Cardiovascular Prevention (IV)

The Importance of Treating Tobacco Dependence

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Smoking is a well-established risk factor for cardiovascular disease (CVD). Stopping smoking confers significant health benefits and is especially important for those with pre-exisiting CVD. Healthcare facilities should have systems in place to enable the identification of people who smoke, and ensure that smokers receive evidence based treatments to provide the best possible chances of stopping for good. Physicians have a crucial role to play to prompt quit attempts by giving brief advice to stop, and offering cessation support. Behavioural support strategies such as telephone, individual and group-based counselling improve the chances of long-term abstinence. Nicotine replacement therapy, bupropion and varenicline are medicines that have proven efficacy in aiding smoking cessation and increase the odds of quitting about 2-3-fold compared to placebo. Even patients with established cardiovascular disease can safely use nicotine replacement therapy to help them quit. For the greatest chance of success, physicians should recommend a combination of behavioural support and pharmacotherapy.

Key words: *Risk factor. Nicotine replacement. Smoking.*

La importancia de tratar la dependencia tabáquica

El tabaquismo es un factor de riesgo de enfermedad cardiovascular (ECV) bien establecido. Dejar de fumar aporta efectos beneficiosos para la salud significativos y es especialmente importante para los pacientes con una ECV preexistente. Los centros sanitarios deben disponer de sistemas que permitan la identificación de las personas fumadoras, y deben garantizar que los fumadores reciban tratamientos basados en la evidencia para obtener las mayores probabilidades de dejar el tabaco. Los médicos desempeñan un papel crucial para fomentar los intentos de dejar de fumar mediante consejos breves y ofreciendo apoyo para dejar de fumar. Las estrategias de apoyo conductual, como las realizadas por teléfono, y el consejo individual y de grupo mejoran las posibilidades de abstinencia a largo plazo. La terapia de sustitución nicotínica y el bupropión o la vareniclina son medicaciones de eficacia probada para ayudar a abandonar el tabaquismo y aumentan las probabilidades de dejar de fumar en alrededor de 2-3 veces respecto al placebo. Incluso los pacientes con una enfermedad cardiovascular establecida pueden utilizar de forma segura una terapia de sustitución nicotínica para facilitar el abandono del tabaco. Para tener las máximas probabilidades de éxito, los médicos deben recomendar una combinación de apoyo conductual y farmacoterapia.

Palabras clave: *Factor de riesgo. Sustitución nicotínica. Tabaquismo.*

INTRODUCTION

Strong evidence links smoking as a risk factor for cardiovascular disease. In turn, studies show that smoking cessation leads to improved cardiovascular health. Just as important as treating hypercholesterolemia and high blood pressure as risk factors for coronary artery disease (CAD), addressing smoking is crucial for primary and secondary disease prevention. Whereas these former conditions are often addressed by clinicians, screening for smoking status and offering cessation treatment are often overlooked. This essay covers the cardiovascular risks caused by smoking, the health benefits of stopping and the steps that physicians and other healthcare professionals can take to help their patients who smoke to quit.

Declaration of competing interests: Dr McRobbie has undertaken research and consultancy for, and received honoraria for speaking at meetings from the manufacturers of smoking cessation medications.
Dr Thornley does not have conflicts of interest to declare.

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CARDIOVASCULAR RISKS ASSOCIATED WITH SMOKING

There are a number of ways that smoking contributes to the pathogenesis of acute cardiovascular events. These

TABLE 1. **Examples of Factors Associated With the Smoking Related Pathogenesis of CVD**

Endothelial cell dysfunction	There is evidence to show that smoking causes dysfunction of endothelial cells.[1] Smoking is associated with blunting of endothelial-dependent vasodilation.[2] This occurs regardless of the whether coronary artery disease is present. A mechanism by which smoking affects vasodilation is via nitric oxide (NO) biosynthesis. Smoking is believed to reduce basal NO production, so contributing to reduced vasodilation[3]
Role of tissue factor	The presence of tissue factor (TF) appears to contribute to thrombus formation. Smokers have significantly greater levels of TF than non-smokers, and circulating TF concentrations significantly increases within 2 hours of smoking just 2 cigarettes[4]
White blood cell count	Smokers have higher white blood cell (WBC) counts compared with non-smokers and ex-smokers.[1] Elevated WBC count has been found to be associated with greater risk of cardiovascular events[5]
Oxidative injury	Smoking causes oxidative injury. Studies that have looked at markers of lipid peroxidation, for example, have shown these to be significantly greater in smokers than non-smokers[6]

include increased platelet activation that leads to a hypercoagulable state, decreased oxygen delivery, coronary vasoconstriction, and increased myocardial work. Components of tobacco smoke also induce endothelial dysfunction, increase blood thrombogenicity, enhance the inflammatory response, cause oxidative stress, and adversely affect lipid profile giving rise to the development of atherosclerosis.[1] Examples of factors involved in the pathogenesis of CAD are shown in Table 1.[2,3]

As well as inducing physiological changes, smoking is a risk factor for hard endpoints, such as onset of angina and myocardial infarction.[7,8] The INTERHEART study provided evidence of the risk of non-fatal myocardial infarction (MI) associated with smoking.[9] Over 12 000 cases of first acute MI were evaluated for a number of factors including smoking status and compared to 14 000 age and sex matched controls. Overall, current smoking was associated with a 3-fold increase in the odds of suffering a non-fatal MI compared to non-smokers (OR, 2.95; 95% CI, 2.77-3.14). The effect of smoking on risk was stronger in younger smokers (age <40 years) with an odds ratio of 5.6 (95% CI, 5.1-6.2). Smoking is also linked with an increased risk (relative risk, 2.3; 95% CI, 1.2-4.0) of sudden cardiac death.[10]

Second hand, or environmental tobacco smoke (ETS) is also an important risk factor for cardiovascular disease. ETS impairs platelet and endothelial function, increases arterial stiffness, oxidative stress and inflammation, and accelerates atherosclerosis.[11] Among non-smokers exposed to ETS, the risk of CAD is increased by 25%-30%.[12]

As well as the adverse effect on coronary disease, smoking damages peripheral arteries. In fact, smoking is a stronger risk factor for peripheral vascular disease (PVD) than for CAD.[13] A similar association has been shown for strength of smoking as a risk factor for aortic aneurysm.[14] PVD often presents late, often when symptoms, such as intermittent claudication, become present. The odds of asymptomatic PVD are increased 3-fold in current smokers, compared to non-smokers.[15] Although this risk is not completely reversed in ex-smokers, it diminishes to approximately half that of current smokers. Smoking also accelerates the progression of PVD so that smokers have twice the amputation rate of non-smokers with PVD[16] and are more likely to experience failure of peripheral artery bypass grafting.[17]

Smoking contributes to 12%-14% of all stroke deaths,[18] by causing increased thrombogenicity and atherosclerosis, similar to CAD. In patients with established stroke, smoking increases the risk of stroke-related mortality.[19]

Smoking and Other Risk Factors for CVD

Like smoking, elevated blood pressure, and cholesterol are major risk factors for CAD. Substantial evidence confirms that treatment of these conditions, in isolation, reduces CAD risk. However, smoking has a multiplicative interaction with such risk factors. For example, if a person has no risk factors for CVD at baseline assessment then the age-adjusted risk of a new cardiac event over a ten year period is about 2.3%.[20] Smoking alone nearly doubles the risk of CAD. When one other factor is present (eg, elevated cholesterol or elevated blood pressure) the risk of CAD increases 4-fold (10.3%). This risk is similar to that present when a person has elevated blood pressure and cholesterol. If all 3 risk factors are present then the age-adjusted risk of a new cardiac event over a 10-year period is almost 19%, which is an 8-fold increase in risk compared to someone with no risk factors.

Risks Associated With Light and Heavy Smoking

Clear evidence shows that smokers that use more cigarettes per day have a higher risk of CVD. For example, compared with non-smokers, the relative risk of fatal CAD for smokers increases with higher daily cigarette consumption.[7] A similar pattern is seen with the relative risk of angina,[7] and more recently, the INTERHEART study showed that the risk of non-fatal

MI also increased with increments in daily consumption.[9] However, smokers of fewer cigarettes are still at risk. Lower daily consumption rates (eg, less than 5 cigarettes) are still associated with increased risk of CAD related mortality.[21,22] This pattern contrasts to the risk relationship of other smoking related diseases such as lung cancer where level of risk depends on total tobacco exposure (ie, number of pack years).[23] This dose-dependent relationship is also found to predict rates of abdominal aortic aneurysm[24] and stroke amongst smokers.[19]

The Health Benefits of Stopping Smoking

Just as smoking contributes to a range of vascular diseases, quitting results in health benefits in both the short and long term. Short-term physiological benefits are typically evident within 24 hours (eg, reduced levels of carboxyhemoglobin). Plasma fibrinogen concentration rapidly declines within 2 weeks following smoking cessation,[25] white blood cell (WBC) count lowers and lipid profiles improve within 3 months of smoking abstinence.[26] Smoking cessation is also linked to a significant decrease in mean platelet volume, reduced platelet aggregation and increased cAMP (associated with inhibition of platelet activity).[27,28] Such changes are expected within 4 weeks of smoking abstinence.

Important long-term benefits from quitting are also observed. Risk of acute MI halves within a few years of stopping smoking.[9] For patients with pre-existing CAD this risk reduction is even faster.[29] For example, stopping smoking after percutaneous coronary revascularisation or coronary artery bypass grafting significantly increases long-term survival.[30,31] Ex-smokers have a reduced risk of nonfatal stroke[32] and smoking cessation reduces the progression of PVD.[33]

Environmental interventions may also reduce the incidence of acute MI. One such study showed a 23% reduction in acute MI hospitalisations following the introduction of a city-wide smokefree policy.[34]

Cutting Down and Light or Mild Cigarettes

Some healthcare professionals advise their patients who smoke to cut down as an alternative to quitting. Although cutting down decreases exposure, and may lead to quitting, it does not eliminate the risk of CVD. As noted earlier, consumption of less than five cigarettes per day is still associated with an increased risk of CVD. Complete cessation is clearly the best outcome.

Tobacco Dependence and Withdrawal

Nicotine was recognised as a drug of dependence as late as the 1970s. Before this time most scientific bodies viewed smoking as a habit rather than an addiction.[35] In the last 2 decades, knowledge of tobacco dependence has accumulated, and it is now widely recognised that nicotine is primarily responsible.[36,37]

Nicotine is an alkaloid found in tobacco, and when burnt is vaporised in tobacco smoke and delivered to the lungs. Here it crosses the alveoli and is rapidly absorbed into the pulmonary circulation, then passes through the left side of the heart into the systemic arterial circulation. Peak arterial concentrations of nicotine are reached within 30 seconds of inhaling tobacco smoke.[38] Nicotine has its primary effect in the central nervous system where it acts on the mesolimbic dopamine system. Nicotine binds to nicotinic acetylcholine receptors (nAChRs) on the cell bodies in the ventral tegmental area (VTA) which initiates action potentials in dopaminergic neurons that project into the nucleus accumbens (NA).[39,40] Such release of dopamine in the NA gives nicotine its rewarding properties and leads to dependence.

Abstinence from smoking results in a tobacco withdrawal syndrome. This comprises of a number of changes such as mood alterations, physical symptoms and signs; as well as biochemical and physiological changes (Table 2[41]). Further, evidence suggests that mouth ulcers and constipation are recognised tobacco withdrawal symptoms.[42,43] Craving is one of the most often reported symptoms during smoking abstinence and frequently predicts relapse.

Most tobacco withdrawal symptoms are short lived. They typically peak in the first few days of abstinence and return to baseline levels within 2-4 weeks.[41] The exception is hunger and craving. Hunger remains elevated until body weight has stabilized and craving may persist for many months after quitting.

More dependent smokers tend to experience greater withdrawal symptoms.[44] Further, smokers with the highest levels of nicotine dependence suffer the most intense urges and the greatest decline in affect.[45,46]

Do Smokers Want to Stop?

In countries such as the UK, the majority (72%) of smokers want to stop smoking.[47] Each year, nearly a third of smokers make a quit attempt[47,48] with almost half making their quit attempt right after making the decision to stop.[49] Although studies show no difference in the proportion of those trying to quit between socio-economic groups, cessation rates are typically lower amongst deprived groups.[50] Other factors linked with lower cessation rates include high levels of dependence, younger age, and lower education levels.

Most smokers attempt to quit smoking without any behavioural or pharmacological support. Studies from the US show that 62% of smokers trying to quit used no treatment.[51] Quitting without any support is linked with low success rates (2%-3% continuous abstinence after 1 year).[52]

TABLE 2. **Valid Symptoms and Signs of Tobacco Withdrawal**

Irritability
Depression
Difficulty concentrating
Restlessness
Insomnia
Impatience
Craving
Decreased heart rate
Hunger
Impaired performance
Increased monoamine oxidase levels
Weight gain

Adapted from Hughes (2007).[43]

HELPING PEOPLE TO STOP SMOKING

Physicians and other healthcare professionals have a key role in helping people stop smoking. The New Zealand Smoking Cessation Guidelines summarised these steps with "ABC"[53] (Figure 1). "A" is for asking all people if they smoke. "B" is for giving brief advice to stop smoking. "C" is for cessation support, which should be offered to all smokers who have an interest in stopping.

Ask About and Document Smoking Status

The first step is to ensure that smoking status is documented for every patient, and updated on an annual basis. Practice systems can ensure that this is routinely checked at every opportunity. These may take the form of screening questionnaires, completed by patients whilst in a waiting room, to assess smoking status and other health-related behaviours.

Figure 1. Directives of the New Zealand Smoking Cessation Guidelines: "ABC". "A" is for asking all people if they smoke. "B" is for giving brief advice to stop smoking. "C" is for cessation support.

Brief Advice to Quit

Secondly, advice to quit smoking from a doctor has an important effect of nearly doubling the chances of long-term abstinence compared to no advice (OR, 1.74; 95% CI, 1.48-2.05).[54] Brief advice increases total cessation rates by 2%-3%. This is via triggering a quit attempt, rather than increasing the chance of success from a given attempt.[55] Advice to stop should be clear and, where relevant, linked to a smoking related illness (such as CAD). Brief advice to quit can be delivered to patients in as little as 30 seconds. There is no ideal way to give such advice, but the message should tell the smoker to stop completely; be linked to a current illness if appropriate; and given to all smokers, not just those who desire to quit. One can acknowledge that stopping may be difficult, but proven treatments are available to make quitting easier and improve their chances of stopping for good.

Cessation Support

Thirdly, wherever possible, brief advice should be followed by an offer of help to stop smoking. There are a number of interventions (behavioural and pharmacological) that are effective in increasing long-term (at least 6 months) abstinence rates. These are summarised below.

Behavioural Support

Behavioural support used during a quit attempt increases the likelihood of a positive outcome. Different psychological strategies can be used (eg, cognitive behavioural therapy, motivational interviewing, withdrawal oriented therapy), however the key active components appear to be setting a quit date and repeated contacts following this. Other general techniques can be added such as boosting motivation, providing skills

TABLE 3. **Formats for Delivering Behavioural Support**

Telephone counselling	Telephone counselling is associated with higher long-term abstinence rates compared to minimal intervention (OR, 1.56; 95% CI, 1.38-1.77)[59]
Individual support	Behavioural support delivered to smokers on a one-to-one basis is associated with higher long-term abstinence rates compared to no treatment (OR, 1.56; 95% CI, 1.32-1.84)[60]
Group based support	Group based support is frequently used for smoking cessation. Group-based interventions show superiority over self-help in achieving long-term abstinence (OR, 2.64; 95% CI, 1.89-3.69)[61]

to avoid or cope with situations that are commonly associated with relapse (eg, stress, low mood, alcohol) and providing information about smoking and stopping smoking. Such strategies can be delivered in a number of ways including telephone and face-to-face support, which may be provided in either individual or group settings (Table 3).

No individual components of treatment are conclusively better than others but treatment in a group setting may produce higher success rates than one-to-one.[56,57] However such data were not from randomised controlled trials and results may be explained by differences between counsellors (eg, those that ran group-based treatment were more experienced) or in the populations treated. Correlational evidence also indicates that more intensive support (ie, more time spent with smokers) predicts higher abstinence rates[58] (Table 3[59-61]).

Nicotine Replacement Therapy

Nicotine replacement therapy (NRT) is not a "magic bullet," but reduces the severity of tobacco withdrawal symptoms and makes a successful outcome more likely. Therefore, NRT should be recommended to any person who is stopping smoking. Six different NRT products are available with no significant difference in efficacy between them (see Table 4[62]).

The primary mechanism of action of NRT is to reduce the severity of withdrawal symptoms associated with smoking cessation. Over 100 randomised controlled trials assessed the efficacy of NRT, together involving nearly 40 000 smokers,[63] and the odds of successfully quitting for at least six months using NRT were significantly greater than for placebo (OR, 1.77; 95% CI, 1.66-1.88).

Choice of which product to use can largely be left to the smoker, but the clinician can guide this choice based on the smoker's level of dependence. For example, a 4 mg nicotine gum confers an advantage over 2 mg gum in highly dependent smokers. A similar dose response relationship is observed with the nicotine lozenge and nasal spray. In this context, a highly dependent smoker is defined as a person who smokes their first cigarette of the day within 30 minutes of waking.[64]

NRT products can be safely combined and such use is associated with increased odds of stopping smoking compared with single product regimens (OR, 1.42; 95% CI, 1.14-1.76).[65] Also, higher dose patches (eg, 44 and 42 mg/24 hours and 25 mg/16 hours) have a modest treatment benefit over standard dose.[55]

NRT is generally used for up to 3 months, although a small proportion may need to continue to use if for longer. Of those who start NRT, 5% may continue to use it for up to a year.[63] Patients who use NRT for longer are typically highly dependent smokers, so long-term NRT may be necessary to maintain long-term abstinence. Such long-term use has not been linked to any safety concerns.

Bupropion (Zyban®)

The precise mechanism of action for bupropion aiding smoking cessation is unknown, but the mechanism may involve inhibition of the neuronal reuptake of dopamine and noradrenaline—both important in nicotine dependence and withdrawal.[66] A high quality systematic review showed that, compared to placebo, bupropion doubled long-term abstinence rates (OR, 2.06; 95% CI, 1.77-2.40).[67] A small number of studies compared bupropion with other smoking cessation medications but overall failed to show significant differences.[67]

Bupropion is a safe treatment when used correctly.[68] Several contraindications and precautions should be checked before prescribing this medication. The most common side effects experienced with bupropion include insomnia and a dry mouth. The medication also has a small (1/1000) risk of seizure.

Nortriptyline

Nortriptyline is the only other antidepressant that improves smoking cessation outcomes. It is a tricyclic antidepressant that inhibits the reuptake of noradrenaline and serotonin, and may aid cessation through its noradrenergic mechanism thereby reducing the severity of withdrawal symptoms. A placebo-controlled trial showed that nortriptyline use long-term significantly improved abstinence rates (OR, 2.14; 95% CI, 1.49-3.06).[67] Nortriptyline has a number of contraindications including in those who have experienced a recent myocardial infarction or arrhythmia, and several common

TABLE 4. **Long-Term Effectiveness of Nicotine Products Relative to Placebo**[a]

Nicotine Product	Odds Ratio	95% Confidence Interval
Gum	1.66	1.51-1.81
Patch	1.84	1.65-2.06
Nasal spray	2.35	1.63-3.38
Inhaler	2.14	1.44-3.18
Sublingual tablet or lozenge	2.05	1.62-2.59
Overall	1.77	1.66-1.88

[a]Adapted from Silagy et al (2006).[62]

side effects such as dry mouth, light-headedness, and blurred vision.[69]

Given that other effective medications for smoking cessation are readily available, nortriptyline is generally regarded as a second-line agent.[58]

Varenicline (Champix®)

Varenicline is a nAChR partial agonist with antagonist properties, that competes with nicotine for the same receptor site.[70] The agonist effect on the nAChR results in dopamine release, but less than with nicotine. Its effect on smoking cessation is, primarily, by reducing the severity of tobacco withdrawal symptoms (agonist effects),[71] but it also reduces the rewarding properties of nicotine (antagonistic effects). The latter may help extinguish smoking behaviour for the week prior to quitting and helping to protect against complete relapse if a smoker lapses.

At present, varenicline is probably the most effective smoking cessation medicine. It almost triples the odds of long-term abstinence compared to placebo (OR, 3.22; 95% CI, 2.43-4.27). It has also been demonstrated to have greater efficacy than bupropion (OR, 1.66; 95% CI, 1.28-2.16).[72] There has been one head-to-head comparison with NRT (patch) in an open label randomised trial. Participants in the varenicline group had greater abstinence rates than the patch group. Although this difference was significant at the end of treatment (12 weeks) this effect was not observed at 1-year follow-up.

Varenicline is usually well tolerated and safe for the majority of smokers who wish to quit. Exceptions to this include people under the age of 18 years and pregnant or breastfeeding women. Caution is recommended in those with renal impairment. Varenicline is not extensively metabolised so that 92% is excreted in urine unchanged. With minimal liver metabolism, it has no clinically significant drug interactions. The most common side effect associated with varenicline is nausea, which may be dose dependent. The titration period before quitting may limit its occurrence.

USING SMOKING CESSATION MEDICATIONS IN SMOKERS WITH CVD

NRT can be safely used in people with CVD.[73-75] NRT guidelines for smokers with CVD[76] recommend that NRT can be recommended to smokers with CVD. Data on the use of NRT in acutely ill patients are more limited. However NRT use is likely to be a lesser hazard than continued smoking.

Experience with newer agents to assist smoking cessation in patients is also limited. Bupropion has been found to be safe for use in smokers with stable CVD, with no adverse effects on blood pressure or heart rate.[77] It has not been studied in patients with acute or unstable disease. There are currently no published data regarding the use of varenicline in patients with CVD, although research is underway.

Other Treatments

A number of other treatments are marketed to assist smokers to quit, for example acupuncture, hynosis, St. Johns Wort and other herbal products, however none have any strong evidence for efficacy in smoking cessation.[78] As such these cannot be recommended.

There are a number of new and emerging pharmacotherapies that may provide further hope for smokers that require help in quitting. These include new NRT products which deliver nicotine faster,[79] other nAChR agonists and agents that are directed at other neurochemical pathways within the central nervous system.[80] Smoking cessation interventions involving exercise hold some promise[81].

CONCLUSIONS

Physicians and all other healthcare professionals have an important role in helping people stop smoking and reducing their risk of future cardiovascular events. Today treatments are available that increase the chances of long-term smoking abstinence. Giving simple opportunistic advice to stop smoking on its own will prompt people to try to stop smoking. This advice should be followed by cessation support, which should, ideally, include a combination of behavioural support and pharmacotherapy. These steps can be simplified to ABC. Ask, Brief advice, and Cessation support.

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