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How to Effectively Help Patients Stop Smoking: A Primer for Cardiologists

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Tobacco smoking is a chronic disorder based on nicotine dependence and is the single most reversible risk factor of cardiovascular diseases.[1] This primer provides an overview of evidence-based smoking cessation interventions, pharmacological and nonpharmacological. Interventions with limited or conflicting data are also discussed. These recommendations are intended for clinicians (physicians and nonphysicians) because smoking cessation services is a fundamental responsibility for health care providers in all settings.

Smoking Cessation Framework

A 5-step smoking cessation framework is denoted by the 5 A's: Ask, Advise, Assess, Assist, and Arrange.[2] Step 1 is to ask the patient about the extent of tobacco and nicotine use, including screening for secondhand exposure to smoke. Step 2 consists of advising patients about smoking cessation, because brief assistance of < 5 minutes can increase the success of smoking cessation. Step 3 involves assessing the patient's willingness to quit, which allows a clinician to understand the smoker's perspective as well. Step 4 is to offer assistance for those who are motivated to quit, including providing appropriate resources and therapies for patients who smoke at least 10 cigarettes a day. Step 5 is to arrange a follow-up 1-2 weeks after the patient's anticipated termination date, allowing the clinician to provide encouragement, assess response to therapy, optimize first-line therapies, and monitor for any adverse side effects of pharmacotherapy. Along similar sentiments, the Canadian-based Ottawa Model for Smoking Cessation is another in-hospital smoking cessation framework built on 3 A's: Ask, Advise, and Act.

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Pharmacotherapy

Three different classes of drugs are approved in Canada for smoking cessation: nicotine replacement therapy (NRT), bupropion, and varenicline. The efficacy of each drug class is supported by the **E**valuating **A**dverse Events in a **Gl**obal Smoking **C**essation **S**tudy (EAGLES) study, a clinical trial that provided head-to-head comparisons of the 3 agents vs placebo in $>$ 8000 smokers.[3] Herein, we review the suggested first-line pharmacotherapies for smoking cessation. The different agents available and their pharmacological profiles are included in Table 1.

NRT

NRTs provide temporary replacement of nicotine from cigarettes and are available as long-acting transdermal patches or short-acting agents such as gum and sublingual tablets/lozenges. Short-acting preparations often require frequent use throughout the day and lead to more fluctuating blood nicotine levels. They are often combined with a nicotine patch to better control cravings and withdrawal symptoms.

Transdermal patch. The transdermal patch provides a slow and continuous release of nicotine over 24 hours and is available in 7 mg, 14 mg, and 21 mg regimens. Each cigarette contains approximately 1-2 mg of nicotine. In Canada, 1 pack contains 25 cigarettes. Therefore, a 1-pack per day smoker is receiving approximately 25 to 50 mg of nicotine every day. Compared with cigarettes, which produces spikes in blood nicotine levels when used, the patch produces more consistent blood nicotine levels. However, cravings might still persist when using the patch if nicotine levels fall below the peaks produced during cigarette use. Major side effects include localized skin irritation, insomnia, and vivid dreams.

Nicotine gum. In Canada, Nicotine gum is available as 2 mg and 4 mg preparations. Chewing the gum releases nicotine, which is absorbed through the oral mucosa. A proper method of chewing, referred to as "chew and park" is paramount for

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Table 1. First-line medications used for smoking cessation in adults

Drug	Dosing	Administration	Advantages	Disadvantages	Major adverse effects
Nicotine patch	• 14 mg for $\leq$ 10 cigarettes per day • 21 mg if 10-19 cigarettes per day • 28 mg if 20-29 cigarettes per day • 35 mg if 30-39 cigarettes per day • 42 mg for $\geq$ 40 cigarettes per day	• Apply 1 patch daily • May start patch before quit date • Rotate application site • Tapering dose is not required	• Provides steady nicotine level • Easiest nicotine product to use	User cannot increase nicotine level in case of craving	Skin irritation, insomnia, vivid dreams
Nicotine gum	• 2 mg if first cigarette $\geq$ 30 minutes after waking • 4 mg if first cigarette $<$ 30 minutes after waking	• 1 piece every hour as needed • Maximum: $\leq$ 24 pieces per day • No food or drink for 30 minutes before and during use	• Nicotine dose controlled by the user • Oral substitute for cigarettes	• Can damage dental work • Difficult for denture wearers to use • Exacerbate temporomandibular disorders	Mouth irritation, jaw soreness, heartburn, hiccups, or nausea
Nicotine lozenge	• 2 mg if first cigarette $\geq$ 30 minutes after waking • 4 mg if first cigarette $<$ 30 minutes after waking	• 1 Piece every 1 to 2 hours as needed • Maximum: 5 lozenges per 6 hours, 20 lozenges per day • No food or drink for 30 minutes before and during use	• Nicotine dose controlled by the user • Can be used by smokers with dentures or in users with temporomandibular disorders	Unpleasant taste	Mouth irritation, hiccups, heartburn, or nausea
Bupropion	150 mg pill	• 150 mg/d for 3 days, then 150 mg twice a day • Start 1 to 2 weeks before quit date	• Oral agent (pill) • Blunts post cessation weight gain while being used	• Monitor for neuropsychiatric symptoms • Contraindicated in patients with seizure disorder or predisposition	Insomnia, agitation, dry mouth, headache
Varenicline	0.5 mg pill to start, then titrate up to 1 mg pill	• 0.5 mg/d for 3 days, then 0.5 mg twice a day for 4 days, then 1 mg twice a day • Start 1 to 2 weeks before quit date • May be started up to 5 weeks prior to quit date	• Oral agent (pill) • Relieves nicotine withdrawal and blocks reward from smoking	• Reduced dose in patients with severe renal failure • Monitor for neuropsychiatric symptoms	Nausea, insomnia, vivid dreams

optimal results. Dosing is determined by how soon the first cigarette is typically smoked upon awakening, with users possibly using up to 25 pieces of gum per day. The dosage absorbed in the body is also typically only half of the prescribed amount. Common side effects include mouth irritation, jaw soreness, heartburn, and hiccups. Overly vigorous chewing can exacerbate temporomandibular disorders in denture wearers.

Nicotine lozenge. The available formulations include 1 mg and 2 mg strength with pharmacokinetics, dosing regimens, and side effects profile similar to that for the nicotine gum. The maximum daily limit is 16 pieces. The major advantage of the lozenge over the gum is that it can be used in patients with temporomandibular disorders and dentures.

Bupropion

Bupropion is an antidepressant that inhibits the neuronal uptake of norepinephrine, serotonin, and dopamine. Bupropion is prescribed as 150 mg once daily for 3 days, then 150 mg twice daily for 12 weeks. Compared with placebo, bupropion increases the success of smoking cessation (odds ratio [OR], 1.8; 95% confidence interval [CI], 1.60-2.06).[4] Head-to-head comparisons of bupropion with NRT showed similar efficacy. Bupropion use is contraindicated in patients with a history of seizure disorder or recent major head trauma.[4] The risk of seizure with bupropion use is dose-dependent and is most often described in the setting of overdose and/or in patients with other risk factors for seizures. One of the major side effects of bupropion is insomnia.[4] Clinicians should routinely screen patients for changes in sleep behaviour and if insomnia is present, the evening dose can be discontinued.

Varenicline

Varenicline is a nicotine receptor partial agonist. Varenicline has been shown to be the most effective smoking cessation agent available, because it reduces withdrawal symptoms by preventing attachment of nicotine-to-nicotine receptors. The prescribing dose is 0.5 mg once daily for 3 days, then 0.5 mg twice daily for 4 days, followed by 1 mg twice daily for 12 weeks. Varenicline has been shown to increase the odds of quitting compared with placebo (OR, 2.96; 95% CI, 2.12 to 4.12 for 4 trials), indicating it superior to NRT vs placebo (OR 1.71, 95% CI, 1.55 to 1.88 70 trials), and Bupropion vs placebo (OR 1.56, 95% CI, 1.10-2.21 for 12 trials).[4] Common side effects include nausea and insomnia. Similar to bupropion, there were early concerns of neuropsychiatric and cardiovascular side effects with varenicline, which were not supported by subsequent studies including the EAGLES trial.

Electronic cigarettes

Electronic cigarettes are emerging as a potential aid in smoking cessation, albeit with mixed evidence. Electronic cigarettes (ECs) are handheld devices that use a battery source to aerosolize a liquid. Many EC products vary in the rate and amount of nicotine delivery and are currently being evaluated as another method for smoking cessation. A Cochrane meta-analysis consisting of 61 completed studies, representing 16,759 participants, reported moderately good evidence that nicotine ECs increase smoking cessation rates compared with non-nicotine ECs (risk ratio [RR], 1.9; 95% CI, 1.21-3.13), and NRTs (RR, 1.5; 95% CI, 1.21-1.93).[5]

However, using ECs for cessation might not improve successful smoking cessation or prevent relapse as well in the real world compared with in clinical trials. A 2021 US meta-analysis conducted on 55 observational studies and 9 randomized clinical trials reported that ECs were not associated with increased smoking cessation rates in the real-world adult population. Interestingly, the same study reported that there was a high cessation rate reported by EC users than conventional pharmacotherapy users in randomized clinical trials (RR, 1.56; 95% CI, 1.17-2.06), indicating a possibility that ECs are a useful cessation aid when clinician-mediated follow-up is present.

Although EC use is less harmful than cigarettes, prolonged EC use might be a risk factor in cardiovascular disease, including neurohumoral activation, oxidative stress, inflammation, endothelial function, and thrombosis. There is also limited data on the use of ECs on vaping cessation and exacerbating vaping dependency. Thus, more data are needed regarding its effectiveness in smoking cessation before an assessment of its use can be made regarding smoking cessation. Presently, ECs have not been approved for smoking cessation nor has any application been made by EC manufacturers to approve these devices for smoking cessation.

Nonpharmacological Interventions

Cytisine (labelled as a natural health product)

Recent attention has been given to cytisine, a naturally occurring plant alkaloid, as a highly effective smoking cessation agent. Like varenicline, it is a partial agonist that selectively binds to the $\alpha_4\beta_2$ nicotinic acetylcholine receptor subtype, which mediates nicotine dependence in the body. Cytisine has been sold in Eastern Europe as an inexpensive smoking cessation aid for the past 50 years, although it is currently unavailable elsewhere. A 2014 pragmatic, non-inferiority trial in New Zealand with 1310 adult daily smokers that compared cytisine use with NRT for 8 weeks revealed that cytisine was superior to NRT in smoking cessation (9.3% improvement; 95% CI, 4.2-14.5), but it was associated with higher self-reported adverse effects. The side effects of nausea, vomiting, and sleep disorders were also reported in other studies.

Behavioural therapy

A variety of behavioural therapy interventions to aid in smoking cessation are available, with tailored programs provided through specialty clinics or smoking cessation programs. A 2017 systematic review of 49 trials (approximately 19,000 participants) revealed that individual behavioural therapy for smoking cessation was more effective than a minimal contact control arm (of brief advice, standard of care, or provision of self-help materials) when pharmacotherapy was not offered to any participants (RR, 1.57; 95% CI, 1.40-1.77; $I^2 = 50\%$).

It is noted that for some patients, brief clinician counselling in the office is the only viable option for face-to-face care.

This option can be supplemented by external resources, such as telephone quit-line support and counselling. A 2013 systematic review and meta-analysis of various smoking cessation methods revealed that telephone counselling helped increase cessation rates when not initiated by helplines (51 studies; 30,000 participants; RR, 1.27; 95% CI, 1.20-1.36). Acupuncture, hypnotherapy, and alternative medicine might commonly be sought out by patients, however, evidence is lacking on their efficacy to improve cessation rates compared with placebo and is thus not recommended for smoking cessation. Overall, combination therapy of pharmacotherapy plus behavioural therapy with regular follow-ups and prolonged use should be the preferable approach to smoking cessation.[1]

An expanded overview on smoking cessation with complete citations are provided in the Supplementary Material.

Conclusion

This primer provides an overview of evidence-based smoking cessation interventions following the 5 A's framework: ask, advise, assess, assist, and arrange. All patients should be screened for smoking status regardless of clinical setting, because clinicians should be experienced in routinely prescribing evidence-based smoking cessation therapies. For hospitalized patients, smoking cessation interventions should be started in-hospital. Clinicians should be familiar with the various smoking cessation therapies available, including pharmacotherapies (NRT, bupropion, varenicline), ECs, cytisine, and behavioural therapy. On the basis of the available evidence, we suggest varenicline as the first-line therapy for smoking cessation, with combination therapy when possible.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2022.05.001.