

## Nicotine replacement therapy: A smoking cessation aid... an overview

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### Abstract

Cigarette smoking is one of the most important causes of illness and premature death. The tobacco problem in India is very complex, due to large use of an array of smoking forms well as smokeless tobacco products. Several recent publications have highlighted the requirement for the dental profession to get involved with tobacco intervention.

Although approximately all of the toxicity of smoking is due to other harmful components present in cigarette smoke, the pharmacological effects of nicotine leads to tobacco addiction. Hence, all the attempts to quit smoking are aimed to remove tobacco addiction by replacing tobacco nicotine with clean nicotine. The most important cessation aid used, out of all the cessation aids, is nicotine replacement therapy or NRT.

Nicotine replacement therapy (NRT) replaces much of the nicotine from tobacco, which is mixed with harmful chemicals, with clean nicotine, thus reducing motivation to consume tobacco and also lessening nicotine withdrawal symptoms, thus easing the transition from cigarette smoking to complete abstinence. NRTs show good results and have minimal adverse effects.

The review aims to summarize literature on various modes of nicotine replacement therapy methods currently used and to discuss future possible approaches. Also, the safety and need of NRTs in various special conditions have been discussed.

**Keywords:** Nicotine replacement therapy, Important cessation, Cigarette smoking.

### Introduction

Smoking is one of the greatest causes of illness and premature death in developed and developing countries, but giving up smoking can prevent most of the harm. Jha *et al.* have estimated that around 1 million deaths a year in India will be attributable to smoking by the early 2010s.<sup>1</sup>

The tobacco problem in India is very complex, due to large use of an array of smoking forms well as smokeless tobacco products. Many of these products are manufactured as cottage and small-scale industries using varying mixtures and widely differing processes of manufacturing.<sup>2</sup>

The damaging and harmful effects of tobacco usage on oral health are now well recognized. These include, in particular, a higher prevalence and severity of periodontal diseases among smokers<sup>3,4</sup> and the association of tobacco use of any kind with oral malignancies.<sup>5,6</sup> Tobacco use has also been directly implicated in numerous oral morbidities, including oral cancer, stomatitis nicotina, oral leukoplakia, periodontitis, gingival recession and soft-tissue changes<sup>7</sup> as well as lead to nicotine addiction and dependence.<sup>8</sup>

Several recent publications have reviewed the scientific evidence relating to the oral disease burden attributable to tobacco use<sup>9</sup> and have highlighted the role and the need for the dental profession to get involved with tobacco intervention.<sup>10</sup> Studies have shown that almost 80 percent of daily smokeless tobacco users have an identifiable soft tissue lesion.<sup>11</sup>

Passive smoking or Second-hand tobacco smoke is much more toxic than active smoking. Almost one-third adults are regularly exposed to Passive smoking in their housed as well as work place. Out of 4000 chemicals identified in tobacco smoke, approximately 250 are recognised as harmful. Also, these toxins cling to clothes;

furniture etc and other also can recycle back into the air through the filters. They are known as “third-hand smoke.”<sup>12</sup> The evidence concludes that both second and third hand smoking increases the risk of cardiovascular diseases, cancers, and respiratory diseases in adults as well as sudden infant death syndrome in children.<sup>2</sup>

Nicotine is the main active ingredient in tobacco products that causes tobacco addiction<sup>12-14</sup> but it is tobacco's other components which cause widespread mortality and morbidity.<sup>15,16,17</sup> Although approximately all of the toxicity of smoking is due to other harmful components present in cigarette smoke, the pharmacological effects of nicotine leads to tobacco addiction. Hence, all the attempts to quit smoking are aimed to remove tobacco addiction by replacing tobacco nicotine with clean nicotine.

The most commonly used cessation aid used, out of all the cessation aids, is nicotine replacement therapy or NRT.<sup>18</sup> It is sometimes also called therapeutic nicotine, medicinal nicotine, or nicotine reduction therapy. NRT reduces motivation of tobacco consumption and the physiological and psychomotor nicotine withdrawal symptoms via timely delivery of clean nicotine.<sup>19</sup>

The rationale for nicotine-assisted reduction to quit is that using NRT boosts nicotine levels, making it easier for the smoker to smoke fewer cigarettes, and making compensation less likely, which in turn should mean that the smoker will inhale fewer toxins. By reducing their reliance on cigarettes for their nicotine intake, some smokers can then stop smoking completely.

The nicotine in cigarettes enters the bloodstream via the lungs within 10 seconds. As nicotine levels quickly rise, the brain is stimulated. The smoker may experience pleasure, alertness and relaxation. Nicotine released from NRT replaces some of the nicotine that brain is used to; at a

slower, less intense pace than cigarettes, allowing the body to adjust while quitting.

Recent studies indicate that nicotine replacement therapy is an effective in achieving long term smoking abstinence for smokers who have no intention or are unable to quit smoking. They found that twice the number of smokers sustained six months' abstinence with of nicotine replacement therapy as compared to placebo.<sup>20</sup>

### Forms of NRT

Nicotine containing products are the most widely studied and used pharmacotherapy for managing nicotine dependence and withdrawal.<sup>21</sup> A nicotine delivery product that delivers nicotine to the brain as rapidly as a cigarette – but without toxic tobacco smoke – has long been the “holy grail” of NRT.<sup>22</sup> Faster acting NRT preparations have greater efficacy compared with slower-acting ones because they provide quicker dopamine release in the reinforcement pathway of the brain.<sup>23</sup>

### Common NRT Products

The NRT products that are commonly available over the counter include Patches, gum, lozenge, mini-lozenge, oral inhaler, nasal spray and sub-lingual tablets. Patches uses skin as the way of delivery while and other products deliver nicotine through the mouth. The gum, lozenge and inhaler release nicotine faster than the patch, but slower than cigarettes, making them useful for cravings. Evidence suggests that using a nicotine patch whilst smoking either as a ‘pre quit’ tool or to ‘cut down to stop’ can improve rates of success.<sup>24,25</sup>

### Combination Therapy

Combination pharmacotherapy is the provision of fast acting products (such as gum, lozenge or inhaler) to combine with the slow acting patch. It can increase the chances of quitting.<sup>24</sup> Combinations therapy are indicated for people who have faced difficulties in quitting in the past or are experiencing significant cravings with single NRT. It is also helpful in highly dependent patients or those who have had multiple failed attempts.<sup>26</sup> Studies have shown higher rates of short and long term abstinence with the combination therapy.<sup>27</sup>

### E-Cigarettes

Electronic cigarettes (ECs), a class of battery-powered devices designed as an alternative to tobacco smoking, were invented by the Chinese engineer Hon Lik in the early 2000s.<sup>28</sup>

On lighting a traditional cigarette, the tobacco burns, releasing smoke that contains nicotine. This smoke when inhaled by the user, delivers nicotine to the lungs. An electronic cigarette doesn't rely on this process of combustion. Instead, it heats nicotine liquid which is converted into vapour, or mist, that is inhaled by the user.

It was hypothesised that e-cigarettes may reduce cravings more effectively than NRT, have of better adherence rates and delivery of clinically significant levels of nicotine into the blood.<sup>29,30,31</sup>

Newer models contain fewer toxicants than older ones<sup>32</sup> and enable vapers to absorb a greater amount of nicotine at a

quicker rate.<sup>33</sup> Indeed, in the hands of experienced vapers, some devices are able to match the nicotine delivery profile of a cigarette.<sup>34</sup>

Recent ECs appear to facilitate pulmonary absorption, with absorption in the blood equivalent to that with smoking tobacco.<sup>35</sup> The faster mode of action should improve the management of cigarette withdrawal symptoms early on in a quit attempt and make stopping smoking easier. Another factor unique to ECs is the level of sensory and behavioral replacement they offer. Even ECs that do not resemble conventional cigarettes have the potential to provide smokers with many of the tactile rituals, sensations, and behaviors associated with smoking. Such factors are thought to play a key role in the addictive potential of cigarettes.<sup>36</sup>

### Nicotine Preloading

Nicotine preloading means using nicotine patch before stopping smoking, while smoking normally. This may reduce a person's drive to smoke and weaken the addiction, thereby reducing cravings after stopping smoking and increasing the chance of stopping smoking successfully. Evidence supports that nicotine preloading is modestly effective at increasing long-term smoking cessation, but the data is limited. Mainly, the preloading helps by reducing the intensity of urges to smoke, leading to reduced consumption, thus, undermining the learnt drive to smoke. After quitting, this reduced drive causes reduced intensity of cravings for cigarettes and, hence, the chance of abstinence is increased.<sup>37</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. But there is lack of evidence suggesting the use of other forms of NRT for precessation is more effective than starting use on the quit day.<sup>24</sup>

### Nicotine Vaccines

Nicotine vaccines are a new approach to the treatment of nicotine dependence. They are currently under investigation. Nicotine-based vaccines, like other vaccines, prime the immune system to recognize nicotine as foreign body and mount an immune response against the drug.<sup>38</sup>

The nicotine conjugate vaccine acts by mobilising drug specific antibodies, which bind the nicotine molecules in the blood and prevent the drug from distributing to the brain, thereby reducing its behavioural effects. The nicotine addict will not experience any satisfaction from smoking and a first time user cannot become addicted.<sup>39</sup>

### Special Cases

#### Pregnant Women and NRT

Numerous studies have shown increased risks of pregnancy complications and adverse neonatal outcomes associated with maternal smoking, including placental abruption,<sup>40</sup> placenta previa,<sup>41</sup> spontaneous abortion,<sup>42</sup> stillbirth,<sup>43</sup> fetal growth restriction,<sup>44</sup> preterm delivery,<sup>45</sup> low birth weight,<sup>46</sup> and sudden infant death syndrome.<sup>47</sup>

The antenatal phase provides opportunities for the early identification and assessment of smokers and smoking cessation advice and support.<sup>48</sup> The earlier abstinence is achieved during pregnancy the better.<sup>49</sup> Ideally, smoking cessation during pregnancy shall be achieved without NRT. However for women unable to quit on their own, NRT shall be offered as the risk to the fetus is lower than tobacco smoking.<sup>50,51,52</sup>

Standard doses of NRT may not be sufficient for a beneficial effect in late pregnancy. One of the reasons why NRT may not be effective in pregnancy might be related to increased metabolism of nicotine during late pregnancy, making conventional doses of NRT insufficient for pregnant women.

### Breastfeeding and NRT

The delivery of nicotine to infants via breast milk is unpredictable and depends upon the serum concentration of nicotine in the mother and rate of milk production. Intermittent dosing products (i.e. lozenge, gum and inhalers) shall be used while breastfeeding.<sup>50</sup> Symptoms of mild nicotine toxicity in children include nausea, vomiting, diarrhoea, increased salivation, pallor (from peripheral vasoconstriction), excessive sweating, weakness, and dizziness.<sup>53</sup> Possible strategies to minimise the amount of nicotine in breast milk may be to prolong the duration between NRT administration and breastfeeding (ideally 23hours).<sup>54</sup>

### Children and Adolescents and NRT

NRT should not be used for patients under 12 years of age. The levels of nicotine in NRT are not suitable for children under 12. Children are likely to be affected by nicotine and it could cause severe toxicity, which can be fatal.

Adolescent smokers are different from older smokers in that their motivation to stop smoking tends to be more unstable.<sup>55</sup> It is sensible, therefore, to check that they are fully committed to trying to stop smoking permanently before offering them NRT.

Nevertheless NRT is safe in this group. NRT shall only be used by adolescents in conjunction with a counselling program. Counselling is needed in this age group because NRT is likely to be ineffective in the absence of counselling. Studies in which NRT has been used by adolescents have found no significant problems.<sup>56,57</sup> Hanson and colleagues found that NRT reduced craving in adolescents (compared with placebo) and concluded that although larger trials were needed on efficacy.<sup>58</sup>

### Cardiovascular Disease and NRT

Cigarette smoking appears to precipitate acute cardiac events by at least three mechanisms. First, is by producing a hypercoagulable state and promoting thrombosis. A second mechanism is the delivery of carbon monoxide, which limits oxygen delivery to the heart. A third mechanism is through hemodynamic effects of nicotine. These include an increase in heart rate and blood pressure.<sup>59</sup>

NRT has less intense cardiovascular effects. Nicotine increases cardiac output by increasing both heart rate and myocardial contractility. Intravenous nicotine, nicotine nasal spray and nicotine chewing gum all acutely increase heart rate upto 10 to 15 beats/min and increase blood pressure up to 5 to 10 mm Hg, responses similar to the effects of cigarette smoking.<sup>60,61,62</sup> Transdermal nicotine appears to cause lesser acute hemodynamic changes than smoking.<sup>63</sup>

Clinical trials of NRT in patients with underlying stable cardiovascular disease suggest that nicotine does not increase cardiovascular risk and can be used safely by smokers with less severe cardiovascular disease.<sup>64,65,66</sup>

### Diabetics and NRT

Patients with diabetes mellitus shall be advised to monitor their sugar levels more closely than usual when NRT is initiated as catecholamines released by nicotine can affect carbohydrate metabolism and vasoconstriction may delay/reduce insulin absorption.<sup>67</sup>

### Mental Health Co-Morbidity

People with mental problems are more of a challenge to quit smoking as the symptoms of nicotine withdrawal may be more pronounced. Also, they can be on medications that can interact with NRTs.

NRT helps such people in smoking cessation.<sup>68</sup> Usually, NRT is well tolerated by such people who are motivated to quit smoking. Although, they may prefer gradual approach to quitting and hence, may require NRTs for extended periods.<sup>69</sup> NRT also helps by reducing depression, anxiety and negative moods produced by tobacco withdrawal.<sup>70</sup>

Smoking interacts with some medications by increasing metabolic rate, making medications pass through the system more quickly. Health professionals shall carefully monitor and adjust prescribed medications during smoking cessation. Combination therapy for NRT should be offered.

### Side Effects of NRT

In a recent review involving 120 studies of NRT, it was concluded that the side effects of NRT may be discomforting for the patient but not life threatening.<sup>70</sup> Generally, the side effects are mild and are present in the local area only, i.e. the mouth for oral types and the skin for patches.<sup>12</sup>

The most commonly seen side effects of NRT<sup>70</sup> includes heart palpitations/chest pains, nausea/vomiting (oral products only), indigestion or gastrointestinal complaints (higher risk with oral products), insomnia (patch), skin irritation (patch), mouth and throat soreness (oral products), mouth ulcers (oral products), and coughing (oral products). Significant medical problems due to NRT are extremely rare.<sup>71</sup>

To calculate relative risk, the side effects of NRT should be compared with the side effects of smoking.<sup>72</sup> Cigarettes contain 69 identified cancer-causing substances,<sup>73</sup> which are absent in medicinal Nicotine. Thus, the NRT is much safer than smoking.

Smokers, generally, greatly overestimate the risks of NRT. This is partly due to not understanding that tobacco smoke is very much more risky than nicotine alone. Another reason may be that because NRT is a medicine it comes with lots of detailed information about side effects, whereas cigarettes don't.<sup>74</sup>

### Failure of NRT

NRT, though widely used, have only modest success rates and also requires additional behavioural or counselling support. One of the reasons for lower success rates maybe that the present formulations do not provide the extremely rapid, rewarding and high nicotine concentrations that can be obtained from the tobacco smoke.

Underdosing may be another possible explanation. In standard doses, the NRT products give less than half of plasma nicotine concentrations that is required by a moderate to heavy smoker. A Nicotine skin patch provides nicotine at a slow but steady rate. The user has no control over dosing. Hence, it delivers less nicotine than as obtained from cigarettes. Nicotine chewing gum, nasal spray, and lozenges provide acute dosing which is under the control of the user. Also, like smoking, their use provides sensory stimulation. But, they can have irritant side effects which can lead to underdosing. Also, the correct technique for their use is difficult to master.<sup>75</sup>

### Discussion

Tobacco use is the one of the main risk factor of chronic disease including cancer, lung diseases and cardiovascular disease.<sup>76</sup> The main problem with nicotine delivered by cigarettes is that it causes people to breathe in tobacco smoke over long periods.<sup>77</sup> Cigarette smoke contains over 4000 toxic substances, many of which are teratogenic or carcinogenic. Of particular concern are carbon monoxide, oxidizing chemicals, aniline, phenol, ammonia, lead, and nitrogen oxide.<sup>50</sup>

Studies have shown that nicotine is not the direct cause of tobacco-related disease but only leads to tobacco addiction. The symptoms of nicotine withdrawal include 2 or more of the following within 24 hours of cessation or reduction in nicotine intake<sup>78</sup> i.e. anxiety, malaise or weakness, mouth ulceration, irritability or restlessness, increased cough, increased appetite, reduced concentration, dysphoric mood, insomnia, craving for tobacco (or other nicotine-containing products). These symptoms of withdrawal cause clinically significant distress, are not due to a general medical condition and are not better accounted for by another mental disorder.<sup>79</sup> Effective management of nicotine dependence in patients will depend to a large extent on the timeliness of management of withdrawal symptoms with NRT. The elimination half-life of nicotine is <2 hrs, which means that many patients will seek to smoke unless withdrawal symptoms can be prevented via timely and regular provision of NRT. NRT aims to replace some of the nicotine obtained from cigarettes, thus reducing withdrawal symptoms when stopping smoking.

Nicotine replacement increases the odds of quitting smoking by around 60% compared to placebo.<sup>24,80-82</sup> It reduces cravings for cigarettes and dampens nicotine withdrawal symptoms such as irritability, anxiety, depression and restlessness.<sup>24</sup> The idea is to use "clean" nicotine, without the many additional toxins in tobacco smoke, for a limited period to "wean" off cigarettes.<sup>77,83,84</sup> Compared to single types of NRT, quit rates can be increased by combining patches with 2mg oral nicotine products, for example, the gum, inhaler, lozenge or tablet.<sup>24</sup>

A variety of clinicians in primary care settings including dentists and dental hygienists can play an important role in promoting smoking cessation. Two approaches have strong evidence of efficacy for smoking cessation: counseling and pharmacotherapy. Within the standard treatment times, the dentist and the office team can encourage patients to quit using tobacco by pointing out the damage caused by tobacco to oral tissues and highlighting the general health benefits of quitting. Besides modifying risk behavior, prescribing approved pharmaceutical agents is known to increase the quit rates, and several reported trials have used these agents in various dental settings. The most significant barrier remains a lack of education of dentists and hygienists on cessation activities during their formative years of training. Effective training modules both at undergraduate and continuing education levels need to be introduced and implemented to allow the dental team to engage in smoking cessation activities at the primary care level. Most trials in dental settings report a quit rate comparable to what has been achieved by physicians.<sup>85</sup>

### Conclusion

Nicotine addiction is the major cause of failure of smoking cessation. The Nicotine Replacement Therapy helps by timely delivering pure nicotine, and therefore poses less risk and reduces cravings. Several nicotine medications are available in different forms, doses and flavours. The choice of NRT product should normally be guided by the patient's preference. Evidence suggests that, NRT increases the chances of successfully stopping smoking and long-term abstinence.

The dentist and the office team has the responsibility to encourage patients to quit using tobacco by pointing out the damage caused by tobacco to oral tissues and highlighting the general health benefits of quitting. Besides modifying risk behaviour, prescribing approved pharmaceutical agents is known to increase the quit rates. For all patients' sake, the dental office must continue to work towards universal adoption of tobacco cessation intervention.

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