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Smoking cessation and the cardiovascular patient

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Purpose of review
Smoking remains the leading cause of preventable morbidity and mortality. Our review highlights research from 2013 to 2015 on the treatment of cigarette smoking, with a focus on heart patients and cardiovascular outcomes.

Recent findings
Seeking to maximize the reach and effectiveness of existing cessation medications, current tobacco control research has demonstrated the safety and efficacy of combination treatment, extended use, reduce-to-quit strategies, and personalized approaches to treatment matching. Further, cytisine has gained interest as a lower-cost strategy for addressing the global tobacco epidemic. On the harm reduction front, snus and electronic nicotine delivery systems are being widely distributed and promoted with major gaps in knowledge of the safety of long-term and dual use. Quitlines, comparable in outcome to in-person treatment, make cessation counseling available on a national scale, though use rates remain relatively low. Employee reward programs are gaining attention given the high costs of tobacco use to employers; sustaining quit rates postpayment, however, has proven challenging.

Summary
Evidence-based cessation treatments exist. Broader dissemination, adoption, and implementation are key to addressing the tobacco epidemic. The cardiology team has a professional obligation to advance tobacco control efforts and can play an important role in achieving a smoke-free future.

Keywords
cigarette, nicotine, quitline, tobacco

INTRODUCTION

About 1 billion men and 250 million women use tobacco currently, and consumption is increasing [1▪▪]. Rising tobacco sales in China alone have offset reductions in North America, the United Kingdom, Australia, and Brazil. Today, 80% of the world's smokers live in low- and middle-income countries.

The costs in loss of human life are astounding. Smoking remains the leading cause of preventable morbidity and mortality. Globally, over 6 million deaths annually are attributed to tobacco use, with the accumulated loss of life expected to reach 1 billion by the end of the 21st century [1▪▪]. Half of long-term smokers die from tobacco-related diseases, and heart disease is the leading cause of death among smokers [2,3].

The US Surgeon General first reported on the serious negative health consequences of tobacco use in 1964. Last year's anniversary report concluded that the reduction in smoking prevalence over the past 50 years – from about half of US men and a third of US women to 20.5% and 15.3%, respectively – is one of the major factors contributing to US declines in cardiovascular disease (CVD) [4▪▪,5▪]. Cigarette smoking produces endothelial dysfunction, constricts blood vessels, activates platelets, creates a chronic inflammatory state, and causes dyslipidemia [6]. These effects accelerate atherosclerosis, destabilize coronary artery plaques, and precipitate acute coronary events and sudden death. Among nearly 85 000 postmenopausal women in the Women's Health Initiative followed for over a decade of life, smoking was one the strongest determinants of heart failure risk [7]. Quitting smoking provides immediate cardiovascular health benefits [4▪▪], reducing the recurrence risk of coronary events to

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KEY POINTS

- Promising approaches for enhancing quit rates with existing cessation medications include combination treatment, extended use of pharmacotherapy, reduce-to-quit strategies, and personalized approaches to treatment matching.
- Cytisine has gained interest as a lower-cost strategy for addressing the global tobacco epidemic.
- On the harm reduction front, snus and electronic nicotine delivery systems are being widely distributed and promoted but with major gaps in knowledge of the safety of long-term and dual use.
- Quitlines, comparable in outcome to in-person treatment, make cessation counseling available on a national scale though use rates remain relatively low.
- Employee reward programs are gaining attention given the high costs of tobacco use to employers; sustaining quit rates postpayment, however, has proven challenging.

that of a nonsmoker within 3 years and reducing mortality following a heart attack by half over 3–5 years [8,9]. Among patients with symptomatic peripheral artery disease, quitting smoking is associated with improved limb-related outcomes and overall survival [10].

This review highlights recent research on the treatment of cigarette smoking, with a focus on heart patients and CVD outcomes.

EFFORTS TO INCREASE THE EFFICACY OF TOBACCO CESSATION PHARMACOTHERAPY

Cessation pharmacotherapy is recommended for all smokers trying to quit, unless contraindicated [11]. Though acting by different mechanisms of action, cessation medications can reduce physical withdrawal from nicotine as well as the immediate, reinforcing effects of nicotine absorbed via tobacco if an individual does smoke. Network meta-analyses have examined the absolute and relative efficacy and cardiovascular safety of tobacco cessation pharmacotherapy. In a 2013 Cochrane network meta-analysis including 267 studies with over 100 000 participants, nicotine replacement therapy (NRT), bupropion, varenicline, nortriptyline, and cytisine were found superior to placebo; bupropion and NRT were comparable in efficacy; and varenicline was superior to single forms of NRT and bupropion [12]. Neither bupropion nor varenicline showed excess cardiovascular risk relative to placebo. A 2014 network meta-analysis examined CVD events associated with cessation medications utilizing two definitions: first, all CVD events, including minor events such as tachycardia, and second, limited to the Food and Drug Administration (FDA) definition of major adverse CVD events [13▪]. None of the cessation medications was associated with major CVD events, and the findings were suggestive of a protective effect for bupropion. NRT was associated with an increase in overall CVD events, driven by lower-risk events, typically tachycardia, a known and largely benign effect of NRT [14]. Findings when analyses were restricted to individuals with a history of CVD were comparable.

Varenicline, the most recently approved cessation medication, came to market in the United States in 2006. With no new medications on the near horizon, approaches to maximize the effects of existing cessation pharmacotherapies have included the following: combination treatment, extended use, reduce-to-quit protocols for smokers unready to quit, and treatment-matching via precision medicine. Interest in cytisine as a lower-cost treatment alternative has emerged in recent years.

Combination cessation pharmacotherapy

Combination cessation pharmacotherapy combines drugs that act by different mechanisms and/or have different pharmacokinetics. Combining nicotine patch (slow release) with nicotine gum, lozenge, inhaler, or nasal spray (rapid release) is more effective than the use of single NRT products [15], and equally effective as varenicline [12]. Bupropion with nicotine patch is more effective than bupropion alone [15], and adding bupropion to combination NRT improved efficacy over combined NRT alone [16]. Two recent trials tested varenicline and NRT patch in combination. The larger trial ($N = 435$) initiated nicotine versus placebo patch 2 weeks prior to the target quit date, followed by varenicline for 1 week prior to target quit date, and then 12 additional weeks in combination. The NRT plus varenicline combination resulted in significantly greater quit rates than varenicline alone out to 24 weeks (49% versus 36%, $P = 0.004$) [17▪]. A smaller, and likely underpowered, trial ($N = 117$) initiated varenicline 1 week prior to quit date and then nicotine or placebo patch at the target quit date and reported quit rates of 38 and 29% at 12 weeks ($P = 0.14$) [18]. Although varenicline is a partial agonist/antagonist of the α4β2 nicotinic acetylcholine receptor, it is thought that either nicotine from NRT still interacts with this receptor to some degree or nicotine from NRT affects different nicotinic receptors contributing to the addictive effects

of nicotine. In both studies, the combination was well tolerated, with vivid dreams the most common side-effect. Recently, the addition of bupropion to varenicline was compared with varenicline alone for 12 weeks [19▪]. The combination resulted in significantly greater prolonged abstinence from week 2 at 26 weeks (37% versus 28%), but not at 52 weeks (31% versus 25%). Combination therapy was associated with greater anxiety and depressive symptoms over the first 2 weeks, with no difference in depressive symptoms by week 4 [20]. Studies of combination cessation medication generally show increased abstinence relative to single forms of treatment with no strong signal of CVD safety concerns.

Extended cessation treatment for relapse prevention

Cessation medications generally are recommended by the manufacturers for 8–12 weeks. The use of cessation medications for 6 months or longer, however, appears well tolerated and may be helpful to prevent relapse. The concept of continuing care for smoking cessation is analogous to the use of lipid lowering medications for dyslipidemia or insulin for diabetes. With only a handful of controlled trials in the literature, the evidence in support of extended cessation treatment varies by medication and study design. A 2015 study suggested the safety but lack of long-term benefit of extended (24-week) or maintenance (52-week) nicotine patch therapy relative to standard 8-week treatment [21▪]. The study design extended nicotine patch, regardless of initial treatment response; at the end of standard treatment, fewer than a third of the sample were abstinent. Medication compliance was lowest among those in the 52-week treatment (i.e., fewer than a third reported patch use 6 days or more per week). More akin to clinical practice are extended treatment studies of varenicline and bupropion use, randomizing abstainers at 12 weeks to continued active drug or placebo. Varenicline dosed for 6 months yielded 44% continuous abstinence versus 37% for placebo, with FDA approval for extended treatment [22]. In smokers with schizophrenia or bipolar disorder, 52 weeks of varenicline therapy yielded 30% sustained abstinence at 76 weeks compared with 11% for those randomized to placebo during the maintenance phase [23▪]. In two earlier studies of 52-week bupropion therapy, abstinence was increased at 1 year but not sustained at the 2-year follow-up [24,25]. To date, only varenicline has demonstrated benefit of extended use for relapse prevention, though combination NRT is worth testing in the same way. Limiting extended use to those who initially show benefit will likely improve adherence. It will be important to examine in whom extended cessation pharmacotherapy is beneficial, such as smokers with schizophrenia or other coexisting disorders.

Reduce to quit approaches

Although motivational approaches have demonstrated utility in engaging smokers not intending to quit [11], medication use has traditionally been reserved for smokers who have identified a quit date. Expanding the use of cessation medication as an engagement strategy and a tool to facilitate abstinence by reducing cigarette consumption is, however, showing promise. Smokers unwilling to quit in the next month, but willing to reduce smoking and make an attempt within 3 months, were randomized to 12 weeks of varenicline or placebo with direction to reduce by half the number of cigarettes smoked per day by week 4, reduce by 75% or more by week 8, and then quit completely at week 12 [26▪]. Varenicline or placebo was continued for an additional 12 weeks after the quit date. Abstinence was significantly higher in the varenicline versus placebo-treated group from weeks 21 to 24 (38% versus 13%) and weeks 21 to 52 (27% versus 10%). The beneficial mechanism of varenicline pretreatment may be reduced craving and extinguished reward effects, making cigarettes less desirable and easier to quit.

Pharmacogenomics for treatment tailoring

Precision medicine is an emerging approach to treatment. Long-term abstinence with cessation pharmacotherapy rarely exceeds 30%, and there is interest in understanding individual differences in medication response and ways to personalize treatment. Smokers tend to regulate their nicotine intake, which has led investigators to study the rate of nicotine metabolism as a potential predictor of response to smoking cessation treatment. Measured in smokers' blood, saliva, or urine, the ratio of the nicotine metabolites trans-3'-hydroxycotinine to cotinine, termed the nicotine metabolite ratio (NMR), is highly correlated with nicotine clearance and associated with level of dependence and cessation pharmacotherapy response [27]. In retrospective studies, slow metabolizers respond well to nicotine patch, with no incremental benefit from bupropion. Normal metabolizers respond better to bupropion than the patch. A 2015 clinical trial stratified patients by slow or normal NMR and compared treatment with nicotine patch, varenicline, and placebo [28▪]. Varenicline was more effective than the patch in normal but not in slow metabolizers. Side effects from

varenicline were more common in slow metabolizers. For personalizing treatment, use of NMR appears to inform differential response, such that slow metabolizers are predicted to do well on the patch, with lower cost and potentially fewer side-effects. Whether this approach is feasible in clinical practice and cost-effective remains to be determined.

Cytisine as a global tobacco treatment strategy

Cytisine, a plant alkaloid with high affinity for the alpha4beta2 nicotinic acetylcholine receptor subtype, is derived from the plant *Cytisus laburnum*. Cytisine was first used for quitting smoking over 50 years ago in Eastern and Central Europe, before the approval of any smoking cessation aids in the western world. In meta-analyses, cytisine's treatment effect was comparable to prior effects for NRT, bupropion, nortriptyline, and clonidine [29] and even stronger when restricted to the two more recent and higher quality randomized placebo-controlled trials [30]. The absolute sustained long-term quit rates, however, were modest for cytisine (8.5%) and placebo (2.1%) at 1 year, attributed to the minimal behavioral support provided and the study locations (Poland and Kyrgyzstan) characterized by permissive tobacco use laws and high smoking prevalence [31]. A 2014 open-label randomized comparative effectiveness trial in New Zealand reported 22% sustained abstinence for cytisine at 6-month follow-up compared with 15% for NRT patch [32▪]. Naturally grown and inexpensively produced cytisine is from less than half to 1/20th the cost of other cessation medications, and, based on existing efficacy data, should be considered a cessation aid globally, especially where other treatments are unavailable or unaffordable.

ALTERNATIVE NICOTINE DELIVERY PRODUCTS

Noncombustible nicotine products have been promoted as harm reduction alternatives to tobacco cigarettes for smokers unable or unwilling to quit. Particularly popular are snus, the Swedish form of snuff, and electronic nicotine delivery systems (ENDS; e.g., e-cigarettes, e-hookah, vape pens), which are battery-powered devices that generate an aerosol, typically containing nicotine, for inhalation. Relative to combustible cigarettes, cardiovascular effects of snus and ENDS have received far less study.

Snus

A 2014 longitudinal study from Sweden found that discontinuation of snus use after a myocardial infarction (MI) was associated with a nearly 50% reduction in mortality risk, similar to the benefit associated with quitting smoking, suggesting the use of snus after MI should be discouraged [33▪]. The findings are consistent with a 2009 meta-analysis of smokeless tobacco and CVD risk in Sweden and North America, which reported an increased risk for fatal MI [34], though a 2012 meta-analysis found the increase to be nonsignificant [35].

Electronic nicotine delivery systems

Analysis of 12 first-generation (cigarette-like) brand ENDS found varying levels of toxic compounds in the aerosol across brands, about 9–450 times lower than in cigarette smoke [36▪]. The ENDS aerosol particle size distribution is similar to conventional cigarettes, raising concern about contribution to inflammatory processes and increased risk of CVD [37▪▪]. Only two randomized controlled trials have tested the efficacy of ENDS for smoking cessation, one with treatment seekers and the other with unmotivated-to-quit smokers, and both found no significant difference for nicotine-containing versus placebo devices [38,39]. Large observational studies indicate ENDS users are more motivated to quit smoking and hence may be seeking ENDS as a cessation tool. Some have argued that daily ENDS use is needed to support cessation, though a recent large web-based epidemiologic study found no overall benefit for quitting smoking among daily ENDS users relative to nondaily ENDS users and nonusers [40▪]. Because there is no exposure to toxic combustion products, ENDS are likely a harm reduction option for CVD; unstudied, however, are the long-term health effects of repetitive, daily, extended use or dual use with traditional cigarettes, which is common.

TELEHEALTH AND INCENTIVES

Telephone quitlines

Toll-free telephone quitlines (e.g., 1-800-QUIT-NOW) providing national access to tobacco cessation counseling have proliferated over the past decade. Clinical referrals of smokers to these programmes are needed, as studies indicate that fewer than 10% of smokers who are trying to quit and aware of quitlines are actually using them [41]. A 2015 study of cardiac patients treated in Dutch hospitals concluded that quitline counseling support had comparable efficacy and was cost-effective relative to in-person counselling [42▪]. The findings were consistent with a 2014 meta-analysis of telehealth smoking cessation interventions in cardiac rehabilitation, which found comparable effects relative to center-based supervised services [43▪]. A

2013 meta-analysis concluded that quitline effects are stronger when multiple counseling sessions are provided [44].

Pay to quit or charge to smoke?

Monetary incentives have been tested to motivate cessation. A 2011 meta-analysis of nine trials concluded that incentives increased abstinence while the payments were provided, but effects were lost once the rewards ended; variable- versus fixed-payment made little difference, nor did paying for outcome (quitting) versus participation (program attendance) [45]. One trial provided a substantial cash reward of $750, and reported a three-fold increase in quitting from 5 to 15% after 9–12 months [46]. Notably, in real-world implementation, the participating company opted for insurance premium penalties for smokers rather than payment incentives for quitting [47]. A 2015 follow-up study found that reward-based programs ($800 incentive for quitting smoking) were more acceptable than deposit-based programs ($150 returned deposit plus $650 for quitting), though deposit-based programs yielded higher abstinence rates [48▪]. In both reward and deposit-based conditions, about half of participants relapsed 6 months postpayment. In the United Kingdom, pay-for-performance provider incentives have been associated with observed increases in clinical documentation of assessing and treating tobacco use, with evidence of declines in patient smoking prevalence over time [49▪]. The US Affordable Care Act recommends provider reimbursement covering at least two tobacco cessation attempts per year with counseling and any FDA-approved cessation medications for a 90-day treatment regime.

CONCLUSION

Clinical practice guidelines recommend that tobacco use be assessed in all clinical encounters, advice to quit be provided to all smokers, and the use of cessation pharmacotherapy be facilitated and encouraged. Recent innovations in cessation pharmacotherapy include combined use, extended use, use in unmotivated-to-quit smokers, and the exploration of individual factors for treatment matching. The last few years also have seen appreciation for the old (cytisine) and enthusiasm for the new (ENDS) as possible modalities for addressing the global tobacco epidemic, the former demonstrating evidence and the latter being widely distributed and promoted, though in need of greater research. Assistance with smoking cessation is a fundamental element of the management of the cardiovascular patient. Cardiovascular specialists have a professional obligation to assist with the initiation of cessation treatment and advance tobacco control efforts, and can play an important role in achieving a smoke-free future.

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Conflicts of interest

Dr J.J.P. and Dr N.L.B. have served as expert witnesses against the tobacco companies in lawsuits, for which they have received fees for the work, and have provided consultation to Pfizer, which makes medications for quitting smoking. Additionally, Dr N.L.B. has served as a consultant to GlaxoSmithKline with respect to smoking cessation medications.

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