Smoking Cessation:
Benefits versus Risks of Using Pharmacotherapy to Quit

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Smoking cessation benefits health and lengthens life expectancy at any age.\textsuperscript{1,2} With that rationale, smoking cessation figures centrally in comprehensive tobacco control initiatives, including the recommendations of the US Preventive Services Task Force and the World Health Organization.\textsuperscript{3,4} The population of the United States has recognized the personal benefits of stopping smoking and, at present, the majority of those who have ever smoked cigarettes have stopped.\textsuperscript{2,5} Public health benefits have been realized. Smoking cessation is a powerful driver of the decline in cardiovascular mortality over the last 4 decades and also of the more recent declines in rates of smoking-caused cancers among men.\textsuperscript{2,6,7}

The decline in smoking over the last four decades reflects the combined effects of multiple factors, including the widespread recognition of the adverse health consequences of smoking, clean indoor air laws and regulations, the general denormalization of tobacco smoking, rising prices, and the promotion of cessation; the latter has been accomplished through education, engagement of the health care community, quitlines, and use of various therapies, including pharmacotherapy, to increase the success of quit attempts. Nicotine-replacement therapy (NRT), launched as nicotine gum in 1984, was the first pharmacological therapy for cessation to be approved by the FDA. Subsequently, other forms of NRT were licensed including the patch, lozenges, inhaler, and nasal spray. NRT was switched to over-the-counter (OTC) access in 1996. Following NRT, bupropion, an anti-depressant, was shown to be an effective smoking cessation therapy and released as Zyban® (GlaxoSmithKline) in 1997. The most recently licensed pharmacological agent for smoking cessation is varenicline, licensed as Chantix® (Pfizer) in the United States in 2006. The mechanisms of action for these three medications differ; NRT by directly replacing the nicotine in tobacco products; bupropion by mitigating symptoms of withdrawal; and varenicline by acting as a partial nicotine agonist. Each
of these medications, used in conjunction with appropriate counseling and support, increases the likelihood of sustained cessation; in a 2013 meta-analysis, bupropion and NRT approximately doubled quit rates while varenicline had a significantly higher success rate, almost three-fold that of placebo⁸. Each of these agents has also been linked to diverse adverse effects, including recent and controversial concerns for cardiovascular disease (CVD) risk⁹,¹⁰.

In this issue of Circulation, Mills and colleagues report findings of a network meta-analysis on risks for cardiovascular events associated with these three medications.¹¹ Their analytical approach facilitates a full utilization of available data, making an assessment possible of the comparative risks for cardiovascular events between the three therapies. Their findings are clear: neither bupropion nor varenicline was associated with increased risk for all CVD events versus placebo, while there was significantly increased risk associated with NRT (RR=1.81, 95% credible interval 1.35-2.43). As would be anticipated, the network meta-analysis showed lesser risk for CVD events in association with bupropion and varenicline compared with NRT. An exploratory analysis showed that the excess risk associated with NRT reflected “less serious events”, and not major adverse cardiovascular events (MACE).

These findings concerned with relative risk for adverse events need interpretation with consideration of the ways that smoking increases risk for CVD and also of the temporal pattern of changes in risk for CVD after smoking cessation. Major mechanisms by which smoking contributes to risk for CVD include: (1) endothelial dysfunction, (2) a prothrombotic effect, (3) inflammation contributing to atherogenesis, (4) altered lipid metabolism, (5) increased demand for myocardial oxygen and blood, and (6) decreased supply of myocardial blood and oxygen.²,¹² Of these mechanisms, several—endothelial cell dysfunction, the prothrombotic consequences, and oxygen demand—can reverse over months, while smoking’s contribution to atherosclerosis
is relatively fixed. Reflecting these mechanisms, the temporal pattern of risk for CVD in former smokers, compared with continuing smokers, shows a relatively immediate decline of about 50% over the first year after successful cessation and a continuing decline over the next decade approximately.¹¹,¹³ While the evidence considered in the systematic review was limited, after excluding studies with only 12 months of follow-up the increased risk for all CVD events associated with NRT was increased to 3.03 (95% credible interval 2.04-4.67).

This temporal pattern of increased risk associated with NRT is not readily explained by understanding of the mechanisms by which nicotine may contribute to increasing CVD risk.¹² Some pharmacologic consequences during the period of nicotine administration could increase risk for CVD; i.e., as a sympathomimetic agent nicotine increases heart rate and cardiac contractility, and acutely increases blood pressure and constricts coronary arteries. It may also contribute to endothelial dysfunction and metabolic abnormalities. Such effects would not be anticipated to extend beyond the period of NRT therapy. In the trials included in the systematic review, therapy was only of a few months duration in most and only two involved nicotine administration over 52 weeks. Thus, the increase in risk substantially after NRT was discontinued cannot be readily explained based on understanding of nicotine’s pharmacological effects. The finding of decreased risk for MACE associated with bupropion also cannot be readily interpreted as to biological plausibility.

Could the findings be an artifact of the analytical method? A network meta-analysis leads to inferences that are based on both direct comparisons of one agent to another and on indirect comparisons.¹⁴ The evidence reviewed by Mills and colleagues includes only six direct comparisons among the three agents, and a comparison of the direct and indirect evidence, e.g., the coherence, is not provided by the authors. Given the sparse outcome data, further probing
with sensitivity analysis might be informative as to the studies that are driving the key findings for NRT.

The findings also need to be interpreted in a population framework that extends beyond the relative risks for individual smokers,\textsuperscript{15} the target of the systematic review and meta-analysis by Mills et al. Smoking cessation has benefits for population health that extend beyond CVD; the increased risk for CVD associated with NRT needs to be placed within the declines in risk for CVD and other diseases that follow successful cessation. For example, Apelberg et al. (2010) modeled the potential benefits of increased NRT use in the United States with and without the assumption of increased risks associated with therapy for CVD, lung and other smoking-related cancers, and all-cause mortality.\textsuperscript{16} Even with the assumption of a maintained excess risk associated with NRT, the population-level benefits far exceeded the estimated increase associated with NRT. The findings of the Lung Health Study, a randomized trial involving people with asymptomatic airway obstruction, that used nicotine gum, are also relevant to the findings of Mills et al.\textsuperscript{17} On follow-up at up to 14.5 years, all-cause mortality was significantly lower in the intervention arm and CVD mortality was comparable in the intervention and control groups. The 2010 report of the Surgeon General concluded that: “The use of nicotine or other medications to facilitate smoking cessation in people with known cardiovascular disease produces far less risk than the risk of continued smoking.”\textsuperscript{12}

Again, from the population perspective, with multiple pharmacotherapies available to enhance quitting, the mix of therapies used should be optimized to achieve the highest overall rate of successful cessation for the population. Clinical experience indicates that therapy should be tailored for individuals. Additionally, as understanding of the genetic basis for nicotine addiction advances, the therapeutic approach to cessation may be further individualized and
NRT, bupropion, varenicline or another agent may be determined to be the “best” pharmacotherapy for particular smokers.

The findings of the review by Mills et al. do support their overall conclusion that “Smoking cessation therapies do not appear to raise the risk of serious CVD events.” and, of course, “Physicians often weigh the benefits and risks of available treatments, including cessation pharmacotherapies.” The findings of Mills et al. highlight the difficulty of characterizing adverse effects of pharmacotherapies, even relatively common events such as CVD. The pooling of 63 trials provided only an imprecise and uncertain picture of the potential adverse consequences of pharmacotherapy for smoking cessation. Trial data are problematic for identifying adverse events because of the limitations of sample size and population selection.

The evidence is not of sufficient strength to warrant reconsideration of guidelines, particularly when underlying mechanisms are considered. Given the number of smokers who will quit with pharmacotherapy, we need better information on any risks that they may face from the drugs used to increase the success of cessation. Additionally, if nicotine delivery products other than combustible tobacco products, e.g., electronic cigarettes, come into widespread usage, the long-term consequences of nicotine alone will assume increasing significance.

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