

# Nicotine replacement therapy: A friend or foe

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## ABSTRACT

According to the World Health Organization (WHO) Framework Convention for Tobacco Control (FCTC), tobacco cessation is a primary health-care service that should be provided not only to the people having adverse habits of consuming tobacco but also to the nonconsumer, as they can also be harmed due to its deleterious effects. Tobacco has been regarded as a potential risk factor for oral diseases such as oral potentially malignant disorders and oral cancers. Various aids of achieving cessation have been studied, including education of the ill effects of tobacco to the patient, behavioral counseling, and pharmacotherapy. Various pharmacological interventions are available nowadays but nicotine replacement therapy (NRT) is most widely used. The various types of NRT products results in general and breakthrough craving relief with immediate release of nicotine. All of these products have different levels of efficacy and variable rates of nicotine absorption. Knowledge of these will be beneficial for the patients, the budding dentist and the nation in the upcoming days ahead.

**Keywords:** Nicotine gum, nicotine lozenges, nicotine patch, nicotine replacement therapy, nicotine spray, tobacco

## Introduction

A wide range of ailments caused by tobacco are one of the substantial threats the general population is facing. It continues to be the substance causing maximum health damage globally.<sup>[1]</sup> The tobacco plant refers to any of various members of the genus *Nicotiana* in the nightshade (*Solanaceae*) family.<sup>[2]</sup> Tobacco contains nicotine as the main alkaloid, which is the principal modulator of the psychopharmacological effects associated with its addiction.<sup>[3,4]</sup> The prevention and control of tobacco use is one of the rising issues globally. Tobacco cessation is one of the method which helps in improving the life expectancy and reducing the morbidity.<sup>[5]</sup> Various aids of achieving cessation have

been studied, including education of the ill effects of tobacco to the patient, behavioral counseling, and pharmacotherapy. Various pharmacological interventions are available these days but nicotine replacement therapy (NRT) is most widely used.<sup>[6]</sup> Nicotine replacement products (NRPs) contain pure nicotine with an aim to reduce the patient's inclination towards tobacco consumption and the physiological and psychomotor withdrawal symptoms.<sup>[3,7]</sup> They increase nicotine levels in the bloodstream, due to which the person will smoke fewer cigarettes, resulting in reduction in the consumption and toxicity related to it.<sup>[8]</sup>

The dentists play a crucial role in optimizing the heavy death tolls caused by use of tobacco as dentists comes in regular close contact with the patients. The family physicians and practitioners should also be enlightened with the possible intervention aids of tobacco addiction as they can spread awareness and encourage the users in the quitting process by maneuvering the social relation of the family. Mostly, a physician's advice often works as a great motivation for the patient in quitting.

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## Mechanism of Action

Chemical name of nicotine is (S)-3-(1-methylpyrrolidin-2-yl)pyridine. It has a pyridine and a pyrrolidine ring, both having a tertiary amine.<sup>[9]</sup> Nicotine acts as a full agonist resulting in stimulation of neural nicotinic acetylcholine receptors in the ventral tegmental area of the brain, which then releases the dopamine in nucleus accumbens thereby leading in reduction of nicotine withdrawal symptoms in regular smokers who tries to quit smoking.<sup>[10]</sup> It also assists in providing coping mechanism, which makes the tobacco less active. During cigarette smoking, blood concentration of nicotine rises quickly and is at its highest level when it is about to end.<sup>[5]</sup> Nicotine absorbed from smoke quickly reaches different parts of the body resulting in desensitization of nicotinic acetylcholine receptors when its levels in the brain are high. It again resensitizes when the level falls, resulting in its withdrawal effects.<sup>[11]</sup>

## Types

The various types of NRT products results in general and breakthrough craving relief with immediate release of nicotine. All of these products have different levels of efficacy and variable rates of nicotine absorption.<sup>[3]</sup> They are available under these agencies: US, FDA (OTC), MHRA (OTC), and MHRA (Rx).<sup>[12]</sup>

### Nicotine gum

The first easily accessible NRT product was nicotine gum (Nicotine Polacrilex). It comes in the form of 2 and 4 mg dosages. Studies showed that 4 mg chewable gum has more success rate of withdrawal as compared to 2 mg. The dosage number is reduced gradually per day after a few weeks or months of usage. It is prescribed for 6–12 weeks, with maximum for 6 months. After 2–3 months, the chewing time is decreased, or the gum is divided into small pieces, or the nicotine gum is replaced with sugar-free gum thereby stopping it completely.<sup>[13]</sup> Delivery is done through transmucosal route. It is chewed intermittently and retained in the mouth until the taste is strong (approximately 30 min) and then it is placed in the vestibule for allowing it to absorb into the bloodstream.

It is recommended that the patients should refrain from consuming acidic beverages such as soda, coffee, and beer for at least 15 min both before and after, as they may impede with the buccal absorption of nicotine.<sup>[14]</sup> It should be used cautiously in patients with temporomandibular joint diseases and denture users. Nicotine gum has certain disadvantage that some people dislike its taste and have feeling of fullness in their mouth. They may even complain of mouth soreness, hiccups, dyspepsia and jaw aches.<sup>[15]</sup> Hansson *et al.*<sup>[16]</sup> performed a study to compare relief of urges to smoke, up until 5 h following treatment with a new 6 mg nicotine gum versus currently marketed 4 mg nicotine gum and concluded by saying that the 6 mg nicotine gum provided a greater reduction, faster and longer relief of urges to smoke than the 4 mg nicotine gum.

### Rapid-release gum

Rapid release gum provides biphasic delivery of nicotine through use of a unique gum base that allows a combination of rapid initial nicotine release.<sup>[17]</sup> It also increases pH to facilitate rapid absorption through the oral mucosa. Increase in the dose of nicotine was done in order to provide rapid relief from craving and overdosing. Niaura *et al.*<sup>[18]</sup> performed a study to assess the comparative efficacy of rapid-release nicotine gum vs. nicorette in relieving smoking cue-provoked craving and found that rapid-release nicotine gum has an advantage over conventional nicotine gum as they are rapid and results in complete relief from nicotine craving.

### Nicotine lozenges

Nicotine lozenges can replace nicotine gum in patients who needs intermittent and controlled doses of nicotine but are unable to chew them for longer period of time. They are available as 1, 2, and 4 mg formulations.<sup>[19]</sup> Only 20 lozenges in 24 h are recommended. It is placed sublingually for 30 min, which releases nicotine into systemic circulation.<sup>[20]</sup> Studies showed that the amount of nicotine absorbed per lozenge appears to be somewhat higher than that delivered by gum. The advantage of nicotine lozenge is that they are easy to use and its taste is acceptable to the patient. However, they should be advised not to drink or eat 15 min before or during usage and also not to swallow and chew excessively during its consumption.<sup>[5]</sup> Xiao *et al.*<sup>[19]</sup> conducted a study to evaluate the efficacy in smoking cessation of 2 and 4 mg nicotine mint lozenges and concluded that the 4 mg nicotine lozenge provided a directionally significant improvement in smoking cessation rates.

### Nicotine patches

Nicotine patch is a transdermal patch which is easy to use and results in slow release of nicotine. They are available in the ranges from 5, 10, and 15 mg doses patch, which can be worn over 16 h; however, 7, 14, and 21 mg doses patch can be worn over 24 h. Patients can place the patches over the clean and unbroken skin once in the morning, rather than using throughout the day.<sup>[21]</sup> The 16 h patch should be removed before bedtime and 24 h patch to be removed the next morning.<sup>[18]</sup> Plasma concentration of nicotine gets elevated during the day with the usage of nicotine patch than with any other acute NRT (nicotine gum, spray, lozenges, and inhalers) use. Patients may have side effects of insomnia and even local skin irritations are reported.<sup>[19]</sup> DeVaugh-Geiss *et al.*<sup>[22]</sup> conducted a study to compare the single-dose pharmacokinetics of the 21-mg/24-h patch and the 25-mg/16-h patch and concluded by saying that the 21-mg patch provided a maximal nicotine concentration faster than did the 25-mg patch.

### High-dose nicotine patches

Initially, the high-dose nicotine patches were available in 22-mg which were able to replace only half of baseline serum nicotine and cotinine levels in smokers. Therefore, a need for higher doses ( $\geq 42$  mg) of transdermal nicotine patches was required.

It can be used once daily on clean unbroken skin and removed before bedtime. Patients may suffer from local irritation and sleep disturbances.<sup>[5]</sup> Schnoll *et al.*<sup>[23]</sup> conducted a study to assess whether extended transdermal nicotine therapy increases abstinence from tobacco more than standard duration therapy in adult smokers and they concluded that extended therapy reduced the risk for a lapse and increased the chances of recovery from lapses.

### Nicotine oral inhaler

Nicotine inhaler consists of a mouthpiece and a plastic cartridge containing nicotine, which mimics a cigarette/cigar. Each cartridge contains 10 mg nicotine.<sup>[13]</sup> It can be sprayed in the mouth (not inhaled nor swallowed for few seconds); however, care should be taken that it does not touch the lips. It is mainly used in patients when they have craving for smoking. Delivery of nicotine is about 36% in the oral cavity, esophagus, stomach, and about (4%) in the lungs. Rate of absorption through the inhaler is same as that of nicotine gum which mainly occurs through oral mucosa. Its use can lead to irritation of mouth and throat.<sup>[5]</sup> Bolliger *et al.*<sup>[24]</sup> conducted a study to determine whether use of oral nicotine inhalers can result in long term reduction in smoking and concluded by saying that nicotine inhalers effectively and safely achieved sustained reduction in smoking over a period of 24 months.

### Nicotine nasal spray

It is available as a multidose bottle with a pump which is fitted to a nozzle. It was designed to deliver doses of nicotine more rapidly. It delivers 0.5 mg of nicotine per 50 µL single spray. Patient is asked to take shallow puffs approximately every 2 s or alternatively 4 puffs every minute and continuing it for 30 min. It has been shown through various studies that there is more rapid delivery of nicotine in nicotine nasal sprays (NNS) when compared to other NRT products. It should not be given to patients with asthma. NNS sometimes results into nose irritation, coughing and watery eyes.<sup>[5]</sup> Rubinstein *et al.*<sup>[25]</sup> conducted a study to determine the feasibility and utility of using NNS in adolescent smokers who want to quit smoking and concluded by saying that the use of NNS as an adjunct to counseling for adolescent smokers wishing to quit was not supportive due to its unpleasant side effects, poor adherence, and consequent lack of efficacy.

### Nicotine sub-lingual tablet

The recommended dose of sublingual tablet for highly nicotine dependent individuals is 16 to 24 tablets daily (i.e. 2 mg tablets maximum 30 tablets throughout the day), whereas for low dependency is 8–12 tablets daily.<sup>[26]</sup> The tablet is placed sublingually and does not require chewing. It is recommended for at least 8–12 weeks and after that the numbers of tablets are reduced subsequently.<sup>[3]</sup> It should be used cautiously in patients with nicotine dependence. Insomnia and mouth soreness are the major side effects associated with it. Tonnesen *et al.*<sup>[27]</sup> conducted a trial study to evaluate the efficacy of nicotine sublingual tablets and two levels of support for smoking cessation in COPD

patients. They showed that NRTs can be used for a longer duration in the population of COPD smokers.

## Electronic Nicotine Delivery Systems (Ends) or Electronic Cigarettes

An electronic cigarette (e-cig, shisha pen, or personal vaporizer) is a device that produces vapor that resembles the look and feel of smoking.<sup>[5]</sup> Each device contains an electronic vaporization system, rechargeable batteries, electronic controls and cartridges of the liquid that vaporizes.<sup>[3]</sup> The vapor usually contains some nicotine and a base liquid mainly propylene glycol, glycerol, water.<sup>[28,29]</sup> It comes in a variety of flavors that people can choose from. e-cig have become popular among this generation because of their realistic look, feel, and taste as compared to conventional cigarettes.<sup>[30,31]</sup> However, Food and Drug Administration has reported that e-cig contains harmful components and that their usage should be stopped or as NRPs.<sup>[32]</sup> Hajek *et al.*<sup>[33]</sup> conducted a study to compare the efficacy of e-cig and NRT and found that e-cig were more effective for smoking cessation than NRT.

Jackson *et al.*<sup>[34]</sup> conducted a study to assess whether dual e-cig users have lower smoking cessation rates than exclusive cigarette smokers or dual users of NRT and cigarettes. They concluded by saying that dual use of e-cig is not associated with reduced overall quit rates compared with exclusive smoking or dual use of NRT. However, dual use of e-cig is associated with a slightly higher quit attempt rate than exclusive smoking but lower than dual use of NRT.

### Combined therapy

People with intolerable withdrawal symptoms can be treated by combined therapy. A transdermal nicotine dose of 7, 14, and 21 mg along with dosage of any one acute form is the choice of combination most commonly used. To recompense the level of nicotine during abrupt craving, NRT patches can be used along with nicotine gum or a nasal spray.<sup>[35]</sup> Nicotine patches and acute nicotine forms should be used together. These combinations help in achieving a significant though small success rate of NRT when compared to use of individual NRT separately.<sup>[36]</sup> Combination therapy is contraindicated in nicotine dependence and insomniac patients. Mouth and airway irritation, nausea and vomiting are the most commonly reported adverse effects.<sup>[13]</sup> Leung *et al.*<sup>[37]</sup> conducted a study to compare the effectiveness of combined nicotine patch with gum versus nicotine patch alone in smoking cessation and concluded by saying that Smokers prescribed with combined NRT were more likely to quit smoking as compared to single NRT.

### Nicotine vaccines

Nicotine vaccines are the latest innovation in NRT. A nicotine-based vaccine recognizes nicotine as foreign body and initiates an immune response against the drug. They mobilize drug specific antibodies, which results in the binding of nicotine molecules present in the blood. This prevents the drug being

distributed to the brain, thus reducing its behavioral effects.<sup>[8,38]</sup> They are currently under investigation.

### Nicotine preloading

Nicotine preloading means using a NRT prior to a quit date while smoking normally. It results in reduction of a person's drive to smoke deteriorating the level of addiction, resulting in decreased cravings after quitting smoking. It increases the rate of quitting and is assumed that nicotine preloading is reasonably effective in tobacco cessation; however, the data are limited.<sup>[8,39]</sup>

### Contraindications

NRT products are contraindicated in the following conditions [Table 1].

Table 1: Contraindications of NRT	
Conditions	Consequences
Pregnancy	Increased risks of pregnancy complications and adverse neonatal outcomes: <sup>[8]</sup> Placental abruption <sup>[40]</sup> Placenta previa <sup>[41]</sup> Spontaneous abortion <sup>[42]</sup> Stillbirth <sup>[43]</sup> Fetal growth restriction Preterm delivery Low birth weight Sudden infant death syndrome
Children	NRTs are not suitable for children under 12 years of age. Children may suffer from severe toxicity, which can also be fatal.
Cardiovascular disease	Nicotine increases heart rate up to 10-15 beats/min, blood pressure by 5-10 mm Hg and also myocardial contractility therefore increases the total cardiac output. <sup>[44]</sup> Transdermal nicotine appears to be less harmful as it causes few acute hemodynamic changes as compared to smoking.

### Precautions

NRT should be given cautiously in the following conditions [Table 2].

### Advantages

NRT has the following advantages<sup>[5,8]</sup> [Table 3].

### Side effects of NRT

To calculate relative risk, the side effects of NRT should be compared with the side effects of smoking, thereby making NRT much safer than smoking.<sup>[8,13,32,47-49]</sup> [Table 4].

### Conclusion

Various forms of NRT are available in different forms, doses and flavors that can help people to quit smoking. There are several advantages of NRTs but certain circumstances still hinder their recommendation. Some considerations should be given while prescribing them in these following conditions. The sugar levels should be priorly checked in diabetic patients, it should be given carefully in breast feeding females and in patients with mental health disorders. Prescribing NRTs is contraindicated in pregnant ladies, young children who are under 12 years of age, and in patients who have cardiovascular disorders. There are certain side effects associated with the use of NRTs such as nausea, vomiting, insomnia, headaches, throat soreness, and skin irritation. To calculate relative risk, the side effects of NRT should be compared with the side effects of smoking, thereby making NRT much safer than smoking.

This article reflects a way to educate and sensitize the doctors about the various choices of NRT products available in the market which can be prescribed to the tobacco users who are at the will of quitting. The doctors can further educate the society about the quitting protocols and the ease of use of these products and help in making a tobacco free society. Keeping in

Table 2: Precautions of NRT	
Conditions	Consequences
Breast feeding	Amount of nicotine delivered to the fetus through breast milk is uncertain as it depends on the rate of milk production and the concentration of nicotine in the mother's serum. Lozenge, gum, and inhalers shall be used in intermittent dosing: <sup>[8,45]</sup> Mild nicotine toxicity in children include: Nausea and vomiting Diarrhea Hypersalivation Pallor Excessive sweating Weakness Dizziness
Diabetics	Sugar levels should be monitors closely when NRTs are given in diabetic patients as catecholamines are released by nicotine that can disrupt carbohydrate metabolism which further causes vasoconstriction leading to delayed or reduced insulin absorption. <sup>[8,46]</sup>
Mental health comorbidity	NRT should be given cautiously in patients with mental problems as they can be on medications that can interact with NRTs thereby increasing metabolic rate, which results in quickly passing of medicines through the system. Combination therapy for NRT should be offered. <sup>[8]</sup>



**Table 3: Advantages of NRT**

Advantages	It is convenient to use It reduces the craving for tobacco use It does not contain the harmful chemicals which are found in cigarettes and tobacco smoke It does not stain teeth It is cost-effective
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**Table 4: Side effects of NRT**

Sides effects	Nausea, vomiting, indigestion, and gastrointestinal disturbances Insomnia and sleep apnea Headaches Oral ulcers Skin irritation Heart palpitations/chest pains Coughing Throat soreness Dry mouth Increase caries-risk profile Taste impairment Difficulty in speech in denture wearers Hyperkeratosis Localized mucosal irritation
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mind the benefits of NRT, it is essential for the professionals to become familiar with them for achieving successful tobacco cessation. Even incorporating it into an organized teaching of the undergraduate curriculum to improve confidence and knowledge will be beneficial for the patients, the budding dentist and the nation in the upcoming days ahead.

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### Conflicts of interest

There are no conflicts of interest.

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