

## **Review Article**

### **Nicotine Replacement Therapy: An Overview**

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#### **Abstract**

Today tobacco use is the single greatest preventable cause of death in the world. Tobacco use is often incorrectly perceived to be solely a personal choice. This is contradicted by the fact that when fully aware of the health impact, most tobacco users want to quit but find it difficult to stop due to the addictiveness of nicotine. Henceforth, Nicotine replacement therapy (NRT) came into existence which temporarily replaces much of the nicotine from tobacco to reduce motivation to consume tobacco and nicotine withdrawal symptoms, thus easing the transition from cigarette smoking to complete abstinence. Various alternative nicotine sources (*gum, transdermal patch, nasal spray, inhaler and sublingual tablets/lozenges*) have been incorporated into tobacco cessation programs. Recent research is more focusing on rapid delivery of nicotine (Nicotine preloading, true pulmonary inhaler) and immunological approaches (nicotine vaccine) to tackle nicotine dependence. These NRTs are in general well tolerated and have minimal adverse effects. The review aims to summarize literature on various modes of nicotine replacement therapy methods currently used to treat nicotine dependence, and to give an overview about future possible approaches to treat tobacco use disorder.

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## Introduction

Nicotine is the main active ingredient in tobacco products that reinforces individual to tobacco addiction behavior, <sup>(1, 2, 3)</sup> it is tobacco's other components which cause widespread mortality and morbidity. <sup>(4, 5, 6, 7)</sup> Although almost all of the toxicity of smoking is attributed to other components in cigarettes, it is the pharmacological effects of nicotine that lead to tobacco addiction. Therefore, pharmacological interventions for tobacco cessation continue to evolve with our growing knowledge of the neurochemical basis of nicotine addiction. Nicotine is the main alkaloid of tobacco smoke and the principal modulator of the psychopharmacological effects associated with addiction. <sup>(8)</sup> Nicotine replacement therapy (NRT) aims to reduce motivation to consume tobacco and the physiological and psychomotor withdrawal symptoms through delivery of nicotine. <sup>(9)</sup> The evidence that NRT helps to stop smoking is now well accepted, and many clinical guidelines recommend NRT as a first line treatment for people seeking pharmacological help to stop smoking. <sup>(10)</sup> This review aims to summarize literature on various modes of nicotine replacement therapy methods currently used to treat nicotine dependence, and to give an overview about future possible approaches to treat tobacco use disorder.

## Materials and Methods

A thorough literature search was performed to understand and identify the updates in the field of NRT. Electronic database PubMed was searched from January 1990 up to May 2015 for the relevant literature using key phrase of "nicotine replacement therapy". Citation pearl growing technique employed and reference articles of the selected article were referred. We included systematic reviews, narrative reviews, clinical trials, comparative studies and reports/guidelines of international health agencies. Only articles reported in English were considered for review.

## Mechanism of action of nicotine

Nicotine acts by stimulation of neural nicotinic acetylcholine receptors (NACHRs) in the ventral tegmental area of the brain. This causes release of dopamine in the nucleus accumbens. Which lead to reduction in nicotine withdrawal symptoms in regular smokers who

abstain from smoking. <sup>(11)</sup> NRT may also provide a coping mechanism, making tobacco products less rewarding. It does not completely eliminate the symptoms of withdrawal because none of the available nicotine delivery systems reproduce the rapid and high levels of *arterial nicotine* achieved when cigarette smoke is inhaled. <sup>(12)</sup> All the available medicinal nicotine products rely on *systemic venous absorption* and do not therefore achieve such rapid systemic arterial delivery. <sup>(13)</sup> It takes a few seconds for high doses of nicotine from a cigarette to reach the brain; medicinal products achieve lower levels over a period of minutes (for nasal spray or oral products such as gum, inhalator, sublingual tablet, or lozenge) and hours (for transdermal patches). <sup>(13)</sup>

## Forms of Nicotine Replacement Therapy

The most widely studied and used pharmacotherapy for managing nicotine dependence and withdrawal is therapeutic use of nicotine containing medications. <sup>(14)</sup> NRT products take a number of forms: gum, transdermal patch, nasal spray, oral inhaler, and tablet. Transdermal Patch is a slow sustained release form of nicotine delivery. Other products like gum, nasal spray, oral inhaler, and tablet are acute dosing forms of nicotine. They provide general craving relief and breakthrough craving relief with immediate release of nicotine. <sup>(15,16)</sup> All of these products have different levels of efficacy and variable rates of nicotine absorption, and they are most effective when the consumer also receives parallel cessation-counseling, but nevertheless are effective even without accessory behavioral therapy. <sup>(13)</sup>

## Transdermal patch

Nicotine patches are applied to the skin and deliver nicotine through the skin at a relatively steady rate. <sup>(14)</sup> Patches are available in a range of dosages, which permits higher dependent smokers to use the strongest patches and lower-dependent smokers to use a lower. The range of dosages allows users to gradually decrease their nicotine intake over a period of several weeks or longer to enable a gradual adjustment of their bodies to lower nicotine levels and ultimately to a nicotine-free state. <sup>(13)</sup> Current evidence supports the safety of long-term use of nicotine patch treatment for tobacco abstinence. <sup>(17)</sup> The main advantage of

nicotine patches over acute NRT formulations is that compliance is simple; the patient simply places the patch on the body in the morning, rather than actively using a product throughout the day. <sup>(12)</sup> It delivers nicotine more slowly than acute NRT formulations, although nicotine plasma concentrations can get higher during the day with patch use than with acute NRT use. <sup>(18)</sup> They are available in different doses, and deliver between 5mg and 22mg of nicotine over a 24-hour period, resulting in plasma levels similar to the trough levels seen in heavy smokers. <sup>(11)</sup> The most frequently reported side effects are local skin reactions. <sup>(11)</sup> Moving the site of patch application daily as instructed can reduce the incidence of skin reactions to the patch. Sleep disturbances have also been commonly reported with 24-hour patches. <sup>(13)</sup>

### **Acute Dosing Nicotine Products**

Acute-dosing products have the benefit that both the amount and timing of doses can be titrated by the user. Thus, smokers with more nicotine tolerance or greater need can get a higher nicotine dose, and smokers who are experiencing acute adverse effects can scale back their intake. Control over the timing of self-dosing enables smokers to use NRT medications as “rescue medication” when they encounter particularly strong cravings or threats to abstinence. <sup>(18)</sup> These acute craving episodes are particularly problematic for some cigarette smokers and are associated with very high risk of relapse. <sup>(19)</sup> Acute dosing nicotine products include gum, lozenge, sublingual tablet, oral inhaler, and nasal spray.

### **Nicotine Gum**

The first NRT that was made available to consumers was transmucosally delivered nicotine polacrilex (nicotine gum). <sup>(20)</sup> It is not chewed like ordinary confectionary gum, but is intermittently chewed and held in the mouth over about 30 minutes, as needed, to release its nicotine. It is available in both 2 mg and 4 mg dosage forms. <sup>18</sup> Smokers that are more dependent have been shown to improve their chances of achieving abstinence with the 4-mg than the 2-mg gum. After a few weeks or months, the number of doses per day is reduced gradually until it is no longer required. <sup>(13)</sup> Acidic beverages have been shown to interfere with buccal absorption of nicotine; therefore, patients should avoid acidic

beverages (eg, soda, coffee, beer) for 15 minutes before and during chewing gum. <sup>(14)</sup>

### **Nicotine Lozenge**

The lozenge is available in 2mg and 4mg formulations. Instructions for use and dosing are similar to nicotine gum, but the lozenge is not chewed; it dissolves in the mouth over approximately 30 minutes with some variation across individuals. As with nicotine gum, nicotine from the lozenge is absorbed slowly through the buccal mucosa and delivered into systemic circulation. <sup>(13)</sup> The lozenge provides an alternative to the gum for persons who need intermittent and controllable nicotine dosing, but who do not find gum chewing acceptable. The amount of nicotine absorbed per lozenge appears to be somewhat higher than that delivered by gum. <sup>(21)</sup>

### **Nicotine Sublingual tablet**

This product is designed to be held under the tongue where the nicotine in the tablet is absorbed sublingually. Like the lozenge, the tablet has the advantage of not requiring chewing. The levels of nicotine obtained by use of the 2mg lozenge and 2mg sublingual tablet are similar. <sup>(22)</sup> It is recommended that smokers use the product for at least 12 weeks. After 12 weeks, the number of tablets used should be gradually tapered. <sup>(14)</sup>

### **Nicotine Oral inhaler**

It consists of a mouthpiece and a plastic cartridge containing nicotine. The vapour inhaler was designed to satisfy behavioral aspects of smoking, namely, the *hand-to-mouth ritual*, while delivering nicotine to reduce physiological withdrawal symptoms produced by tobacco withdrawal. It is important to note that although termed an “inhaler” the majority of nicotine is delivered into the oral cavity (36%) and in the oesophagus and stomach (36%). <sup>(22, 23)</sup> Very little nicotine is delivered to the lung (4%). Because absorption is primarily through the oral mucosa, the rate of absorption is similar to that of nicotine gum. Each inhaler cartridge contains 10mg nicotine, of which up to 4 mg can be delivered and 2 mg can be absorbed following frequent “puffing”. <sup>(24)</sup>

### **Nicotine Nasal spray**

It was designed to deliver doses of nicotine more rapidly. The device available to

consumers is a multi-dose bottle with a pump mechanism fitted to a nozzle that delivers 0.5 mg of nicotine per 50- $\mu$ L squirt. Each dose consists of two squirts, one to each nostril. <sup>(11, 24)</sup> Nicotine nasal spray is absorbed into the blood rapidly relative to all other NRT forms.

<sup>(25)</sup> Patients should be started with one or two doses per hour, which may be increased up to the maximum of 40 doses per day. One dose of nasal spray per hour (1mg nicotine) for 10 hours produces average plasma concentrations of 8ng/ml. <sup>(14)</sup>

**Table 1: Nicotine replacement therapy formulations** <sup>(11,14,24)</sup>

Nicotine products	Available doses	Cautions/ Warnings	Uses	Adverse events	Availability
Transdermal patches	5 mg, 10 mg, 15 mg doses worn over 16 hours 7 mg, 14 mg, 21 mg doses worn over 24 hours	For smokers with insomnia and other sleep-related adverse events, the patches should be removed before bedtime.	One daily on clean, unbroken skin; remove before bed (16 h patch) or next morning (24 h); new patch, fresh site	Local skin reaction  Insomnia	US FDA (OTC),  MHRA (OTC)
Chewing gum	2 mg and 4 mg doses	Temporomandibular joint disease Caution with dentures Do not eat or drink 15 min before or during use	Chew gum until taste is strong, then rest gum between gum and cheek; chew again when taste has faded. Try not to swallow excessively.	Mouth soreness, Hiccups, Dyspepsia and Jaw ache	US FDA (OTC)  MHRA (OTC)
Sublingual tablet	2 mg dose	Nicotine dependence, insomnia	Rest under tongue until dissolved	Mouth soreness	MHRA (Rx)
Lozenge	1mg, 2 mg and 4 mg doses	Do not eat or drink 15 minutes before or during use One lozenge at a time Limit 20 in 24 hours	Allow to dissolve in mouth (about 20–30 minutes), moving from side-to-side from time-to-time. Try not to swallow excessively. Do not chew or swallow whole	Nausea/ Heartburn	US FDA (OTC)  MHRA (OTC)
Nicotine inhalation cartridge plus mouthpiece	Cartridge containing 10mg	May irritate mouth/throat at first	Spray into the mouth, avoiding the lips. Do not inhale while spraying. Use when cigarettes would usually be smoked or if cravings emerge. Do not swallow for a few seconds after spraying	Local irritation of mouth and throat	US FDA (Rx)  MHRA (Rx)

Nicotine metered nasal spray	0.5mg dose/spray	Not for patients with asthma May cause dependence	Take shallow puffs approximately every 2 seconds or alternatively take four puffs every minute. Continue for up to 30 minutes.	Nasal irritation	US FDA (Rx) MHRA (Rx)
Electronic cigarette	-	May cause dependence	E-Cigarette vapor is drawn very slowly in to mouth, then held there for a second or two. Then, it can be inhaled if desired. The vapor is then expelled through the mouth or nose.	Mouth and airway irritation, chest pain, and palpitation <sup>(26, 27)</sup>	Untill now, it is not approved by any agency
High dose nicotine patches <sup>(28)</sup>	≥42 mg daily	Irritation at the patch application site. Sleep disturbances	One daily on clean, unbroken skin; remove before bed	Headache, cardiovascular events, asthenia, dyspepsia, myalgia, and vomiting	Untill now, it is not approved by any agency
Combined Patch + acute forms (nicotine gum, spray, lozenge, & inhaler) <sup>(29, 30)</sup>	transdermal nicotine doses of 7, 14, and 21 mg + dosage of any one acute form	Nicotine dependence, insomnia	Both patch and acute nicotine forms should be used parallel.	Mouth and airway irritation, Nausea and vomiting	US FDA

\*US FDA: U S Food and Drug Administration;MHRA: Medicines and Healthcare products Regulatory  
Rx: Prescription; OTC: Over the counter

## Improving Delivery

### Electronic nicotine delivery systems (ENDS) or Electronic cigarettes

ENDS are devices whose function is to vaporize and deliver chemical mixture typically composed of nicotine to the lungs of the user. Each device contains an electronic vaporization system, rechargeable batteries, electronic controls and cartridges of the liquid that is vaporized.<sup>(31)</sup> The liquid usually contains glycerol, propylene glycol, water, nicotine and a variety of flavors that the user can choose. By using this device, nicotine is delivered to the upper and lower respiratory tract without any combustion involved.<sup>(32)</sup> Nicotine content varies widely among products, typically ranging

between 0 and 34 mg/mL, but recent studies have found discrepancies between labelled and measured nicotine content.<sup>(33)</sup> E-cigarettes are becoming a preferred alternative for nicotine delivery among many smokers because of their realistic look, feel, and taste compared to traditional cigarettes.<sup>(34)</sup> The FDA has reported that e-cigarette cartridges and solutions contain potentially harmful components and they recommend that the sale of e-cigarettes should be prohibited or regulated as dangerous nicotine delivery systems.<sup>(34)</sup> Moreover, for young people who have never smoked, these devices could potentially serve as a gateway drug.<sup>(35)</sup> The current evidence suggests that ENDS are an effective smoking cessation tool, but more

research is needed to confirm its long-term effectiveness and safety. <sup>(36, 37)</sup>

### High-dose nicotine patches

The conventional patches of 22-mg patch can only replace approximately half of the baseline serum nicotine and cotinine levels in smokers. <sup>(38)</sup> Therefore higher transdermal nicotine doses of  $\geq 42$  mg were evaluated. In terms of efficacy, a numerically higher abstinence rate was achieved with high-dose transdermal NRT. <sup>(9,40,41)</sup> However, a recent systematic review concluded that the safety and efficacy of high-dose transdermal NRT for tobacco cessation have not been established in the medical literature. <sup>(28)</sup>

### Rapid release gum

A rapid-release gum has been formulated to provide biphasic nicotine delivery, starting with accelerated delivery to promote rapid craving relief and then leveling off to avoid overdosing. <sup>(42)</sup> A study compared this rapid-release gum to the current gum formulation for rapid craving relief following a provocative stimulus. The rapid-release gum achieved faster and more complete craving relief, differentiating itself from current nicotine gum. <sup>(43)</sup>

### Combined Patch Plus Acute Forms

A strategy for further improving the efficacy of NRT is to combine one medication that allows for passive nicotine delivery (e.g. transdermal patch) with another medication that permits ad libitum nicotine delivery (e.g. gum, nasal spray, inhaler). The rationale for combining NRT medications is that smokers may need both a slow delivery system to achieve a constant concentration of nicotine to relieve cravings and tobacco-withdrawal symptoms, as well as a faster acting preparation that can be administered on demand for immediate relief of break through cravings and withdrawal symptoms. <sup>(32)</sup> The patch provides nicotine in a steady-state and passive form while gum can be manipulated to accommodate the users' needs. Clinical trials suggest incremental efficacy of patch plus gum compared to either product alone. <sup>(44, 45, 46)</sup> Combining the nicotine patch with an oral form of NRT has been shown to increase quit rates by 34–54% compared to using the patch alone. <sup>(47)</sup> Adverse effects and adherence are similar

to monotherapy, but there is a greater financial cost to the patient. <sup>(47)</sup>

## The Future

### Nicotine preloading

The use of nicotine replacement therapy before quitting smoking is called nicotine preloading. <sup>(36)</sup> This approach involves using NRT for a several weeks prior to quitting; it is also known as *pre-cessation* or *pre-quitting NRT*. The most plausible mechanisms include habituation with use of NRT in the lead-up to quitting, attenuation of desire to smoke due to nicotine receptor saturation <sup>(48)</sup> and it reduces satisfaction from smoking by which it undermines the learned association between smoking and reward. <sup>(49)</sup> A review suggests that initiating patch use for a short period before making a quit attempt is moderately more effective than patch use initiated on the quit date itself. There is no evidence that suggests use of other forms of NRT pre-cessation is more effective than starting use on the quit day. <sup>(50)</sup> A meta-analysis on pre-cessation patch treatment found that it will produce a robust increase in quit rates compared to current regimens starting patch at quit day. However, large pragmatic randomized trial concluded that using NRT two weeks before the target quit day was safe and well tolerated but offered no benefit over usual care. <sup>(51)</sup>

### True pulmonary inhaler

A true pulmonary inhaler, unlike the currently available nicotine inhaler, would deliver nicotine to the lung in a manner more comparable to cigarette smoking. <sup>(14)</sup> This would be predicted to deliver a dose of nicotine sufficient to reduce background cravings and withdrawal symptoms, and would allow for rapid relief of acute cravings and morning craving. Because the delivery of nicotine directly to the lung would effectively mimic the effects of cigarette smoking on a physiologic level, the smoker could eliminate the need for tobacco, and subsequently taper the nicotine level over time to alleviate dependence upon nicotine altogether. Although there are substantial technological challenges to producing an effective and acceptable lung inhaler, the greatest barrier to development may be the potential for abuse and the

regulatory implications.<sup>(14)</sup> But the challenge is that nicotine molecules need to be appropriately condensed onto particles of approximately 1-micron median diameter to enable inhalation into the pulmonary alveoli, and the nicotine particles must be designed so as to prevent the production of unacceptably harsh sensory effects.<sup>(14)</sup>

### Nicotine Vaccines

Nicotine vaccines represent a new approach to the treatment of nicotine dependence and are currently under investigation. Because nicotine is a small molecule and an incomplete antigen, it is linked to a carrier protein order to stimulate the necessary immune response. Nicotine-based vaccines can prime the immune system to recognize nicotine as foreign and to mount an immune response against the drug. In doing so, vaccines may reduce the amounts of nicotine penetrating into the brain.<sup>(52)</sup> A

number of organizations have developed vaccines for smoking cessation, with NicVAX developed by Nabi Biopharmaceuticals being perhaps the best known.<sup>(53)</sup> A potential drawback of vaccines to treat tobacco dependence is the fact that smokers will often compensate for decreases in the actions of nicotine, as would be expected when a vaccine decreases concentrations of nicotine penetrating into brain tissues, by increasing their tobacco consumption to overcome this effect.<sup>(53)</sup> Other potential issues related to the successful use of vaccines include difficulties achieving sufficiently high antibody titers, the fact that vaccines are generally short lived, and significant inter-individual variation in response to the vaccine typically observed.<sup>(54)</sup> A recent systematic review reported that there is no current evidence that nicotine vaccine enhance long term smoking cessation and emphasized the need for further trials.<sup>(55)</sup>

### Novel Biological or Vaccine Agents in Clinical Testing for Smoking Cessation<sup>(53,55)</sup>

Vaccine	Sponsor	Clinical trial Phase	Results
<b>NicVax</b> ( Bacterial exoprotein Conjugate vaccine)	Nabi Biopharmaceuticals	III	The preliminary results of the trials showed that the primary endpoint of 16 weeks abstinence measured at 12 months was not met; there was no statistically difference between the NicVAXW and placebo group <sup>(56)</sup>
<b>NIC002</b> (Nicotine Qbeta or CYT002-NicQb)	Novartis	II	Interim analysis showed that the primary endpoint (continuous abstinence from smoking from weeks 8–12 after start of treatment) was not achieved, possibly because NIC002 failed to induce sufficiently high antibody titers. <sup>(57,58)</sup>
<b>TA-NIC</b> (a recombinant cholera toxin conjugate vaccine)	Celtic Pharma	II	Not declared
<b>SEL-068</b> (Synthetically engineered nanoparticle)	Selecta Biosciences	I	Not declared

### Nicotine safety and toxicity

Nicotine stimulates at low doses and depresses neuronal activity at very high doses.<sup>(59, 60)</sup> It can be toxic at high dosages (acute lethal dose of nicotine in 40–60 mg)<sup>(61)</sup> and at very high dosages of 500mg it can cause death by generalized blockade of respiration.<sup>(59)</sup> But, there was no evidence of an increase in life threatening problems with NRT at prescribed dosages.<sup>(62)</sup> Nausea, salivation, abdominal pain, sweating, headache, diarrhea, dizziness, delayed wound healing and weakness are among the symptoms of nicotine overdose.<sup>(61)</sup> During pregnancy the risk of adverse effects from nicotine replacement therapy appears substantially lower than by smoking.<sup>(63)</sup> A large clinical trial [SNAP trial] observed that, there was no evidence for NRT having either a beneficial or a harmful effect on birth outcomes. However, 2-year-olds born to women who used NRT were more likely to have survived without any developmental impairment.<sup>(64)</sup> NRT is safe in stable cardiac disease, but caution is needed in unstable, acute cardiovascular disease, pregnancy, or breast feeding, or in those aged under 18 years.<sup>(12)</sup>

### Patient Compliance with NRT

Most of NRT users discontinue treatment prematurely. Misinformation about NRT is a common cause of poor compliance.<sup>(65)</sup> Several causes of poor compliance with NRT identified; Concerns about safety,<sup>(66, 67)</sup> addictiveness of NRT,<sup>(67)</sup> Lack of confidence in efficacy,<sup>(66, 67)</sup> Side effects, Cost, Relapse<sup>(68, 69)</sup> and 'Should be able to quit on my own'. It was identified that one of the most common reasons for poor compliance with NRT is because it is effective. When craving and withdrawal are well controlled via treatment, patients may mistakenly assume that the treatment is no longer necessary.<sup>(70)</sup> These beliefs undermine the effectiveness of NRT. This can be tackled majorly by providing scientific information by health professionals to the patients undergoing NRT.<sup>(67)</sup>

### Conclusions

Nicotine addiction is the major factor impeding smoking cessation and long-term abstinence. Today, several nicotine medications 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 choice of NRT product should normally be guided by the patient's preference. Current evidence suggests that, all of the commercially available forms of NRT (gum, transdermal patch, nasal spray, inhaler and sublingual tablets/lozenges) increase their chances of successfully stopping smoking. NRTs increase the rate of quitting by 50 to 70%.<sup>(50)</sup> Another meta-analyses also concluded that NRT increased the likelihood of reducing the habit size among smokers who are not willing to stop smoking completely.<sup>(71)</sup> To improve the efficacy of NRT recently research is more focusing on rapid delivery techniques and immunological techniques. These new modalities require more quality research to bring it from bench to bedside. Beholding the potential capacity of NRT, it's essential for health 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 tobacco cessation.

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