lung function is slowed significantly, reducing symptoms and improving quality of life.
Miscarriage and Underdevelopment of Foetus	The risk is preventable if cessation occurs early in pregnancy. However, risk is mitigated by stopping at any time during pregnancy, benefiting both the mother and the baby.

2. Nicotine

Nicotine (C10H14N2) is a plant alkaloid found in the tobacco plant and is the principal constituent of tobacco responsible for its addictive character. Nicotine acts as a ganglionic nicotinic cholinergic agonist in the autonomic ganglia, brain, spinal cord, neuromuscular junctions and adrenal medulla. Nicotine has dose-dependent pharmacological effects and has both stimulant and depressant action.[7]

3. Mechanism Of Action

The chemical structure of nicotine is (S)-3-(1-methylpyrrolidin-2-yl) pyridine. It contains a pyridine ring and a pyrrolidine ring, both of which have a tertiary amine group.[8] Nicotine acts as a full agonist, meaning it fully stimulates the neural nicotinic acetylcholine receptors in the ventral tegmental area of the brain. This then triggers the release of dopamine e in the nucleus accumbens, ultimately reducing the withdrawal symptoms experienced by regular smokers who are trying to quit.[9] Nicotine also helps provide a coping mechanism, making tobacco use less active. During cigarette smoking, the blood concentration of nicotine rises quickly and reaches its peak level just before the end of the smoking session.[10] The nicotine absorbed from smoke rapidly reaches different parts of the body, leading to desensitization of the nicotinic acetylcholine receptors when nicotine levels in the brain are high. When the nicotine level falls, the receptors become resensitized, resulting in the experience of withdrawal effects.[11]

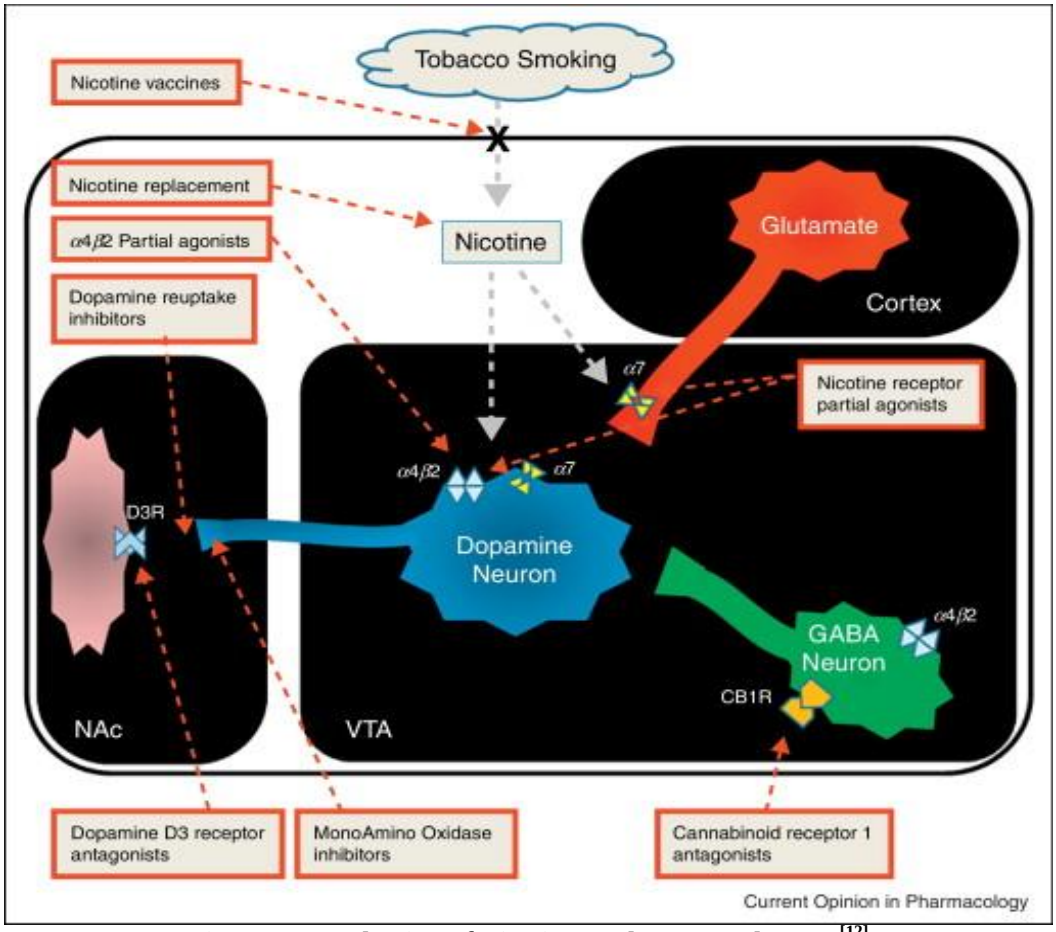

Figure 01: Mechanism of Nicotine Replacement Therapy.[12]

4. Forms of Nicotine Replacement Therapy[13]

1. Nicotine Transdermal Patch
2. Nicotine Gum
3. Nicotine Lozenges
4. Nicotine Sublingual Tablet
5. Nicotine Oral Inhaler
6. Nicotine Nasal Spray
7. Nicotine Vaccine
8. Electronic nicotine delivery systems (ENDS) or Electronic cigarettes
9. Rapid release gum

5. Major Nicotine Replacement Therapy

- **Nicotine Gum**

The first widely available nicotine replacement therapy (NRT) product was nicotine gum (Nicotine Polacrilex). It comes in 2 mg and 4 mg dosages. Research has shown that the 4 mg chewable gum is more effective for quitting smoking compared to the 2 mg version. The dosage is gradually reduced over the course of a few weeks or months of use. Nicotine gum is typically prescribed for 6-12 weeks, with a maximum of 6 months. After 2-3 months, the chewing time is decreased, the gum is divided into smaller pieces, or the nicotine gu m is replaced with sugar-free gum to eventually stop using it completely.[14]

Mechanism

The nicotine is delivered through the transmucosal route. The gum is chewed intermittently and held in the mouth until the taste is strong (around 30 minutes), at which point it is placed in the vestibule to allow the nicotine to be absorbed into the bloodstream.[14]

Adverse Effect

Three well-known side effects of nicotine gum (gastric upset, throat irritation, and nausea) were reported more often in the active gum group. Otherwise, event rates were similar by group, and unremarkable.[15]

Figure 02: Nicotine Gum Brands.

- **Nicotine Lozenges**

Nicotine lozenges are one form of nicotine replacement therapy that can be used to help you stop smoking over a period of time. They're dissolving tablets you can hold in your mouth, and they come in a variety of flavours.

Nicotine replacements can ease nicotine withdrawal symptoms and allow you to control the frequency and amount of your dosage. Lozenges are dosed based on how heavy of a smoker you are. They can also be combined with the nicotine patch.[16]

Types of lozenges[17,18,19,20]

(a) Chewable lozenges (b) Compressed lozenge (c) Soft lozenge (d) Hard lozenge

Advantages[17,18,19,20]

- The medication can be administered to patients who experience difficulty with swallowing.
- The medication is simple to provide to both elderly and pediatric patients.
- The formulation extends the duration of the drug's presence in the oral cavity, enabling it to produce a specific desired effect.
- Straightforward to make, requiring little equipment and time.
- Do not necessitate the submission of a water intake form.
- The systemic absorption of drugs can potentially occur through the buccal (cheek) cavity.

Disadvantages[17,18,19,20]

- Certain drugs may not be compatible with aldehyde-based candy formulations, such as benzocaine.
- Children above the age of 6 can safely use lozenges.
- The non-uniform distribution of drugs within saliva for local treatment.
- Potential drainage of drug from the oral cavity to the stomach along with saliva.
- The lozenge dosage form is that it mistakenly could be used as candy by children.
- The high temperature needed for their creation is the defining characteristic of a hard candy lozenge.
- Solid lozenges turn gritty.

Figure 03: Different Nicotine Lozenges.

- **Transdermal Patches**

To provide the recommended dosage, a transdermal patch is used to penetrate the skin and reach the bloodstream. In 1981, transdermal patch devices received their first approval from the US Food and Drug Administration.

Transdermal administration allows for the repeated injection of medications with brief biological half-lives and also avoids pulsing entry into the systemic circulation and enables ongoing, regulated drug monitoring. The compound Scopolamine patch was the first transdermal route patch to be made commercially available for the prevention of motion sickness. Later,

transdermal patches containing fentanyl, oestradiol, and clonidine were introduced for use in treating hormone replacement therapy, chronic pain, and hypertension, respectively.[21]

Advantages of Transdermal Patches[22,23,24]

1. It can prevent first-pass metabolism
2. The duration of action may be prolonged and predictable
3. To address the difficulties of drug absorption within the gastrointestinal system, the application of TDDS is advised
4. TDDS can serve as a substitute for oral medication when the route is inappropriate, such as in patients experiencing vomiting and diarrhoea
5. The concentration of the drug in plasma can be sustained
6. TDDS is non-invasive, thereby avoiding the inconveniences associated with parenteral therapy.
7. It minimizes the occurrence of fluctuations.
8. It is applicable for drugs that have a short half-life and therapeutic range
9. Drug therapy can be readily discontinued in the event of poisoning
10. It decreases the frequency of drug administration, thereby enhancing patient compliance

Disadvantages of Transdermal Patches[22,23,24]

1. Only drugs with relatively high potency are suitable for transdermal delivery systems, as the limits of drug entry are influenced by the impermeability of the skin.
2. Hydrophilic drugs are generally less appropriate than lipophilic drugs due to their lower permeability.
3. Larger drug molecules (those exceeding 1000 in size) pose challenges for absorption.
4. This method is not applicable for drugs that require high dosages.
5. This system has the potential to cause allergic reactions at the site of drug application, which may include symptoms such as itching, rash, and localized edema.

Figure 04: Different Transdermal Patches Brands.

- **Electronic Cigarettes**

Males are more likely than females to use e-cigarettes and prefer them to traditional cigarettes, suggesting that e-cigarette use varies by gender. According to reports, e-cigarette use is largely influenced by curiosity and peer pressure. For smokers, using e-cigarettes was linked to having a smoking family member or peer. Because e-cigarette users are more likely than nonusers to start smoking traditional cigarettes, e-cigarette use may be a contributing factor to nicotine addiction. Electronic cigarettes come in two different designs: an open design with an e-liquid-filled main chamber and a closed design that can be reloaded or thrown away with prefilled cartridges.[25]

Figure 05: Electronic Cigarette.

6. Future Nicotine Replacement Therapy

1. Nicotine Preloading

Nicotine preloading refers to the use of nicotine replacement therapy (NRT) before quitting smoking. [26] This approach involves using NRT for several weeks prior to the actual quit date, and is also known as precessation or pre-quitting NRT. The proposed mechanisms behind this strategy include the user becoming accustomed to using NRT in the lead-up to quitting, the saturation of nicotine receptors reducing the desire to smoke, and NRT diminishing the rewarding effects of smoking, thereby weakening the association between smoking and the perceived benefits.[27,28]

A review suggests that starting patch use for a short period before the quit attempt is moderately more effective than initiating patch use on the quit date itself. However, there is no evidence indicating that using other forms of NRT before the quit date is more effective than starting on the quit day.[29] A meta-analysis found that precessation patch treatment can significantly improve quit rates compared to the standard approach of starting patch use on the quit day. Conversely, a large randomized trial concluded that using NRT two weeks before the target quit day was safe and well-tolerated, but did not provide any additional benefit over the usual care approach.[30]

2. True Pulmonary Inhaler

A true pulmonary nicotine inhaler, unlike the currently available nicotine inhaler, would deliver nicotine to the lungs in a manner more akin to cigarette smoking. This would be expected to provide a sufficient dose of nicotine to alleviate background cravings and withdrawal symptoms, and would allow for rapid relief of acute and morning cravings. Since the delivery of nicotine directly to the lungs would effectively mimic the physiological effects of cigarette smoking, the smoker could eliminate the need for tobacco and gradually reduce their nicotine dependence over time.

While there are significant technological challenges to producing an effective and acceptable lung inhaler, the primary barrier may be the potential for abuse and the associated regulatory implications. The key challenge is ensuring the nicotine molecules are appropriately condensed onto particles with a median diameter of approximately 1 micron to enable inhalation into the pulmonary alveoli, while also designing the nicotine particles to prevent the production of unacceptably harsh sensory effects.[31]

3. Nicotine Vaccine

Nicotine vaccines represent a novel approach to treating nicotine addiction and are currently under investigation. Since nicotine is a small molecule that cannot independently stimulate an immune response, it is attached to a carrier protein to induce the necessary immune reaction. These nicotine-based vaccines can train the immune system to recognize nicotine as a foreign substance and mount an immune response against the drug. In doing so, the vaccines may reduce the amount of nicotine that reaches the brain. Several organizations have developed vaccines for smoking cessation, with NicVAX from Nabi Biopharmaceuticals being one of the most well-known. However, a potential drawback of using vaccines to treat tobacco addiction is that smokers may compensate for the decreased effects of nicotine, as would be expected when a vaccine reduces the concentration of nicotine in brain tissues, by increasing their tobacco consumption to overcome this effect. Other potential issues with the successful use of nicotine vaccines include difficulties in achieving sufficiently high antibody levels, the fact that vaccines generally have a short-lived effect, and significant variation in individual responses to the vaccine. A recent systematic review found no current evidence that nicotine vaccines enhance long-term smoking cessation, emphasizing the need for further clinical trials in this area.[32,33,34,35]

Table 02: Drugs Utilized in Nicotine Replacement Therapy.[36]

Drug Name	Target	Mechanism	Use	Side effect
Approved Drugs				
Bupropion	Norepinephrine transporter and the dopamine transporter	Inhibits reuptake of norepinephrine and dopamine	Smoking cessation	Insomnia, dry mouth, nausea, headache
Varenicline	α4β2 nAChR	Partial agonist at α4β2 nAChR, reducing nicotine withdrawal symptoms	Smoking cessation	Nausea, insomnia, abnormal dreams
Rimvoxabart	CB1 Receptor	Blocks CB1 receptors in the endocannabinoid system	Smoking cessation, Weight loss in obesity	Depression, anxiety, nausea
Drugs under trial				
α4β2 nAChR partial Agonists	α4β2 nAChR	Partial agonist at α4β2 nAChR	Smoking cessation	Respiratory irritation
Nicotine Vaccines	Targets nicotine as antigen	Stimulates the immune system to produce antibodies	Smoking cessation	Local reaction at injection site, flu-like

		against nicotine		symptoms
Dopamine D3 Receptor Antagonists	Dopamine D3 Receptor	Blocks dopamine D3 receptors	Smoking cessation	Insomnia, nausea, headache
Orexin Receptor Antagonists	Orexin receptors	Blocks orexin receptors	Smoking cessation, Insomnia	Headache, dizziness, fatigue

7. Reasons NRT Should Be Prescription Based

Currently, NRT products are available OTC in many countries, meaning anyone can purchase them without consulting a doctor or pharmacist. While OTC availability increases access to NRT, it also presents risks that could be mitigated by requiring NRT to be prescription-based.

1. The Health Risks of Nicotine

Nicotine is not an innocuous drug. Despite being less dangerous than smoking, nicotine can nonetheless have negative affect the reproductive, neurological, and cardiovascular systems. In certain instances, it could potentially have negative effects when taken with medicines. Users might not be aware of these hazards in the absence of medical supervision, which raises the possibility of consequences.

2. Inappropriate Use

It's possible that many people are unaware of proper NRT usage. Selecting the appropriate product kind, dose, and duration is essential for successful stopping. Additionally, users could not notice overdose warning signals or other negative effects. People can get tailored guidance to guarantee the safe and efficient use of NRT under medical supervision.

3. Lack of Behavioural Support

NRT is most effective when combined with behavioural counselling that addresses the psychological aspects of addiction. However, many smokers using OTC NRT products may not have access to this critical support. Prescription-based NRT would allow healthcare professionals to offer guidance on behavioral interventions and ensure that users receive comprehensive quit plans.

4. Nicotine Dependency Risk

Despite being intended as a temporary solution, some users may develop a dependence on NRT, using it for longer than is advised or in conjunction with other nicotine sources like cigarettes or e-cigarettes. Medical supervision that encourages patients to taper off NRT drugs gradually could avoid long-term nicotine dependence.

5. Abuse and Misuse

The availability of OTC raises the possibility of abuse. For instance, people might take more than is advised, which could result in nicotine poisoning.[37]

8. Combined NRT Therapy

For people who have severe withdrawal symptoms, combined therapy is an option. An NRT patch, which provides a consistent background level of nicotine, is frequently used in conjunction with gum or a nasal spray, which is occasionally used to replenish the nicotine level and prevent unexpected cravings. Research indicates that when compared to a single product, this type of combination offers a slight but significant boost in success rates.[38]

MANAGEMENT AND MONITORING OF NRT PRESCRIPTIONS for PLANNED QUIT

NRT prescribing-review will be determined by the advisor and will normally be as follows:

• 1 week after stopping [to avoid wastage of prescribing products which are unused]

• If patients are successful in stopping smoking after week 4 (preferable with carbon monoxide validation, where this is available) treatment may be given for another four weeks before reassessment.

• If the smoker continues to abstain from smoking at week 8 then a further four weeks treatment may be

offered and NRT gradually withdrawn over the next 4 weeks unless there is a strong likelihood of relapse without continuing treatment.
• NRT should be gradually withdrawn by 12 weeks unless there is a strong likelihood of relapse without continuing treatment.
• If the smoker is unsuccessful in stopping then discontinue treatment and make a fresh start when they are ready again (NICE recommends waiting 6 months unless special circumstances have hampered the person's initial attempt to stop smoking). Sometimes hospital admission may not be the easiest time for an individual to successfully stop smoking and this should bOxford Health NHS FT Drugs & Therapeutics Group Oxford Health NHS FT Drugs & Therapeutics Groupe followed up post-discharge when it is less stressful.
• On discharge from hospital an NRT supply will be given until the next review appointment is due. This should be arranged with the local CCG smoking cessation advisor (see contact details section).[39]

Drug-Drug Interactions

- In addition to having direct interactions with certain medications, nicotine may also have indirect effects on the hepatic metabolism of other medications by counteracting the hepatic enzymes that smoking causes. Ten patients participated in a randomize controlled research that showed that nicotin.
- e amplifies the effects of adenosine and that combining the two increases the risk of tachycardia.[40]
- Cimetidine has been shown to prolong the effects of the same dose by slowing the excretion of nicotine.[41]
- The polycyclic aromatic hydrocarbons found in cigarette smoke strongly stimulate the liver enzymes CYP1A1, CYP1A2, and 2E1.[42,43]

Adverse Effects

- Headaches may result from any type of nicotine replacement treatment.[44]
- Sleep disruptions can result from both lozenges and patches, and local skin responses can be triggered by patches.[45]
- Using smokeless tobacco during pregnancy increases the risk of small-for-gestational-age babies and neonatal apnea, both of which may be mediated by nicotine's effects.[46]
- Breast milk contains a 2.9:1 ratio of nicotine to maternal serum. Infants who are breastfed face unknown risks.[47]

Table 03: Nicotine Replacement Therapy Formulation.[48,49,50]

Product	Nicotine Dose	Absorption Time	Key Features	Advantages	Limitation
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 Lozenges	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	0-15 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	Behavioural replacement	Requires frequent puffing; throat irritation
Nasal Spray	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

Table No 4: Difference between Nicotine Replacement Therapy (NRT) and cigarette Smoking.[51]

Symptom	E-cigarettes (n = 315)		Nicotine replacement (n = 279)		Relative risk (95% ci)†
	Baseline	52 Weeks	Baseline	52 Weeks	
	number (percent)		number (percent)		
Shortness of breath	120 (38.1)	66 (21.0)	92 (33.0)	64 (22.9)	0.9 (0.7–1.1)
Wheezing	102 (32.4)	74 (23.5)	86 (30.8)	59 (21.1)	1.1 (0.8–1.4)
Cough	173 (54.9)	97 (30.8)	144 (51.6)	111 (39.8)	0.8 (0.6–0.9)
Phlegm	137 (43.5)	79 (25.1)	121 (43.4)	103 (36.9)	0.7 (0.6–0.9)

CONCLUSION

Nicotine addiction is the primary obstacle preventing smokers from quitting and maintaining long-term abstinence. Today, a variety of nicotine replacement therapy (NRT) products are available in different forms, doses, and flavors, and their use has been recommended for all tobacco consumers who do not have medical contraindications. The patient's preference should typically guide the choice of NRT product. Current evidence suggests that all commercially available NRT forms, such as gum, transdermal patch, nasal spray, inhaler, and sublingual tablets/lozenges, increase the chances of successfully quitting smoking. NRTs have been shown to increase the rate of quitting by 50 to 70%. Additionally, meta-analyses have concluded that NRT can also increase the likelihood of reducing the habit among smokers who are not willing to quit completely. To further improve the efficacy of NRT, recent research has focused more on rapid delivery techniques and immunological approaches. However, these new modalities require more high-quality research to translate them from the laboratory to clinical practice. Given the significant potential of NRT, it is essential for healthcare professionals to become familiar with all forms of NRT to be able to address the questions and needs of tobacco users who appear to be increasingly interested in quitting.[52,53]

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