Are Nicotine Replacement Strategies to Facilitate Smoking Cessation Safe?

• **Chris Lavelle,** DDS, DSc, FRCPath, FRCD(C), MBA •
• **Catalena Birek,** DDS, PhD •
• **David A. Scott,** PhD •

Abstract

Professional obligations to curb the prevalence of cigarette smoking reflect the importance of this preventable risk factor for innumerable diseases. These include chronic obstructive pulmonary disease and oral, lung and other cancers, although the morbidity and mortality rates for cerebrovascular disease (e.g., ischemic strokes) and cardiovascular disease (e.g., ischemic myocardial infarction) tend to be greater. Various alternative nicotine sources (e.g., transdermal nicotine patches, nicotine gum, nicotine nasal sprays) have been incorporated into smoking cessation programs. This review is intended to increase professional awareness of nicotine delivery systems available in Canada, including safety considerations. The pathogenic potential of nicotine, regardless of source, and the contraindications to the use of nicotine replacement therapies are discussed. However, the systemic nicotine load in individuals undergoing replacement therapy is generally lower than during active smoking. Nicotine is only one of many thousands of constituents of tobacco smoke. Furthermore, nicotine replacement is usually delivered over the short term (a matter of weeks). Therefore, nicotine replacement is recognized as a relatively safe and effective aid to smoking cessation.

MeSH Key Words: *nicotine/administration & dosage; risk assessment; smoking cessation/methods*

This article has been peer reviewed.

Few would contest the pathogenic significance of cigarette smoke in many chronic diseases, yet nearly 25% of adults and up to 35% of high school students maintain the habit in North America.[1] In recent years the *Journal of the Canadian Dental Association* has placed a high priority on disseminating information on the relationship between tobacco use and oral disease,[2,3] and reiterating the obligations of the dental profession to promote smoking cessation.[4–6] More than one-half of adult smokers and nearly three-fourths of adolescents see a dentist each year in North America, yet more than 40% of dentists fail to routinely ask patients about their tobacco use.[1] Thus, tobacco counselling is often not a routine component of patient care.[7] This deficiency is important, since it conflicts with the policy statements on tobacco use adopted by many professional organizations, including the Canadian Dental Association.[6] Some members of the profession may not be aware of such policy statements, may feel they have insufficient training or confidence, do not see themselves in the role of activists in the antitobacco war or hold other conflicting views that prevent their participation in tobacco counselling. This review is intended to increase professional awareness of nicotine delivery systems available in Canada, including safety considerations.

Smoking and Diverse Disease Entities

The growing prevalence of smoking-induced chronic obstructive pulmonary diseases (COPD; e.g., bronchitis and emphysema) clearly emphasizes the need for more work to translate policy statements into actions.[8] These diseases now constitute the fourth primary cause of death in the United States and elsewhere, after cardiovascular diseases, tumours and cerebrovascular diseases.[9] Variations in the incidence, severity and natural history of a broad array of other respiratory illnesses, ranging from the common cold to pneumothorax, pulmonary hemorrhage and various interstitial lung diseases, are also correlated with cigarette smoking, although their prevalence is clearly multifactorial.[10]

Smoking is a well-recognized etiologic factor in squamous cell and small-cell carcinomas of the lung and several other malignant lesions, not limited to oral, laryngeal or esophageal cancers.[11,12]

Data from the Third National Health and Nutrition Examination Survey of 12,329 dentate people has also confirmed the role of cigarette smoking in periodontal disease, since 41.9% (6.4 million) of all cases of periodontitis in the U.S. adult population were attributed to current cigarette smoking and 10.9% (1.7 million cases) were attributed to prior smoking history.[1]

The linkages between cigarette smoking and the pathogenesis of atherosclerotic vascular diseases are arguably more important, because of the high morbidity and mortality rates associated with these diseases.[13,14] Atherosclerosis can affect the entire cardiovascular system, with clinical sequelae including ischemic heart disease and ischemic strokes. As many as 25% of all strokes can be attributed to smoking,[14] independent of such risk factors as hypertension, hypercholesterolemia and sex.[15] The actual risks not only depend on the number of cigarettes smoked[14] but can also be reduced to those of nonsmokers within 5 years of breaking the habit.[16,17] In Canada, smoking causes 40% to 45% of coronary artery disease in people under 65 years of age, with similar risk reductions noted on cessation.[18] As secondhand smoke also contributes to progressive vascular changes such as carotid atherosclerosis[19] and endothelial dysfunction,[20] cigarette smoking is an incontrovertible but preventable risk factor for ischemic disease.

Nicotine Replacement Therapy in Canada

Because of the profound health risks inherent to tobacco use, the need for health care professionals, including dentists, to implement smoking cessation strategies (using the 5 A's: ask, advise, assess, assist and arrange[21] [see **Table** 1]) is almost universally accepted.

Nicotine replacement therapy (NRT) is the most widely used pharmaceutical aid to assist individuals in their attempts to stop smoking. In Canada, nicotine replacement is available in the form of a nicotine patch (Habitrol, Novartis Consumer Health, Mississauga, Ontario; Nicoderm, Pharmacia Consumer Healthcare, St. Laurent, Quebec) and nicotine gum (Nicorette and Nicorette Plus, Pharmacia Consumer Healthcare). Nicotine inhalers, nasal sprays and sublingual tablets are not currently available in Canada but are widely used in several other countries. Nicotine-containing water (Nico Water, QT5, Westlake Village, California) has been patented in the United States, although it is the subject of much controversy, and other alternative nicotine delivery systems are being developed. Nicotine-containing lip balm and nicotine-containing lollipops that also include natural sweeteners and flavourings have recently been sold illegally in the United States. The U.S. Food and Drug Administration has moved rapidly to warn offending pharmacies to stop the sales of such nicotine-containing preparations immediately.[22]

Table 1 **Intervention: the 5 A's used to promote tobacco cessation[a]**

- ***ASK:*** The health care professional should ask the patient about his or her smoking habits at every opportunity, i.e., during every visit to the dental surgery. This may include questions about tobacco use in the patient's home and working environments.
- ***ADVISE:*** The health care professional should continually advise patients to quit, thereby creating a consistent message and emphasizing the importance of this issue.
- ***ASSESS:*** The patient's readiness and motivation to quit should be assessed. Smoking cessation entails a major lifestyle change, requiring preparation, readiness and, usually, several failed attempts.
- ***ASSIST:*** The health care professional should assist those individuals who are motivated to make a quit attempt by informing, suggesting and/or prescribing a pharmacological cessation aid and by providing or referring the patient to counselling and support services, where available.
- ***ARRANGE:*** Follow-up services are often critical. The dentist or other health care provider can help the quitter to remain smoke free by providing back-up services, e.g., advising on the availability of national hotlines, support from nonsmoking friends or colleagues, or community-based support groups.[b]

[a]A more detailed description of the 5 A's approach to tobacco cessation is provided by Fiore and others.[21]
[b]An inventory of Canadian stop-smoking resources for professionals, including details of toll-free telephone support lines for quitters, is maintained by Health Canada and published at http://www.hc-sc.gc.ca/hecs-sesc/tobacco/prof/cessation.html.

Pathogenic Effects of Nicotine

Some combination of the 4,000 or more chemical components of tobacco smoke, including a huge arsenal of toxins and carcinogens, represent the mediators of multiple pathogenic processes. Nicotine, a tertiary amine, should by no means be considered an inert molecule. For example, it can cause vasoconstriction in specific vascular beds but dilatation in others.[23,24] Nicotine can increase the heart rate (by 10–15 beats/min[23]) and the blood pressure (by 5–10 mm Hg[23]) and can induce pathogenic changes to the endothelium that are associated with the atherosclerotic process.[23,25–29] Although smoking is implicated in the development of cancer, nicotine itself is not carcinogenic,[23] unless it undergoes nitrosation to form nitrosamines (a process known to occur during tobacco curing and combustion[23]). The need remains for further studies on the pathogenic potential of nicotine. Several excellent reviews on the pharmacological properties of nicotine are available.[23,30–32]

Relative Safety of NRT

The acute lethal dose of nicotine in humans is believed to be in the range of 40–60 mg (< 1 mg/kg).[33,34] The

nicotine in NRT is delivered in low doses (e.g., nicotine gum is supplied in 2-mg and 4-mg units), with mean circulating nicotine concentrations in subjects receiving NRT in the range of 10 to 15 ng/mL.[23,35–37] Therefore, the risk of fatality from direct nicotine poisoning must be considered remote. However, nicotine overdose can occur through inappropriate use of NRT, such as higher-than-recommended dosing, continuation of smoking while receiving NRT or use of more than one form of NRT. Nausea, salivation, abdominal pain, sweating, headache, diarrhea, dizziness and weakness are among the symptoms of nicotine overdose.[33,34]

The contraindications and major warnings on the use of NRT are summarized in **Table 2**.

Of particular interest might be the effects of NRT in women who are pregnant or breast-feeding. Smoking has been estimated to be responsible for 20% of low-birth-weight babies, 8% of preterm births and 5% of all perinatal deaths.[46] However, studies examining the effects of NRT on pregnancy outcome are limited. Given that systemic nicotine levels in people using NRT appropriately are comparable to or lower than those that occur with active smoking,[23,36] because the plethora of harmful non-nicotine components of tobacco smoke are avoided with NRT and because the risk of tobacco-induced and tobacco-exacerbated conditions are reduced with NRT, it is intrinsically logical to consider NRT to be safer for both mother and fetus than continued active smoking. Recent studies of the short-term influence of nicotine on pregnancy outcomes in humans have suggested that NRT is, indeed, safe,[32,47] and leading researchers have recommended further efficacy trials of NRT as an adjunctive therapy for smoking cessation during pregnancy.[47] Nevertheless, nicotine crosses the placenta and moves into breast milk,[32–34] although perhaps only in minimal amounts.[32] Animal studies show that nicotine can have detrimental effects on fetal development (perhaps through restriction of placental blood flow) and could be involved in the pathophysiology of sudden infant death syndrome.[32] Because of remaining safety concerns, NRT is currently contraindicated during pregnancy and lactation.[33]

Several small studies, including case reports, have shown a potential risk of vascular events in people using NRT.[33,48–53] Such reports may have raised concern among some health care professionals and have the potential to influence the attitude of the general population to NRT. However, recent large-scale studies have suggested that NRT is safe for use by subjects with various cardiovascular abnormalities.[32,39,40] Furthermore, under appropriate dosing regimens, NRT has fewer effects on several markers of cardiovascular risk, such as fibrinogen, b-thromboglobulin, platelet activation markers and intercellular adhesion molecule-1 (ICAM-1), than does cigarette smoking.[36,54] Should nicotine per se contribute to atherosclerosis, the short duration of NRT means that nicotine delivered through NRT products is unlikely to be of any clinical significance.[30] Again because of remaining safety concerns, NRT is contraindicated in individuals with specific vascular conditions, including unstable angina or recent acute vascular events (see **Table 2**).

Acute skin irritation (erythema, irritation, mild edema) related to nicotine is common, occurring in 30% to 50% of those receiving NRT in patch form, and rotation of the site selected for patch administration may help to limit this effect.[33,38,43] Another consideration is the possibility of nightmares and sleep disturbance, although this problem may be alleviated by removal of the patch before going to bed.[38,43] However, many patients report early morning to be a particularly difficult time to resist cigarette consumption, so the concern of nightmares should be weighed against the concern of nicotine deprivation following overnight patch removal. Swallowed nicotine may exacerbate symptoms in individuals with gastritis or peptic ulcers.[34,38]

Because nicotine induces catecholamine release from the adrenal medulla, caution has been advised in the use of NRT for subjects with diabetes mellitus, hyperthyroidism or pheochromocytoma.[33,34,38] The Canadian Pharmacists Association also recommends caution in administering NRT to individuals with renal or hepatic insufficiency and advises removal of the patch before strenuous exercise in any subject, particularly those undergoing cardia rehabilitation.[33,55] The very limited evidence on the influence of NRT on progression or regression of COPD suggests that NRT is a safe medication for subjects with COPD.[56]

Tobacco may act as an antidepressant (since, among other potential mechanisms, tobacco smoke inhibits A- and B-type monoamine oxidases[57]). There is important evidence that profound depression may be a common result of smoking cessation in subjects with mental illnesses (including, but not limited to, schizophrenia, depression, post-traumatic stress disorder and attention-deficit disorder).[38,44,45,58] Therefore clinicians and other health care professionals may wish to consider the mental health of subjects when contemplating a recommendation of tobacco cessation. Alternative aids to tobacco cessation, such as sustained-release bupropion (Zyban, GlaxoSmithKline, Mississauga, Ontario); an antidepressant acting on the dopamine and norepinephrine transmitter systems[43]), could be considered. However, there is a need for further research on such antidepressants, which have only recently been introduced as adjuncts to tobacco cessation strategies, with respect both to smokers with mental illness and to general safety.

Of particular interest to the dental profession is the potential exacerbation of temporomandibular joint disor-

Table 2 **Diseases or conditions in which NRT is contraindicated or where caution is recommended[a]**

Disease, condition or other characteristic	Currently contraindicated	Cautionary approach suggested	Safe
Oral or pharyngeal inflammation		✓[33] (gum)[b]	
Temporomandibular joint disease	✓[33] (gum)		
Denture use		✓[34] (gum)	
Nonsmokers	✓[33]		
Pregnancy	✓[33,34]		
Breast-feeding	✓[33,34]		
Age < 18 years	✓[33,34,38]		
Arrhythmia (serious)	✓[33,34]	✓[30,34,38]	
Unstable or worsening angina pectoris	✓[33,34]	✓[21,34,38]	
Recent cardiovascular or cerebrovascular event	✓[33]	✓[21,34,38]	
Other vascular conditions[b]		✓[30,33,38]	
Stable cardiovascular disease		✓[33,34]	✓[39–42]
Pheochromocytoma		✓[33,34]	
Diabetes mellitus		✓[33,34]	
Hyperthyroidism		✓[34]	
Asthma		✓[33,38]	
Peptic ulcers		✓[33,34]	
Contact dermatitis	✓[33,43] (patch)		
Generalized skin disorders	✓[33]		
Nicotine allergy	✓[33,34]		
History of mental illness		✓[38,44,45]	

[a] *This table reflects current knowledge about contraindications and cautionary approaches to the use of nicotine replacement therapy (NRT). It is based primarily on the current recommendations of the Canadian Pharmacists Association,[33] augmented by important research articles. Thus, Table 2 is not intended as a comprehensive summary of all available data. Excellent summaries of indications, contraindications, warnings, other medications whose metabolism is affected by NRT, storage, poisoning, side effects and adverse reactions, appropriate application and dosing strategies, and adjunctive therapies, particularly counselling and support, are available through MEDLINE Plus (United States)[59] and in the* Compendium of Pharmaceuticals and Specialties *(Canada).[33]*

[b] *Hypertension, occlusive peripheral arterial and vasospastic diseases such as variant (Prinzmetal's) angina and Buerger's disease, and heart failure.*

ders and oral inflammation that might occur through the use of nicotine gum, as outlined in **Table 2**. However, to be efficacious, systemic nicotine delivery from nicotine gum requires prolonged contact with the oral mucosa, and therefore the gum should be used in a manner referred to as "chew, taste, park." The gum should be chewed slowly until it is tasted or until a tingling sensation is felt; then, it should be placed between the periodontium and cheek ("parked") until the taste or sensation disappears.[59] The process is then repeated. Therefore, when used correctly, nicotine gum should be less likely to cause the temporomandibular joint irritation that is seen with regular gum-chewing. It is also easy to imagine that gum may not be the best nicotine delivery system for those with dentures. Interactions between nicotine gum and dentures, as well as other dental work, can be expected to depend on several factors, such as biomaterial composition, rate of salivary flow and xerostomia. For those seeking details of current best practices in tobacco use intervention, the clinical practice guidelines recently published by the U.S. Department of Health and Human Services should prove valuable.[21]

Drug–Drug Interactions

Health care professionals should consider several drug–drug interactions before recommending tobacco cessation and the use of NRT. Smoking cessation has the potential to increase the effects of certain medications, such as aminophylline, insulin, labetalol, oxtriphylline, prazosin, propoxyphene, propranolol and theophylline.[59] Conversely, tobacco cessation has the potential to decrease the effects of other medications, including isoproterenol and phenylephrine.[59]

Concluding Remarks

The purpose of this review has been to increase professional awareness of nicotine delivery systems available in Canada and to remind dental and oral health care professionals that nicotine can be hazardous, irrespective of source. Therefore, the tone has been cautionary at times. However, there is no intention to suggest that NRT is not a generally safe and efficacious aid to smoking cessation. There is no evidence that NRT is either carcinogenic or genotoxic, and its relative safety is reflected in its over-the-

counter availability in Canada. The evidence that NRT can double the chances of successful quitting, at least among those motivated to quit, is strong.[37] Except where contraindicated, NRT should be considered by dental health care providers as an appropriate aid to smoking cessation. NRT should preferably be used as part of a broader smoking cessation strategy tailored to the needs of nicotine-dependent tobacco users. It should always be remembered that the nicotine doses delivered by NRT are, generally, lower than those delivered through cigarette smoking and that tobacco smoke contains a large number of toxins and carcinogens in addition to nicotine (e.g., carbon monoxide, cyanide, hydrogen sulfide, arsenic and lead). Furthermore, NRT is designed for short-term use only (normally up to 12 weeks) and should be discontinued if the smoker continues to relapse over the initial 4-week period.[43] Therefore, even in situations where caution is advised, the risks of NRT administration should be carefully weighed against the continuing detrimental influence of tobacco smoking on multiple facets of health. ✦

Acknowledgment: *Pharmacia & Upjohn (Uppsala, Sweden), a manufacturer of nicotine replacement therapies, provided nicotine patches, logistic support and expenses for the transport of biological samples for a research project, the results of which were published by D.A. Scott and colleagues in reference 36 and elsewhere. However, Dr. Scott certifies that he has no financial interests in Pharmacia & Upjohn or in promoting the views expressed either in this manuscript or the original work contained in reference 36.*

Dr. Lavelle *is a full-time faculty member, faculty of dentistry, University of Manitoba, Winnipeg.*

Dr. Birek *is a full-time faculty member, faculty of dentistry, University of Manitoba, Winnipeg.*

Dr. Scott *is a full-time faculty member, faculty of dentistry, University of Manitoba, Winnipeg.*

Correspondence to: *Dr. David A. Scott, Department of Oral Biology, Faculty of Dentistry, University of Manitoba, 780 Bannatyne Ave., Winnipeg, MB R3E OW2. E-mail: scottda@ms.umanitoba.ca.*

The authors have no declared financial interests in any company manufacturing the types of products mentioned in this article.

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