

# Oral Health and Nicotine Replacement Therapy Product

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## Abstract

Nicotine replacement therapy (NRT) products are used extensively for assisting users in achieving cessation goals through the substitution of pure nicotine with tobacco-less products. Awareness of the adverse oral effects of nicotine replacement products is important for health practitioners. This review highlights the potential effects of NRT products on the oral tissues and management of these adverse effects. Cochrane, PubMed, and MEDLINE electronic databases were utilized in search of the relevant literature related to NRT. The review highlights various adverse effects on oral health status from NRT products, with the underlying mechanisms for these effects remaining inconclusive. There is a need for more education of health professionals in oral health promotion and maintenance in these cases. NRT products have many potential adverse effects on oral health, and it is the responsibility of dental professionals to consider these in the management of patients to optimize a beneficial clinical outcome.

**Keywords:** Mouth neoplasms, nicotine replacement products, oral health, periodontal diseases, smoking, tobacco

## INTRODUCTION

Tobacco-related addiction has huge financial implications, not only for the users but also for the public.<sup>[1,2]</sup> While rates of smoking are declining in 2015, 11.5% of global deaths were attributable to smoking worldwide.<sup>[3]</sup>

A key objective of the Government and all health professionals is to eliminate or to reduce the impact of tobacco usage on the wider population. Current knowledge about tobacco use and its effects has led to the understanding that there is no safe way to use tobacco and that total cessation is imperative to avoid any number of debilitating and eventually fatal conditions.<sup>[4]</sup>

Various methods of achieving cessation have been proposed, including behavioral counseling and pharmacotherapy. The paradigm for cessation has changed over the years with a shift toward viewing addiction as a disease and the contemporary approach toward the management of tobacco addiction centers around a combination of education, counseling, and pharmacotherapy.<sup>[5]</sup>

A method of assisting users in achieving cessation goals has been through the substitution of pure nicotine with tobacco-less products.<sup>[6]</sup> Nicotine replacement products (NRPs) are the collective name for a range of over-the-counter medications containing pure nicotine, designed to aid users of tobacco

products in reducing their intake of such products, or to achieve a total cessation of use.<sup>[1,7,8]</sup> This pathway reduces the withdrawal symptoms associated with a reduction of intake or total cessation.<sup>[1,7,8]</sup> The use of nicotine substitution through one or more NRPs to aid cessation of tobacco use is termed as nicotine replacement therapy (NRT), and in the contemporary setting is considered as first-line therapy for smoking cessation.

NRT products are available in many different forms for consumers, including chewing gums,<sup>[9]</sup> lozenges or mints,<sup>[10]</sup> inhalers,<sup>[11]</sup> patches,<sup>[12]</sup> and vaporizers (also called E-cigarettes or Electronic cigarettes).<sup>[13]</sup> Nicotine drinks, straws, and lollipops are other developed and marketed products.<sup>[14]</sup> These products are available in varying strengths of nicotine based on the tobacco user's habitual intake or "stage of quitting." Except for nicotine patches (where nicotine is absorbed transdermally) and nasal sprays (where nicotine is absorbed through nasal mucosa), all other forms of NRP deliver nicotine

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by transmucosal absorption across the lining of the mouth. Oral delivery systems pose potential implications for the soft- and hard-tissue structures of the oral cavity, and the popularity of oral delivery methods highlights the need for integration of knowledge of potential adverse effects and how these may modify treatment outcomes or risk profiles in an oral and dental context.

NRT products are reported to be an effective adjunct to professional counseling, and other pharmacological aids in achieving sustained abstinence from tobacco<sup>[1,5,7,8,12,15,16]</sup> with some studies reporting success rates as high as 33% compared to 5% with patients quitting on their own.<sup>[11]</sup> One meta-analysis found a 50%–70% higher chance of quitting when using NRT.<sup>[17]</sup> Interestingly, NRT has shown to be effective in achieving sustained abstinence, even in smokers who have no intention of quitting.<sup>[8]</sup>

Combination therapy is a term referring to the use of multiple, different forms of NRT product simultaneously, for example, a nicotine patch used in conjunction with a nicotine spray.<sup>[14,18]</sup> It has been shown to be more effective for cessation than the use of any one product on its own, independent of the provision of any professional counseling.<sup>[5,7,8,15,16]</sup> Combination therapy is often used when initial attempts at cessation with monotherapy (the use of one form of NRT product) has failed to show positive benefit.<sup>[12]</sup>

## THE EFFECTS OF NICOTINE ON THE BODY

Nicotine is the most pharmacologically active component of tobacco and has a wide range of effects on the body, affecting blood flow, the immune response, and the body's healing mechanisms.<sup>[19-23]</sup> Nicotine has been noted to inhibit revascularization,<sup>[24]</sup> has a direct effect on the function and action of immune cells,<sup>[25-29]</sup> impedes tissue-repair mechanisms<sup>[24,30-37]</sup> in the body, and affects almost every organ in the body, including the brain and the heart.<sup>[23,38,39]</sup> Some of the more specific pharmacokinetics of nicotine are outlined below.

### Neurological and cardiovascular effects of nicotine

Nicotine has a very targeted and direct active effect on the nervous systems; nicotinic cholinergic receptors are found in the brain, autonomic ganglia, and the neuromuscular junction.<sup>[23]</sup> Intake of nicotine into the body enhances the release of various neurotransmitters, including adrenaline, noradrenaline, dopamine, acetylcholine, serotonin, vasopressin, glutamate, nitric oxide, calcitonin growth-related peptide and beta-endorphin<sup>[19,23]</sup> producing a myriad of systemic effects.

The main cardiovascular effect of nicotine is sympathetic neural stimulation.<sup>[20]</sup> Nicotine exposure can increase the heart rate by up to 10–15 beats/min and increase blood pressure by up to 5–10 mmHg.<sup>[20]</sup> Nicotine's inhibitory effects on angiogenesis and blood flow locally and systemically<sup>[40,41]</sup> have ramifications not only in a broader general health context but also its vasoconstrictive properties

lend itself toward the impairment of salivary flow in the oral environment and has such as implications on a patient's caries-risk profile. Furthermore, opportunistic oral bacterial infections such as Candidiasis has been reported as a result of low salivary flow.<sup>[42-45]</sup>

### Immunological effects and effect on the healing response

Nicotine has profound immunological effects, influencing all aspects of the immune system, including alterations in humoral and cellular immunity.<sup>[29]</sup> It has been shown to have a range of immunosuppressive actions,<sup>[27,29,46-48]</sup> including inhibition of pro-inflammatory cytokines in macrophages, inhibition of adhesion molecules, and inhibiting proliferation of lymphocytes in the human mixed lymphocyte reaction.<sup>[48]</sup> Nicotine has been observed to directly impair interleukin-1  $\beta$  and superoxide and hydrogen peroxide formation by monocytes as well as the formation of oxygen radical species by neutrophils, effectively inhibiting the defensive functions of these immune cells.<sup>[49,50]</sup>

Nicotine exposure has also been shown to inhibit a range of normal neutrophil functions such as phagocytosis, integrin expression, and protease inhibitor production,<sup>[51]</sup> leading to inhibition of the effectiveness of these immune cells on the body.

It has been documented that nicotine inhibits the actions of B-cells and T-cells<sup>[28,46]</sup> and impairs antigen receptor function and ectonucleotidase activity in lymphocytes,<sup>[25,26,52]</sup> weakening the capacity for these immune cells to respond normally.

Nicotine has been shown to impair cutaneous wound healing,<sup>[30,31]</sup> normal bone healing responses,<sup>[32,33]</sup> revascularization of both hard and soft tissues,<sup>[24,31,32]</sup> as well as healing of the bone following graft and augmentation,<sup>[24,34]</sup> which may be related to the inhibition of various cytokines involved in revascularization and osteoblast differentiation,<sup>[53]</sup> and therefore affecting the healing of both hard and soft tissues of the body. Similarly, nicotine affects fibroblast attachment,<sup>[35-37]</sup> integrin expression<sup>[54]</sup> and inhibits collagen production while enhancing collagenase production,<sup>[55]</sup> leading to impairment of the normal healing response. In a recent publication, it was observed that when nicotine gum was placed directly adjacent to a tooth extraction site, it was reported to produce osteonecrosis of the jaw.<sup>[56]</sup>

### Oral and periodontal effects of nicotine

In some studies, it has been reported that nicotine impairs gingival blood flow<sup>[57]</sup> and leads to local vasoconstrictive effects.<sup>[58]</sup> It has been reported that chronic use of nicotine products could lead to dose-dependent suppression of gingival bleeding.<sup>[59]</sup> However, smoking cessation improves gingival blood flow and gingival crevicular fluid (GCF) flow in humans.<sup>[60]</sup> This impairment of normal blood and GCF flow poses potential issues in the modification of the desired response in periodontal healing and can affect the risk profiles for oral and dental pathology such as dental caries

and Candidiasis.<sup>[43-45]</sup> Furthermore, nicotine binds directly to the root surfaces and results in impaired gingival fibroblast attachment to those periodontally involved root surfaces. Katti *et al.* reported that nicotine levels can be significantly reduced by root planning in the course of periodontal debridement procedures, suggesting the importance of professional oral health maintenance in patients on nicotine products.<sup>[61]</sup>

Similarly, nicotine has been implicated as a standalone modifying factor in periodontal destruction by the way of inducing COX-2 expression in human gingival fibroblasts,<sup>[62]</sup> inducing higher levels of interleukin-1 and interleukin-6 in gingival keratinocytes and fibroblasts,<sup>[63,64]</sup> upregulating lipopolysaccharide-mediated human monocyte secretion of prostaglandin-E2,<sup>[65]</sup> and matrix-metalloproteinases<sup>[66]</sup> which degrade connective tissue, as well as having a stimulatory effect on polymorphonuclear cell apoptosis.<sup>[50]</sup> These processes lead to an upregulation of the inflammatory response and promote the destruction of the tissue.

The negative effects on the immune response, blood flow, and salivary status have the capacity to modify periodontal disease, periodontal treatment outcomes, postsurgical healing and implant placement, and maintenance outcomes. The compromised healing response in both hard and soft oral tissues, as identified above leads to the progression of periodontal disease and impairs surgical healing of extraction sites and other regenerative, mucogingival, and implant surgical procedures.<sup>[51]</sup>

## ADVERSE EFFECTS OF NICOTINE REPLACEMENT THERAPY ON ORAL HEALTH

The smoking status of the patient is always considered in dental management; however, the effect of NRT usage and its implications are not routinely considered in the oral and dental management of patients.

One of the most commonly reported side effects of nicotine and NRT use is dry mouth, resulting in an impairment of the buffering capacity of the saliva.<sup>[16]</sup> Modification of the quality and quantity of saliva by NRT may result in an increase in the patient's caries-risk profile and increased the risk of such conditions as candidiasis, oral mucositis, mouth soreness, taste impairment, dryness, and cracking of the vestibular tissue, and multiple issues for denture wearers as a result of a dry oral cavity including difficulty in speech.<sup>[42-45]</sup> Nicotine delivered orally may also produce other forms of oral changes leading to discomfort, including numbness and tingling, hyperkeratosis, oral lichenoid reactions, burning mouth syndrome, and localized mucosal irritation.<sup>[17,67,68]</sup> Nicotine is a carcinogen and has been shown to modify the progression of oral cancer. Its consumption through an NRT product orally may place a patient at risk of oral neoplastic changes.<sup>[69-73]</sup> There is limited research of NRT links to oral malignancy and impacts in conjunction with head-and-neck radiotherapy.

## ADVERSE IMPACT OF NICOTINE OR NICOTINE REPLACEMENT THERAPY IN PERIODONTAL AND ORAL SURGICAL MANAGEMENT

Smoking cessation in the management of periodontal conditions is well established, due to its major impact factor in the posttreatment and modifying factor in the progression of periodontitis.<sup>[74-77]</sup> Similar complications in postsurgical outcomes following dental implant placement, hard- and soft-tissue grafting procedures, surgical exposure for orthodontics, and excisional procedures are reported.

The above issues are due to nicotine's effects on the immune system and complications of the normal postsurgical healing response in the oral cavity, with delayed healing. An extraction site with impaired blood flow will take longer to heal, and therefore produce an increased risk of secondary infection, impaired soft tissue and bone healing, as well as an extended period of the patient discomfort with a poorly healing socket. This is particularly relevant when the oral NRT product is applied directly adjacent to the healing site (s) and periodontally treated, operative sites after a crown lengthening or mucogingival procedures.

Incidences of postoperative discomfort and superinfection, resulting in opportunistic infections such as candidiasis in the oral environment have been reported.<sup>[43,44]</sup> For patients on bisphosphonate medications, NRT may produce an increased risk of medication-related osteonecrosis of the jaws in the absence of other risk factors or other medical complications such as poorly controlled diabetes.<sup>[56]</sup>

## SMOKING CESSATION AND THE DENTAL PROFESSIONAL

The practitioner, on considering future treatment directions and clinical management of a periodontal patient may encounter differences in healing and treatment outcomes as a result of the direct/indirect impacts of NRT in the absence of any significant medical implications in a susceptible individual. The clinician should have knowledge of NRT's oral and dental effects on the patient, for accurate diagnosis, appropriate management and minimization, or elimination of risk factors. Dolan *et al.* found that 65% of dentists advise smoking cessation, few provided specific counseling on cessation methods, strategies, or routine prescription of products, as this is not a part of the general dental practice.<sup>[78]</sup> At present, there are no guidelines readily available for counseling the patient in the use of NRT and smoking cessation advice, support/counseling as a routine part of the general dental practice.<sup>[78]</sup>

The primary message that the health professionals' recommends in relation to these products is obtained from the manufacturers' advice notes on the effectiveness of such products in smoking cessation. Although various research has highlighted the efficacy of NRT contribution in smoking cessation,<sup>[7,8,79]</sup> the adverse effects of NRT is usually left to the patient themselves.



A deeper understanding of the impact that NRT products have on the oral cavity and the role they play in dental management will have far-reaching positive outcomes for patients, as well as instilling confidence in clinician's advice on smoking cessation.<sup>[80]</sup> There is no formal training provided in the Australian dental school curriculum, regarding the provision of smoking cessation services in a dental setting for oral health professionals. Most patients are simply told that they "must quit smoking,"<sup>[78]</sup> sometimes followed by a recommendation for NRT in general, rather than advice on specific products or their use. Follow-up usually centers on patients' success with cessation rather than considering adverse events that may be associated with NRT.

Of interest to dentists are the questions raised regarding oral and dental pathology risks, as well as postsurgical, periodontal, and implant outcomes for patients utilizing NRT and how to proceed. This is due to increased caries risk, xerostomia, oral mucosal changes, oral cancer, and development of the oral lesions. Currently, there is inadequate knowledge with regard to how NRT may modify treatment outcomes, risk profiles, or the modification of the natural history of particular diseases or conditions.

Research has highlighted patients' safety concerns and fears with respect to NRT products, so the provision of accurate safety information will ensure the highest levels of compliance with therapy and successful smoking cessation.<sup>[80-82]</sup> These studies present a strong case for furthering the available knowledge regarding the specific potential adverse effects of NRPs for health professionals prescribing the use of NRT and managing patients using NRT.

Given the imperative need for evidence-based practice in all health-care settings,<sup>[83]</sup> it is desirable that further information can be obtained regarding specific effects of NRT, to aid diagnosis and prevention of adverse effects on the oral and dental tissues for all health professionals, as well as to ensure appropriate recommendations are made regarding the use of particular products and to ensure the best chances of cessation for patients.<sup>[80-82]</sup> Pharmaceutical companies and manufacturers of NRT products might also benefit from this knowledge in furthering the development of NRT products or the provision of information regarding their appropriate usage.

## CONCLUSIONS

While the clinical implications of patients' smoking status are well known in the management and treatment of the dental patient, the effects of NRT usage are not routinely considered in general patient management. The current body of evidence indicates a lack of knowledge of the effects on the oral cavity of the use of NRT. Further investigation and subsequent promotion of the information to oral health professionals will ensure better dental and oral health outcomes.

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## Conflicts of interest

There are no conflicts of interest.

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