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Advancement with Nicotine Replacement Treatment for Patients with Tobacco Addiction- A Narrative Review

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Abstract

Tobacco use remains a significant public health issue globally as there is a rapid increase in tobacco products among teenagers. Nicotine is the main active ingredient in tobacco products that reinforce individual to exhibit tobacco addiction behaviour. Despite the widely recognized health risks of tobacco use and the proven benefits of quitting, most smokers find it difficult to achieve and sustain long-term abstinence. FDA-approved medications are NRT in the form of gum, patches, lozenge, nasal spray and inhaler, varenicline, and bupropion. The various types of NRT products have different efficacy levels and variable nicotine absorption rates. They are available under these agencies: US, FDA (OTC), MHRA (OTC), and MHRA (Rx). Most of NRT users discontinue treatment prematurely. When craving and withdrawal are well controlled via treatment, patients may mistakenly assume that the treatment is no longer necessary and this beliefs undermine the effectiveness of NRT. This can be tackled majorly by providing information, counselling by health professionals to the patients undergoing NRT. It offer several benefits, but their effectiveness in achieving long-term smoking cessation remains limited. While NRT can be a valuable component of adolescent smoking cessation strategies, it should be supplemented with strong behavioural support and personalized interventions. Recent research is increasingly exploring rapid delivery methods and immunological approaches to enhance NRT efficacy.

Keywords: Nicotine replacement therapy, tobacco addiction, smoking cessation

Introduction

Tobacco use remains a significant public health issue globally as there is a rapid increase in tobacco products among teenagers. Nicotine is the main active ingredient in tobacco products that reinforce individual to exhibit tobacco addiction behaviour[1]. It is the main alkaloid of

tobacco smoke and the principal modulator of the psycho pharmacological effects associated with addiction. India is the second leading producer of tobacco and third-leading consumer of tobacco across the globe[2]. Smoking and smokeless are two common types of tobacco practiced in India. Cigarette, beedi (raw tobacco wrapped in dried leaves of the particular plant), chewing tobacco (tobacco and spices wrapped in betel leaf, a mixture of lime and pieces of areca nut), gutkha or pan masala (aerated tobacco mixed with lime, nut, and mishri (a form of the gel used for rubbing on gums)[3].

Both chewing and smoking tobacco increase the risk of various cancers and other diseases. Many evidence concluded that there is causal relationship between smoking and cancers of the lung, larynx, oral cavity, pharynx, oesophagus, pancreas, bladder, kidney, cervix, and stomach, and acute myeloid leukemia. There is also a link between tobacco and oral problems like gingivitis (72.8%), gingival bleeding (51.2%), and oral malodor or halitosis (39.6%) are all increasing among teenagers who smoke frequently[4]. There is also a higher risk of developing hyperkeratosis, smoking-related melanosis, hairy tongue, and dental caries among tobacco user. Smoking increases the adherence of platelets and macrophages and creates a procoagulant and inflammatory environment that leads to increased risk of cardiovascular diseases[5]. It also increases severity of asthma and chronic obstructive pulmonary disease (COPD).

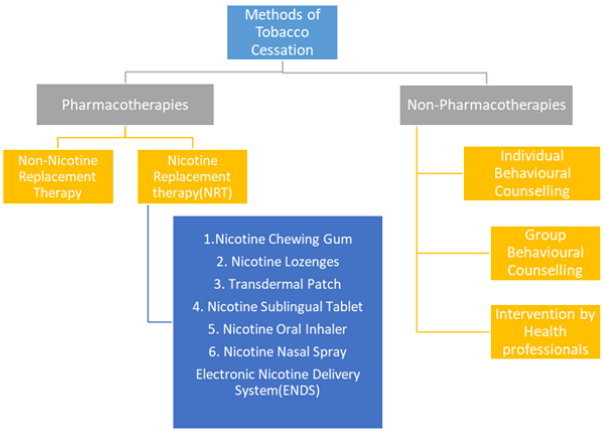
Despite the widely recognized health risks of tobacco use and the proven benefits of quitting, most smokers find it difficult to achieve and sustain long-term abstinence. Indeed, approximately 80% of consumers will relapse within the first month of a quit attempt. Hence, the US Food and Drug Administration (FDA) has approved Nicotine replacement therapy as an aid for tobacco cessation.

Mechanism of Nicotine Addiction

Nicotine is lipid-soluble, has a plasma protein binding rate of ≤5%, and easily crosses the blood–brain barrier. Once absorbed through the lungs, it reaches the brain within 2–20 seconds, where it binds to nicotinic acetylcholine receptors found in autonomic ganglia and neuromuscular junctions. The primary receptor associated with nicotine addiction is the α4β2 nicotinic acetylcholine receptor, located in the ventral tegmental area of the midbrain[6]. When nicotine binds to this receptor, ion channels open, triggering the release of dopamine from nerve fibers projecting to the nucleus accumbens, a key component of the mesolimbic system. This dopamine release induces a temporary sensation of pleasure and reward. One hour after smoking, nicotine levels decline, causing the receptor to close and triggering a craving for nicotine. Repeated smoking reinforces physical nicotine addiction. Beyond dopamine, nicotine also influences the release of other neurotransmitters, including norepinephrine, serotonin, and γ-aminobutyric acid (GABA)[7]. According to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), tobacco use disorder is characterized by three primary features: (a) a gradual increase the amount of tobacco that has been consumed over time; (b) the development of tolerance to the pharmacological actions of nicotine; and (c) the emergence of withdrawal symptoms upon cessation of the use of nicotine-containing tobacco products[8].

With repeated exposure to nicotine, the brain develops tolerance to many of its effects. Over time, it adjusts to the continuous presence of nicotine to maintain normal function and behavior. However, when nicotine use ceases, this adaptation is disrupted, leading to

withdrawal. Nicotine withdrawal activates the corticotropin-releasing factor (CRF) system, which plays a role in the hypothalamic-pituitary-adrenal (HPA) stress response[9]. Symptoms of withdrawal, such as anxiety and stress, are believed to result, at least in part, from reduced activity in the dopaminergic system and increased CRF system activity.



Pharmacotherapies to aid smoking cessation

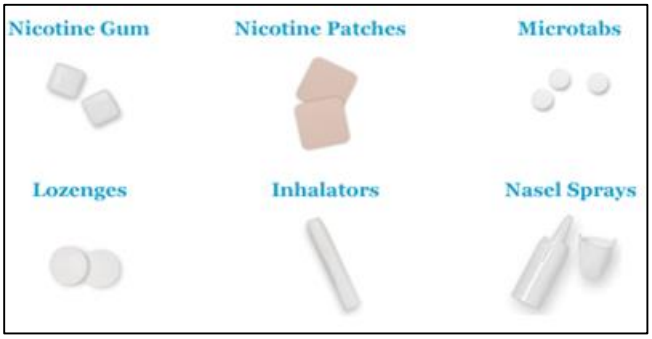
The FDA-approved smoking cessation medications, including dosing guidelines, advantages, disadvantages, adverse effects, and precautions. FDA-approved medications are NRT in the form of gum, patches, lozenge, nasal spray and inhaler, varenicline, and bupropion. Nicotine gums, lozenges, and patches are available over the counter in the United States, while the nicotine nasal spray, nicotine inhaler, varenicline, and bupropion are by prescription only[9]. 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. These medications help smokers to cope with daily triggers and stressors without using nicotine. There are three main mechanisms by which medications can facilitate smoking cessation: (i) decrease in nicotine withdrawal symptoms, (ii) reduction of the rewarding effects of nicotine from smoking by blocking or desensitizing nicotine receptors, and (iii) providing an alternative for nicotine with the desired pharmacologic effect previously provided by nicotine from cigarettes.

Nicotine Replacement Therapy (NRT)

Nicotine replacement therapy is a medically approved way to treat people with tobacco use disorder by taking nicotine through means other than tobacco. It is particularly effective in patients who are heavily dependent upon nicotine and have severe withdrawal symptoms (i.e. irritability/frustration/ anger, anxiety, difficulty in concentrating, restlessness/impatience, depressed mood/depression, insomnia, increased appetite/weight gain)[10]. By temporarily supplying nicotine as a substitute for that obtained from cigarettes, the patient experiences relief from the uncomfortable withdrawal symptoms associated with quitting smoking, making the cessation process more manageable. This also elevates nicotine levels in the bloodstream, leading to a decreased urge to smoke and, consequently, a reduction in cigarette consumption and its associated toxicity.

Types

The various types of NRT products have different efficacy levels and variable nicotine absorption rates. They are available under these agencies: US, FDA (OTC), MHRA (OTC), and MHRA (Rx)[11].



Nicotine gum

The first NRT that was made available to consumers was transmucosally delivered nicotine gum[12]. The gum used in rapid-release products with gum base that enables

both biphasic nicotine delivery and speedy initial nicotine release. It also elevates the pH to hasten absorption through the oral mucosa. Rapid-release nicotine gum offers an advantage compared to regular nicotine gum because it is quick and completely relieves nicotine cravings. It is not chewed like ordinary 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[1]. It is prescribed for 6–12 weeks, with maximum for 6 months. After 2–3 months either the chewing time is reduced, or the gum is divided into small pieces, thereby stopping it completely. Nicotine gum has some disadvantage that some people dislike its taste and have feeling of fullness in their mouth. They may also complain of mouth soreness, hiccups, dyspepsia and jaw aches[11,13].

Nicotine lozenges

Nicotine lozenges can be replace nicotine gum by patients who need sporadic and periodic nicotine dosages but are not able to chew gum for long period of time. They are available in doses of 1, 2, and 4 mg formulation. It is placed sublingually for 30 min, which releases nicotine into systemic circulation[11]. The advantage of nicotine lozenge is that its taste is acceptable to the patient and they are easy to use .However, it is advised that not to drink or eat 15 min before or during usage and also not to swallow and chew excessively during its consumption. Also not use more than 1 lozenge at a time and do not use one right after another. Side effects include Nausea, hiccups, heartburn, trouble sleeping, headache and cough.

Transdermal patch

Nicotine patch is a transdermal patch which is easy to use and progressively absorbed through the skin once nicotine patches are applied. The key advantage of nicotine patches over other NRT formulations is the simplicity of compliance; rather than actively using a medicine throughout the day, the patient only needs to apply the patch to their skin for particular period of time mostly in morning[14]. Patients can place the patches over the clean and unbroken skin once in the morning, rather than using throughout the day. The 16 hr patch should be removed before bedtime and 24 hr patch to be removed the next morning[15]. The side effects reported are insomnia and even local skin irritations. High dose nicotine patches are available with dose ≥42 mg. According to the medical literature, high-dose transdermal NRT has not been demonstrated to be safe or helpful for smoking cessation[4].

Nicotine sublingual 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[16].The recommended for at least 8–12 weeks and after that the numbers of tablets are reduced gradually. The major side effects are insomnia and mouth soreness. The sublingual tablets are seeming to be beneficial for COPD patients.

Nicotine Oral Inhaler

A nicotine inhaler resembles a cigarette or cigar and is made of a mouthpiece and a plastic cartridge filled with nicotine. 10mg of nicotine are contained in each cartridge[17]. It has also tiny breath operated valve that allows the user to control how much air they inhale. So, the amount of puffs in one charge (or dose) of the inhaler device that is regulated by the user's depth of inhalation determines the speed at which nicotine is administered from that charge. As its absorption is primarily through the oral mucosa, the rate of absorption is similar to that of nicotine gum. It can be sprayed in the mouth (not inhaled nor swallowed for few seconds) but care should

be taken that it does not touch the lips. Beneficial for patients who have craving for smoking

Nicotine Nasal Spray

It is 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 and it delivers 0.5 mg of nicotine per 50-uL squirt. Each dose consists of two squirts used in each nostril. It is absorbed into blood rapidly than other NRT forms. It should not be given to patients with asthma, allergies, nasal polyp or sinus. And other side effects are nose irritation, coughing, sneezing and watery eyes[11].

Electronic Nicotine Delivery System (ENDS) or Electronic Cigarettes

An electronic cigarette, also known as an e-cig, shisha pen, or personal vaporizer, is a device designed to simulate the experience of smoking by producing vapor. It consists of an electronic vaporization system, rechargeable batteries, electronic controls, and liquid-filled cartridges. The liquid, primarily composed of propylene glycol, glycerol, and water, often contains nicotine[11,18]. Recent systematic studies and meta-analyses found a 28% lower chance of smoking cessation among e-cigarette users. Some advantages are that the experience is comparable to that of a regular cigarette for the customer, it offers a variety of tasty flavors, appealing designs and ENDS are thought to be less dangerous than regular cigarettes. Also they have lower concentrations of tobacco-specific nitrosamine and volatile chemical compounds than in conventional cigarettes. Cons of E-cigarettes are that it may be first nicotine-containing product used by young people so, it may also serve as a starting point for using other nicotine products, such as regular cigarettes, several e-liquids contained aldehydes and ketones, metals, additional tobacco-specific nitrosamines, and volatile organic chemicals in a wide range of concentrations. The prevalence of serious lung diseases such as chronic obstructive pulmonary disease (COPD), asthma, and lung cancer are increasing among E-cigarettes user[4].

Combined Therapy

People with intolerable withdrawal symptoms can be treated with combined therapy. To recompense the level of nicotine during abrupt craving, NRT patches can be used along with nicotine gum or a nasal spray[19]. A transdermal nicotine dose of 7, 14, and 21 mg can be combined with dosage of any one acute form is the choice of combination most commonly used. Combination therapy is contraindicated in nicotine-dependent and insomniac patients. Mouth and airway irritation, nausea and vomiting are the most commonly seen adverse effects. The reasoning behind combining NRT medications is that smokers often require both a slow-release system to maintain a steady nicotine level for managing cravings and withdrawal symptoms, along with a fast-acting option that can be used as needed for immediate relief from sudden cravings and withdrawal episodes[1].

Nicotine vaccine

Nicotine vaccines are the latest innovation in NRT. A nicotine-based vaccine recognizes nicotine as a foreign body and initiates an immune response against it. They mobilize drug-specific antibodies, which results in the binding of nicotine molecules present in the blood. This prevents its distribution to the brain and reduces behavioural effects. Many organizations have developed vaccines for smoking cessation, with NicVAX developed by Nabi Biopharmaceuticals which is best known[20]. One of the possible limitations of vaccines for treating tobacco dependence is that smokers may compensate for the reduced effects of nicotine that result from lower nicotine levels reaching the brain due to the

vaccine—by increasing their tobacco use to counteract this reduction.

NicVAX

Nicotine vaccination, which relies on adaptive immunity against the nicotine molecule, offers a potential new approach for treating tobacco dependence and preventing relapse. It works by stimulating the immune system to produce antibodies that bind to nicotine molecules, enlarging them and preventing their passage across the blood-brain barrier. As a result, nicotine cannot reach its receptors in the brain to trigger the pleasurable sensations that contribute to addiction.[21]

Nicotine Preloading

The use of nicotine replacement therapy before quitting smoking is called nicotine preloading. This approach of using NRT for several weeks before quitting is also known as pre-cessation or pre-quitting NRT. It results in a reduction of a person's drive to smoke, reducing the level of addiction and decreasing cravings after quitting smoking. The most probable mechanisms include becoming accustomed to NRT use before quitting, experiencing a decreased urge to smoke due to nicotine receptor saturation, and finding smoking less satisfying, which weakens the association between smoking and reward.

Some points to be considered while choosing types of NRT

- Nicotine gums, lozenges, and inhalers are put into the mouth and let consumer control the dosage to deal with cravings.
- Nicotine gums and lozenges are generally sugar-free. But if a consumer is diabetic and have any doubts, check the package or contact the manufacturer.
- Nicotine nasal spray works very quickly.
- Nicotine inhalers allow to mimic the use of cigarettes by puffing and holding the inhaler. They also work very quickly.
- Nicotine patches are convenient and only have to be put on once a day. They provide a steady level of nicotine for 24 hours.
- Inhalers and nasal sprays require a doctor's prescription.
- Some people may not be able to use patches, inhalers, or nasal sprays because of allergies or other conditions.
- Nicotine gum may stick to dentures or dental work, making it hard to chew before placing it between the cheek and gums.

Advantages of NRT: They are easy to use and help curb tobacco cravings. Unlike cigarettes and tobacco smoke, they do not contain harmful chemicals. Additionally, they do not stain teeth and are a cost-effective option.

Side Effects of NRT: Common side effects include nausea, vomiting, indigestion, gastrointestinal disturbances, insomnia, sleep apnea, headaches, oral ulcers, skin irritation, heart palpitations or chest pain, coughing, throat soreness, dry mouth, and an increased risk of dental cavities, taste impairment, difficulty in speech in denture wearers, hyperkeratosis and localized mucosal irritation. Serious adverse effects were infrequent, with no reported cases of nicotine poisoning or cardiovascular events.

Contraindications of NRT: There is a heightened risk of pregnancy complications and negative neonatal outcomes, including placental abruption, stillbirth, preterm birth, low birth weight, and sudden infant death syndrome. Nicotine replacement therapies (NRTs) are not recommended for children under 12, as they may experience severe toxicity, which can be life-threatening.

Safety profile of NRT: Nicotine stimulates at low doses and depresses neuronal activity at very high doses. It can be toxic at high dosages (acute lethal dose of nicotine in 40–60 mg) and very high dosages of 500mg, it can cause death by generalized blockade of respiration[22]. NRT is safe for stable cardiac disease but should be used with caution in unstable, acute cardiovascular disease, pregnancy, or breastfeeding, or those aged under 18 years. Most NRT users discontinue treatment prematurely. When craving and withdrawal are well controlled via treatment, patients may mistakenly assume that the treatment is no longer necessary and this beliefs undermine the effectiveness of NRT. This can be tackled majorly by providing information, counselling by health professionals to the patients undergoing NRT. Several causes of poor compliance with NRT are identified like concerns about safety, addictiveness of NRT, lack of confidence in efficacy and relapse.

Conclusion

Nicotine addiction is the primary obstacle to quitting smoking and maintaining long-term abstinence. Today, several nicotine medications are available in different forms, doses, flavors and their use has been recommended for all tobacco consumers who do not have medical contraindications. Current evidence suggests that, all of the commercially available types of NRT (gum, transdermal patch, nasal spray, inhaler and sublingual tablets/lozenges) increase their chances for successfully stopping smoking. NRTs increase the rate of quitting by 50 to 70%[23]. NRTs offer several benefits, but their effectiveness in achieving long-term smoking cessation remains limited. While NRT can be a valuable component of adolescent smoking cessation strategies, it should be supplemented with strong behavioral support and personalized interventions. Recent research is increasingly exploring rapid delivery methods and immunological approaches to enhance NRT efficacy. Additionally, healthcare professionals play a crucial role in educating the public about quitting protocols and the accessibility of these products, contributing to a tobacco-free society.

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