CARDIOLOGY Rounds®

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Smoking Cessation

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Cigarette smoking is the leading contributor to premature death, illness, and healthcare expense. Smoking cessation reduces the risk, slows the progression of tobacco-related diseases, and increases life expectancy. Pharmacological therapies, in conjunction with behavioural support, doubles the chance of success in maintaining abstinence from nicotine, a highly addictive substance. This issue of *Cardiology Rounds* reviews smoking cessation, focusing on the cardiovascular risks associated with nicotine dependence, the benefits of smoking cessation, the appropriate use of current treatment options, and upcoming treatment options. The differences between the nicotine in cigarettes and nicotine in nicotine replacement therapy (NRT) is explored, along with the evidence that justifies the safe use of NRT in stable cardiac patients.

Clinical significance of smoking

Cigarette smoking is an undisputable cause of cancer, cardiovascular disease (CVD), and chronic obstructive pulmonary disease (COPD). The fact that smoking causes 17% to 30% of all of the deaths attributed to CVD is of particular interest to cardiologists.[1] In the presence of other coronary risk factors, smoking has an even more important impact on coronary artery disease (CAD) morbidity and mortality.[1]

Although the prevalence of smoking in Canada has slowly declined over the last two decades (it was 38.1% in 1981), smoking rates are still high.[2] In Canada, it is estimated that, every year, approximately 45,000 people will die from smoking-related illnesses.[3] Of every 1,000 Ontarians aged ≥20 years who smoke, half will die from smoking and 250 of these deaths will occur before age 70.[4]

Many of the effects of smoking on the cardiovascular system are reversible with smoking cessation. In the Framingham Heart Study, patients who stopped smoking by the age of 65 reduced their risk of coronary events by 50% compared to those who continued to smoke.[5] After 5 to 10 years, the risk of a coronary event is the same as for a nonsmoker.[3] Smoking cessation has also been shown to decrease the rate of restenosis after coronary angioplasty and reduce the risk of premature graft closure post-coronary bypass surgery.[5]

The physiology of nicotine dependence

Nicotine acts on presynaptic nicotine receptors, stimulating the release of neurotransmitters such as acetylcholine, norepinephrine, dopamine, and serotonin.[6] The resulting improved memory, anxiolytic, and pleasurable effects reinforce smoking behaviour (positive reinforcing effects). With chronic nicotine exposure, an upregulation in nicotine receptors occurs, which is one of the features that determine the development of nicotine tolerance and dependence.[6] Smokers inhale more frequently and more deeply to sustain the positive reinforcing effects. Smoking cessation leads to withdrawal symptoms, beginning within a few hours and peaking within 48 hours.[6] Although most withdrawal symptoms decrease in intensity over 2 weeks, cravings can persist for several months to years after smoking cessation.[7] These withdrawal symptoms are the determinant factor for relapsing.

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The role of healthcare providers

Smoking cessation interventions delivered by a healthcare provider are effective. Minimal contact with a healthcare provider increases quit rates by 20% over non-intervention controls, while ≥10 minutes of counseling doubles quit rates.[1] An effective strategy consists of asking the patient whether they smoke, providing advice, and assisting in the process of cessation. It is important to assess the patient's motivation and readiness to quit. This process is referred to as "the stages of change" in the smoking cessation literature. The stages of change include:

- precontemplation
- contemplation
- preparation
- action
- maintenance.

Typically, a smoker must go through all 5 stages and make on average 3 to 5 attempts before achieving long-term abstinence.[3] There are several guidelines to assist the physician in identifying the stage of change and to adapt his/her intervention accordingly.[8,9] The U.S Agency for Health Care Policy and Research has issued a clinical-practice guideline, *Treating Tobacco Use and Dependence* (available at http://www.surgeongeneral.gov/tobacco) to assist healthcare professionals in caring for their patients.

Pharmacological options

The most successful method to enhance smoking cessation is a multi-pronged approach, by coupling behavioural modification with pharmacological therapy, particularly in moderate to high nicotine-dependent patients. Patients who smoke within 30 minutes of awakening and smoke >10 cigarettes per day have a moderate to severe nicotine dependence and benefit from pharmacological therapy.[8] In Canada, >60% of daily smokers, aged ≥15 years, smoke their first cigarette of the day within 30 minutes of waking.[10]

Two approved first-line therapies are recommended: nicotine replacement therapy (NRT) and bupropion sustained release (SR). Without these therapies, <10% of smokers who quit on their own will remain abstinent for 1 year.[9] In contrast, all of the approved first-line pharmacological treatments have shown efficacy in randomized, double-blind trials, by doubling the one-year abstinence rates compared to placebo.[9] Typical rates of smoking cessation with pharmacological treatment and counseling are 40% to 60% at the end of drug treatment and 25% to 30% at one year.[9] There are few trials that have directly compared one form of pharmacological treatment with another; therefore, the treatments are considered equally effective. Nortriptyline and clonidine are also effective for smoking cessation, however, their less-desirable side effect profile has placed them as second-line agents.[9]

NRT: There are 3 NRT products, all available without the need for prescription: the nicotine patch (Nicoderm®, Habitrol®), gum (Nicorette®), and inhaler (Nicorette®). A recent meta-analysis of well-designed randomized trials involving >35,000 participants, in which NRT was compared to placebo, revealed an odds ratio (OR) for abstinence of 1.77 for NRT compared to control (95% confidence interval (CI), 1.66 to 1.88).[10] The OR for different forms of NRT are listed in Table 1. Dosing of these products is indicated in Table. 2. Although there are limited studies assessing the effectiveness of combination NRT, clinical practice guidelines recommend the use of the nicotine patch with another type of NRT, used on a "as per required" basis, as a second-line therapy for patients who are unable to quit on a single type of NRT or bupropion.[11]

Table 1: Efficacy of nicotine replacement therapy (NRT)[10]

NRT	Odds ratio	95% confidence interval
Nicotine patch	1.81	1.63-2.02
Nicotine gum	1.66	1.52-1.81
Nicotine inhaler	2.14	1.44-3.18

Minimum 6 month follow-up

Safety of NRT in CAD

Despite data to the contrary, there is still a reluctance to use NRT in patients with CVD due to a fear of increasing cardiovascular events. This may stem from case reports in the 1990s that suggested that NRT may cause vascular events.[12] However, subsequent analysis from the U.S. Food and Drug Administration advisory committee con-

Table 2: Nicotine replacement products

Nicotine-replacement product	Dose	Duration of treatment	Common side effects
Transdermal patch (Nicoderm®, Habitrol®)	**If smokes ≥15 cig/day:** 21 mg/day x 6 weeks, then 14 mg/day x 2 wks, then 7 mg/day x 2 wks **If smokes 10-14 cig/day:** 14 mg/day x 6 wks, then 7 mg/day x 2-4 wks	≥10-14 weeks	Skin irritation, insomnia
Nicotine polacrilex gum (Nicorette®, Nicorette Plus®)	2 mg (<25 cig/day) 4 mg (≥25 cig/day) 1 piece per hour while awake x 1 month, then change to prn schedule and taper weekly (max. 20 pieces/day)	≥6 months	Mouth irritation, sore jaw, dyspepsia hiccups
Nicotine Inhaler (Nicorette® inhaler)	6-12 cartridges/day (delivered dose, 4 mg/cartridge). Inhale for 5 mins at a time prn.	≥6 months	Mouth and throat irritation, cough

cluded that these events are not to be related to nicotine.[12] Nevertheless, the fact that nicotine has sympathomimetic effects leading to increased heart rate and blood pressure, and the fact that there are few trials investigating the use of NRT in cardiac patients, has likely caused hesitation in using these products in cardiac patients. However, this must be weighed against the risks of ongoing cigarette smoking. Cigarette smoking is thought to contribute to CVD via several mechanisms (see below); the many toxins in cigarette smoke, other than nicotine, likely contribute to these effects:[13]

- increased myocardial demand via sympathetic stimulation
- platelet activation
- vasoconstriction
- carbon monoxide-mediated reduction in oxygen carrying capacity of the blood
- endothelial dysfunction.[13]

There are differences in the cardiovascular effects from nicotine in cigarettes versus nicotine in NRT. The rapid absorption of nicotine from a cigarette causes a very high arterial nicotine concentration with a greater biological effect.[14] In contrast, all NRT products are absorbed through the skin or mucous membranes at a slower rate than via cigarette smoking. The term "replacement" is, therefore, somewhat of a misnomer since NRT never achieves the high concentrations that are achieved with cigarettes. As well, NRT at recommended doses causes only minor disturbances in autonomic control compared to cigarette smoking.[14]

Cigarette smoking is well known to cause platelet activation. Indeed, chronic smokers have demonstrated a steady supply of activated platelets in their circulation, whereas NRT (patch and gum) does not cause platelet activation (noted by no change in fibrinogen levels).[13,15] Unlike cigarette smoking, NRT does not contain the 4,000 chemicals, including carbon monoxide, that significantly contribute to ischemia, nor does it cause coronary vasoconstriction.

Most initial trials of NRT excluded patients with CVD or recent cardiovascular events. However, there are 2 double-blind, randomized, placebo-controlled studies that support the safety of NRT in stable CAD.[16,17] The first included 156 patients with CAD, randomized to receive either nicotine patch or placebo for 5 weeks.[16] Patients were excluded if they had an acute myocardial infarction (MI) within 3 months of study entry, vasospastic conditions, symptomatic valvular disease, uncontrolled heart failure (HF), or serious ventricular arrhythmias. There was no significant difference in the frequency of angina, overall cardiac symptom status, arrhythmias, or episodes of ischemic ST segment depression. The second study that evaluated the use of NRT in cardiac patients included 584 patients with at least one diagnosis of CVD (history of MI, aortocoronary bypass surgery, angioplasty, stenosis of ≥50% in at least one major artery, history of angina, HF, cor pulmonale, arrhythmia, peripheral vascular disease, CVD).[17] Patients received a 10-week course of therapy with the nicotine patch. Patients were excluded if they experienced an acute event or revascularization within 2 weeks of study entry. The primary endpoint of death/MI/cardiac arrest/admission to hospital secondary to angina, arrhythmia/HF was not statistically different (5.4% in the nicotine group compared to 7.9% in the placebo group; p=0.23).

There is a lack of data on the use of NRT in acute coronary syndromes since this patient population was excluded from trials. One small analysis of smokers (n=374) admitted with acute coronary syndrome who subsequently underwent angiogram, revealed that those treated *with* nicotine patch had the same short- and long-term mortality as those not treated with the nicotine patch.[18] A larger, randomized trial is needed to confirm these findings.

Bupropion SR: Bupropion SR (Zyban®) is the only non-nicotine, oral product available as first-line treatment for smoking cessation. Bupropion relieves or suppresses nicotine withdrawal symptoms by inhibiting neuronal reuptake of noradrenaline and dopamine in the central nervous system.[19] Unlike other commonly prescribed antidepressants, bupropion has no effect on serotonin.

The efficacy of bupropion as a smoking cessation aid has been investigated in several randomized controlled clinical trials.[20] It has been shown to double cessation rates, even in patients without a history of major depression.[9,11,21] A meta-analysis of 19 randomized controlled trials demonstrated a combined odds ratio of abstinence of 2.06 (95% CI,1.77 to 2.40).[22] It is equally effective in women, men, and in African-Americans.[21]

One of the first trials compared bupropion SR 100 mg, 150 mg, and 300 mg per day vs placebo for 7 weeks in 615 motivated patients.[23] At the end of the 7th week of treatment, smoking cessation rates were 19% in the placebo group, 28.8% in the 100 mg group, 38.6% in the 150 mg group, and 44.2% in the 300 mg group (overall p<0.001). Cessation rates for each of the active treatment groups were significantly better than with placebo. Patients who received 300 mg/day had better cessation rates than those who received 100 mg/day (p=0.005). At one year, the smoking cessation rates were 12.4% (placebo), 19.6% (100 mg), 22.9% (150 mg), and 23.1% (300 mg). Although the point prevalence (not smoked within the last 7 days) was similar with the 150 mg and 300 mg dose, only the 300 mg/day dose showed statistically significant better continuous abstinence rates.

A second double-blind, placebo-controlled trial investigated the efficacy of bupropion alone, bupropion in combination with nicotine patch, nicotine patch alone, and placebo in 893 patients.[24] Smoking cessation rates at 12 months were 15.6% (placebo), 16.4% (NRT), 30.3% (bupropion; p<0.001), and 35.5% (for the bupropion and

nicotine patch combination; p<0.001). Although all active treatment groups led to statistically significant differences from placebo in cessation rates, the abstinence rates between bupropion alone vs the bupropion/NRT combination were not statistically significant. A higher incidence of hypertension was noted in the group receiving the combination of bupropion with the nicotine patch. For this reason, clinical practice guidelines recommend the use of combination of bupropion and nicotine patch as second-line therapy in patients who have relapsed on single therapy.[11]

Clinical trials have shown bupropion to be a well-tolerated medication, with only 10% of patients stopping therapy due to drug-related adverse effects.[21] The most common side effects are dose-related and include insomnia (30%-45%) and dry mouth (5%-15%).[21] These side effects do not usually result in medication discontinuation. In contrast to tricyclic antidepressants, bupropion has little effect on the cardiovascular system, specifically no significant alpha-blockade, anticholinergic effects, or effects on cardiac conduction. However, treatment-emergent hypertension has occurred in patients receiving combination therapy with bupropion SR and NRT.[21] For patients with preexisting hypertension, blood pressure should be optimally-treated and monitored periodically thereafter during the course of bupropion therapy. With bupropion, there have been rare anecdotal reports of myocarditis, MI, and cardiac death.[21] The US Surgeon General's Clinical Practice Guidelines indicate that bupropion can be safely used in the immediate 2-week period following an MI.[11] This recommendation is based on bupropion's mechanism of action and established cardiac safety in depression studies, rather than on safety and efficacy data in the acute cardiovascular setting (for which data are lacking).

The Zyban as an Effective Smoking Cessation Aid for Patients following an Acute Coronary Syndrome (ZESCA) study, to be initiated at St. Michael's Hospital, will help clarify the risk/benefit of starting bupropion in the acute cardiology setting. Although there have been no reports of seizures in smoking cessation trials, depression trials showed a dose-related incidence of seizures of 0.1% with 300 mg/day and 0.4% with 450 mg/day.[20,21] For this reason, it is important to screen for predisposing risk factors for seizures before prescribing bupropion (Table 3).[21] Bupropion is absolutely contraindicated in patients with current or history of seizure disorder. Other contraindications are listed in Table 4.[21]

The suggested dose for bupropion SR is 150 mg orally, once daily, for 3 days, followed by 150 mg po, twice daily, for 7 to 12 weeks.[19] A longer duration of therapy may be appropriate if relapse is a concern since it has been shown to help prevent relapses when used for up to 1 year.[25] Since it takes about 7 days to achieve steady state blood levels, patients should be instructed to start taking bupropion 1 week prior to their quit date. Patients with mild-moderate hepatic impairment require dosage adjustment because bupropion is extensively heptically metabolized.[19] There are no studies evaluating the pharmacokinetics in renal impairment; however, it is known that bupropion is metabolized to active metabolites that are renally excreted.[19] Caution should be exercised if bupropion and drugs that are metabolized by the CYP2D6 isoenzyme are used concomitantly (Table 5).[19] When drugs that are metabolized by CYP2D6 are added to existing bupropion therapy, or if bupropion is added to the treatment regimen of a patient already receiving one of these drugs, a reduction in the dosages of the drugs that are metabolized by CYP2D6 should be considered. Certain medications, including protease inhibitors and fluoxetine, are known to significantly increase bupropion levels and a dosage adjustment and closer monitoring is mandated.[19]

Table 3: Predisposing risk factors for bupropion-induced seizures[20,21]

- Drugs that lower seizure threshold (eg, tricyclic antidepressants, neuroleptics, high-dose theophylline)
- Abrupt withdrawal of benzodiazepines, alcohol
- History of/or active alcohol consumption
- Diabetes treated with hypoglycemics
- Addiction to opiates, cocaine or stimulants
- Anorexia, bulimia
- History of/or active seizure disorder
- Hyponatremia
- Previous head injury
- Central nervous system tumour

Table 4: Contraindications to bupropion[19]

- Current or history of seizure disorder
- Already taking bupropion as an antidepressant (Wellbutrin®)
- Use of MAO inhibitors (MAOIs) or thioridazine within the past 14 days. (note: St. John's Wort, an alternative product, has MAOI effects)
- Current or prior diagnosis of bulimia or anorexia nervosa
- Excessive alcohol intake
- Known hypersensitivity to bupropion

MAOIs = monoamine oxidase inhibitors

Table 5: Important bupropion drug interactions[19]

Increased levels of the following medications (dosage adjustment may be required)	Increased bupropion levels (dosage adjustment of bupropion is required)	Drugs affecting seizure (use with caution)
• Type 1C antiarrhythmics (propafenone, flecainide) • Metoprolol • Antipsychotics (risperidone, haloperidol, perphenazine) • Cyclic antidepressants (imipramine, desipramine, nortriptylline) • SSRI (Venlafaxine, fluoxetine, sertraline, paroxetine) • Theophylline	• Protease inhibitors (ritonavir, nelfinavir, efavirenz)	• Antipsychotics • Tricyclic antidepressants • Antimalarials • Theophylline (high doses)

SSRIs = selective serotonin reuptake inhibitors

Counseling

Nicotine dependence includes not only the physical dependence, but also psychological, behavioural, and social factors. These factors need to be addressed to improve smoking cessation success. It is important for the individual to learn to identify smoking cues, then to use methods to break the link with smoking. Since stress is often a trigger for smoking, strategies for coping with stress are important. Relapses are to be expected and are often considered by smokers to be signs of failure when, in fact, they are opportunities to identify the triggers and the mechanisms to avoid them in subsequent scenarios.

Newer therapies on the horizon

The central cannabinoid (CB1) receptors have recently been implicated in "brain reward function" and have a role in controlling food consumption and in dependence and habituation.[26] Chronic tobacco exposure may disrupt the endocannabinoid system, leading to an imbalance in signals transmitted by the CB1 receptor. Rimonabant is the first, selective, cannabinoid type 1, receptor antagonist; it was initially developed as a possible treatment for obesity. Phase lll trials are underway to test the safety and efficacy of rimonabant for long-term smoking cessation. Preliminary data shows that rimonabant at 20 mg/day doubles the smoking cessation rate compared to placebo (36.2% and 20.6% for rimonabant and placebo, respectively) without causing weight gain.[26] The most frequent dose-related adverse effects are nausea, dizziness, and upper respiratory tract infections.[26] No major cardiovascular events have been reported thus far during treatment with rimonabant.[26]

Cost-effectiveness

Treating smoking-related illnesses results in substantial healthcare costs in an already stressed environment. The Ontario Research Tobacco Unit estimates that a 10% drop in smoking prevalence over the next 5 years would save 785 lives, almost 41,000 hospital days, and $468 million in healthcare costs over this period.[27] Cost-effective analyses have shown that, for each additional quitter after a period of 12 months, 1.46 life years and 1.97 quality-adjusted-life years (QALYs) are saved.[28] This translates into a cost-per-life years and QALYs gained that is lower than $10,000. Interventions costing <$20,000 are well worth supporting, as dictated by recent Canadian guidelines.[28]

Conclusion

Smoking contributes significantly to morbidity and mortality. In the highly technical field of cardiology, a "low technological" intervention such as smoking cessation has great benefits and should have high priority. Both NRT and bupropion are effective first-line therapies with proven efficacy rates when used with behaviour support. These therapies need to be considered to reduce the intensity of withdrawal effects, a determining factor for relapses. NRT has different hemodynamic and biochemical effects compared to cigarette smoking, which makes it a much safer alternative in all patients, including those with stable CAD. Similar to hypertension and hyperlipidemia, smoking is a chronic condition that requires the same recognition and long-term management in order to improve the patient's overall health and well-being.

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