

Smoking cessation: lessons learned from clinical trial evidence

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Purpose of review

Cigarette smoking and exposure to secondhand smoke cause coronary heart disease. Cessation dramatically reduces the incidence of primary and secondary cardiac events. The review presents up-to-date information regarding nicotine dependence, recent findings related to its treatment, and recommendations for addressing smoking cessation for the primary and secondary prevention of coronary heart disease.

Recent findings

Bans on smoking in public places are associated with significant reductions in the incidence of acute myocardial infarction. Counseling and pharmacotherapy (nicotine replacement therapy, bupropion) are proven, effective treatments for nicotine dependence. Clinical trials of two new pharmacotherapies, varenicline and rimonabant, have recently been reported. Varenicline is a safe and efficacious medication for smoking cessation, and has been approved in the US, Canada and Europe. Rimonabant has shown mixed results for smoking cessation and is undergoing further evaluation.

Summary

All patients should be screened for tobacco use. Clinicians can effectively treat nicotine dependence in the general population using counseling and first-line pharmacotherapies (nicotine replacement therapy, bupropion, varenicline). These same treatments, with some modification, are appropriate for smokers with coronary heart disease; however, brief interventions without follow-up are not effective in this population. For smokers with coronary heart disease, the best time to intervene may be during hospitalization.

Keywords

counseling, intervention, medications, nicotine dependence, smoking cessation

Abbreviations

ACS	acute coronary syndrome
CHD	coronary heart disease
CI	confidence interval
NRT	nicotine replacement therapy
OR	odds ratio

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Introduction

Coronary heart disease (CHD) is the most common cause of morbidity and mortality in the developed world [1,2], and smoking is the most potent modifiable CHD risk factor [3]. Thirty percent of CHD deaths are attributable to smoking [4]. Smoking is associated with a three-fold greater risk of nonfatal myocardial infarction [5] and a two- to five-fold increase in the risk of sudden cardiac death [4]. Not only smokers are at risk – exposure to secondhand smoke has immediate adverse effects on the cardiovascular system and causes CHD [6**]. Case-control and cohort studies carried out in multiple populations consistently indicate about a 25–30% increase in risk of CHD from exposure to secondhand smoke [6**]. Detrimental effects of smoking and secondhand smoke on the cardiovascular system include increased blood coagulability, platelet aggregation and thrombus formation, reduced oxygen delivery, increased oxidative stress and vascular inflammation, coronary vasoconstriction and increased myocardial work [7–11].

Quitting smoking reduces heart disease risk to that of a nonsmoker 3–5 years after cessation [12,13]. Laws to reduce secondhand smoke exposure are associated with rapid reductions (11–40%) in hospitalizations for acute myocardial infarction [14,15*,16]. In smokers with existing CHD, quitting smoking is associated with a 32% reduction in nonfatal reinfarction risk and a 36% reduction in mortality risk [17]. Quitting smoking reduces mortality risk more than other secondary prevention measures such as statins, aspirin, β -blockers or angiotensin-converting enzyme inhibitors [17]. Without intervention, most smokers hospitalized with CHD will be smoking 1 year later [12,18,19].

The review will present up-to-date information regarding nicotine dependence, recent findings related to its treatment, and evidence-based recommendations for addressing smoking cessation for the primary and secondary prevention of CHD.

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Nicotine dependence

Nicotine dependence, typically in the form of regular cigarette smoking, is characterized by a loss of behavioral control and compulsive drug-seeking behavior [20]. Nicotine in tobacco smoke plays a central role in nicotine dependence [20], assisted by conditioned reinforcers present in the smoke [21] and other cues/stimuli in the smoker's environment [22]. When inhaled in cigarette smoke, nicotine travels quickly to the midbrain where it interacts with nicotinic acetylcholine receptors triggering dopamine release in the mesolimbic system, which provides the smoker with a pleasurable sense of reward [20,22]. Chronic intake of nicotine from cigarettes causes changes to the neural circuits in the midbrain increasing the 'drive' to smoke following periods of abstinence, accentuated by the presence of specific environmental cues [22]. Smokers frequently experience a range of unpleasant mood and physical symptoms (e.g. irritability, nervousness, increased appetite, depression, difficulty concentrating), referred to as tobacco withdrawal syndrome, when they cannot smoke [22,23]. Psychological and social factors also contribute to nicotine dependence. Many smokers believe that smoking helps them manage stress, anxiety and/or boredom. They may enjoy the company of other smokers and associate smoking with other pleasurable activities.

Treatments for smoking cessation

Given the complex physiological, psychological and social forces underpinning nicotine dependence, many smokers have difficulty addressing their addiction. From a population perspective, 95–97% of smokers who make unaided quit attempts will relapse to smoking within 1 year [24]. Smokers with CHD have higher spontaneous quit rates, yet, without assistance, most will be smoking 1 year following CHD-related hospitalization [12,18,19]. Numerous meta-analyses of randomized controlled trials have demonstrated that behavioral counseling and pharmacotherapy, used either alone or in combination, improve long-term quit rates compared with no treatment or placebo [25–29,30**,31**]. Quit rates are highest when counseling and pharmacotherapy are combined [25,28]. With the most efficacious behavioral and pharmacological approaches in the primary care setting, quit rates in the 10–25% range at 1 year are typical. In contrast, among smokers hospitalized with CHD, interventions for smoking cessation can boost quit rates at 1 year to 35–70%.

Behavioral counseling

Three components of behavioral counseling for smoking cessation have been found to be effective: (1) skills training, (2) intra-treatment social support and (3) extra-treatment social support [25]. Skills training includes teaching smokers how to prepare for quitting, and how to cope effectively with internal states (e.g. stress,

boredom) and external situations (e.g. other smokers, social situations) that increase risk for relapse [32]. When provided as an adjunct to pharmacotherapy, skills training should include teaching about the proper use of cessation medications [33]. Intra-treatment social support consists of providing encouragement and supporting confidence in the smoker's ability to quit. Extra-treatment social support includes assisting people to seek out and request support from others, and information about supportive community programs and services [32].

While even a single occasion of brief counseling from a health professional has a significant effect over no counseling in smokers without CHD [27], brief interventions without some follow-up contact are not effective in CHD patients [34,35**]. Generally, there is a strong dose–response relationship between treatment intensity and abstinence from smoking [25,35**]. Person-to-person treatment sessions lasting at least 10 min per session for four or more sessions, providing total contact time of at least 30 min, are particularly efficacious in the primary care setting [32]. A recent meta-analysis showed behavioral counseling with several follow-up contacts and lasting more than 4 weeks after initial intervention is more effective than brief intervention [12 trials, pooled odds ratio (OR) 1.98, 95% confidence interval (CI) 1.49–2.65] in patients with CHD [35**]. [Where cessation is the outcome, the OR is defined as (number of quitters in treatment group/number of smokers in treatment group)/(number of quitters in control group/number of smokers in control group). The OR will be greater than 1 if people have been more likely to quit in the treatment group.] Both in-person (10 trials, OR 1.65, 95% CI 1.28–2.13) and telephone-based counseling (11 trials, OR 1.58, 95% CI 1.26–1.98) are effective [35**]. There is good evidence that a variety of healthcare clinicians (e.g. physicians, psychologists, nurses and pharmacists) can effectively deliver smoking cessation treatment [25,36]. Interventions commenced during hospitalization in cardiovascular disease patients are more effective than those commenced following hospitalization [36].

Pharmacotherapy

Three types of pharmacotherapy have been specifically approved to aid smokers attempting to quit: nicotine replacement therapy (NRT), bupropion (Zyban) and varenicline (Champix in the EU and Canada; Chantix in the US).

Nicotine replacement therapy

NRT reduces the severity of the tobacco withdrawal symptoms associated with stopping smoking by replacing nicotine in the blood. It is important to realize that patients receiving NRT have levels of nicotine in their system that are dramatically below those which would be

achieved by smoking. NRT delivers nicotine slowly into the venous system and a steady state is achieved. (When smoking, nicotine is absorbed quickly across the alveolar membrane and very high arterial levels of nicotine are rapidly attained.) NRT is available as chewing gum, skin patches, nose spray, inhalers and lozenges/tablets; not all forms have been approved in all countries. Longer-acting NRT products such as the skin patch provide moderate blood nicotine levels with good compliance, whereas the other short-acting products (gum, nasal spray, inhaler, lozenge/tablet) offer the potential for greater dose control and the ability to prevent relapse by allowing the former smoker to titrate nicotine in order to forestall the development of withdrawal symptoms [37]. Typically, patients initiate NRT on the quit date and continue on therapy for 8–12 weeks. The effectiveness of NRT has been reviewed many times; the most recent systematic review and meta-analysis were completed in 2004 [26]. The pooled OR of abstinence for any form of NRT relative to control was 1.77 (103 trials, 95% CI 1.66–1.88). There is no clear evidence that one form of NRT is more effective than another; however, combinations of different forms of NRT are somewhat more efficacious than monotherapy [26].

Three clinical trials have examined NRT in participants with stable cardiac disease [38–40]. None of the studies found evidence of increased ischemia or adverse cardiovascular events when active NRT patch was compared with placebo. These studies excluded patients with acute coronary syndrome (ACS). A recent retrospective study provides preliminary evidence that NRT is safe for smokers with ACS. Meine *et al.* [41] evaluated 194 smokers who were admitted with ACS and received transdermal NRT. After propensity-matched analysis, they found no difference in 7-day, 30-day or 1-year mortality in patients who did or did not receive NRT. The American College of Cardiology and the American Heart Association guidelines for the management of patients with ST-elevation myocardial infarction recommend pharmacotherapy (including NRT), commenced at the time of hospital discharge, along with counseling and formal cessation programs for patients recovering from ST-elevation myocardial infarction [42].

Bupropion

Bupropion is an atypical antidepressant that reduces urges to smoke and the severity of other tobacco withdrawal symptoms. Its effectiveness for smoking cessation is independent of its effects on depression and it can be used in people without a history of depression or depressive symptoms during smoking abstinence [31**]. It is thought to work through its dopaminergic effects on pleasure and reward pathways in the midbrain, and its antagonistic effects on nicotinic acetylcholine receptors [33]. Dosing for smoking cessation is 150 mg once a day

for 3 days increasing to 150 mg twice a day continued for 7–12 weeks. The quit attempt is generally initiated 1 week after starting pharmacotherapy [31**]. Bupropion is contraindicated in those predisposed to seizures (dose-related, particularly in those with a history of seizure activity, bulimia or anorexia, or recent head injuries), using a monoamine oxidase inhibitor and any who are taking other forms of bupropion. When used as the sole pharmacotherapy, bupropion doubles the odds of cessation (31 trials, OR 1.94, 95% CI 1.72–2.19) [31**]. In these studies, the control group quit rate averaged 10% while the bupropion quit rate averaged 19%. There is insufficient evidence that adding bupropion to NRT provides an additional long-term benefit [31**]. A clinical trial of the safety and efficacy of bupropion for 248 smokers hospitalized for acute cardiovascular disease was recently reported [43*]. Bupropion improved short-term but not long-term smoking cessation rates over intensive counseling. Bupropion and placebo groups did not differ in cardiovascular morbidity and mortality at 1 year.

Varenicline

Varenicline is an $\alpha_4\beta_2$ nicotinic acetylcholine receptor partial agonist recently approved for smoking cessation treatment. Varenicline partially stimulates the receptors (producing some of the effects associated with smoking and forestalling the emergence of withdrawal symptoms) while at the same time blocking the receptor and preventing any 'benefit' that might occur with exposure to nicotine. The drug is started at a dose of 0.5 mg/day and titrated over the course of several days to a dose of 1 mg twice daily. Four studies examining the efficacy of varenicline for smoking cessation have been published in the past year [44,45,46*,47*]. All studies showed varenicline was significantly more efficacious than placebo for long-term abstinence. The pooled OR for continuous abstinence at 12 months for varenicline vs. placebo was 3.22 (95% CI 2.43–4.27) [30**]. Across these studies, the control group quit rate averaged 8% while the varenicline quit rate averaged 21.4%. The pooled OR for varenicline vs. bupropion was 1.66 (95% CI 1.28–2.16) [30**]. In another trial, 24 weeks of varenicline treatment was superior to 12 weeks for the purposes of maintaining smoking abstinence [48]. A trial evaluating varenicline in patients with stable cardiovascular disease is currently underway [30**].

Comparative efficacy

The comparative efficacy of NRT, bupropion and varenicline for smoking cessation was assessed in a recent systematic review and meta-analysis [29]. Randomized trials evaluating smoking cessation outcomes at 1 year with biochemical validation were included. Results indicate that NRT (70 trials, OR 1.71, 95% CI 1.55–1.88), bupropion (12 trials, OR 1.56, 95% CI 1.10–2.21)

and varenicline (four trials, OR 2.96, 95% CI 2.12–4.12) all provide therapeutic effects in assisting with smoking cessation. There was no difference in 1-year cessation rates when bupropion was compared to NRT; however, existing comparisons show varenicline was superior to bupropion (three trials, OR 1.58, 95% CI 1.22–2.05). The superiority of varenicline needs to be confirmed in future independent studies.

Other novel compounds

Results of phase III trials for rimonabant, another compound for the treatment of smoking cessation [49], were released recently. Rimonabant is a selective cannabinoid receptor-1 blocker that appears to decrease nicotine-seeking behaviors among dependent smokers [20]. Two large, multicenter trials have been completed [STRATUS (Studies with Rimonabant and Tobacco Use)-US and -EU]. In both trials, 10 weeks of rimonabant 5 and 20 mg were tested against placebo. In the STRATUS-US study, quit rates at the end of treatment were 28% for the 20-mg, 16% for the 5-mg and 16% for placebo groups. Quit rates in the 20-mg and placebo groups were significantly different [50]. In the STRATUS-EU study, the corresponding quit rates were reportedly 25, 24 and 20%; they were not significantly different [20]. Currently, rimonabant has not been approved for smoking cessation; however, additional trials are underway.

Recommendations for addressing smoking cessation for the primary and secondary prevention of coronary heart disease

At the patient level, the principles of effective nicotine dependence treatment remain the five 'A's: ask about tobacco use, advise to quit, assess willingness to quit, assist with counseling and pharmacotherapy, and arrange follow-up support and assistance [25]. These principles apply to both the primary and secondary cardiac care settings.

Clinicians should ask about patients' tobacco use over the past 6 months and document this information in the patient chart. This will help identify not only current users, but those who may have quit recently and be at increased risk for relapse over the next few months. All tobacco users should be advised to quit in a clear, unambiguous manner.

The type of assistance provided to smokers will vary depending on the presence or absence of CHD and, for those with CHD, disease stability. In the primary prevention setting, clinicians can effectively assist smokers using brief or more intensive counseling and first-line pharmacotherapies (nicotine replacement therapy, bupropion, varenicline) selected on the basis of patient preference and the presence or absence of

specific contraindications. For smokers hospitalized with acute CHD, intervention for smoking cessation should commence during the period of hospitalization. Regarding pharmacotherapy, there is clinical trial evidence that bupropion is safe in patients hospitalized with CHD; however, there is no evidence for its long-term efficacy in helping patients achieve abstinence. Bupropion may take several days to reach levels sufficient to reduce the symptoms of tobacco withdrawal. NRT can be commenced immediately in hospitalized patients with stable CHD (e.g. those admitted for diagnostic catheterization, elective percutaneous coronary intervention, elective coronary artery bypass grafting surgery). In patients with ACS, NRT would typically commence at the time of hospital discharge if blood pressure and heart rate are stable. Knowledge of the pharmacodynamics of nicotine, the development of tolerance to its effects among smokers, and an understanding that nicotine delivered by NRT patches enters the venous system at levels markedly lower than those produced in the arterial system by the inhalation of tobacco smoke and produces lesser effects with respect to increasing myocardial work or coronary vascular resistance provide a theoretical basis for its use in any situation in which a smoker may continue smoking [8]. Selected ACS patients may be candidates for NRT commenced during the hospital stay if they are experiencing serious withdrawal symptoms and are unable to abstain from smoking. For smokers with CHD, brief counseling interventions without some follow-up contacts are not effective. If the patient is not willing to quit smoking, counseling should focus on the pros and cons of continued smoking vs. cessation, considering the reason for hospitalization. NRT can be recommended for patients experiencing serious withdrawal symptoms, as described above.

Clinical practice guidelines have stressed the importance of healthcare 'system' changes to institutionalize nicotine dependence treatment rather than relying solely on clinicians to take action [25,51]. Clinicians need to create a system to help smokers obtain the quitting assistance they need [52]. Examples of how such a system can be created to promote smoking cessation during hospitalization for CHD have recently been described [53].

Conclusion

In summary, smoking cessation strategies should be implemented in every professional setting for patients who smoke. The development of a systematic approach to the identification and treatment of such smokers will, predictably, have a significant effect on reducing smoking and dramatically reducing otherwise unacceptably high risks of primary cardiac events and recurrence or complication in patients with existing CHD.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 380–381).

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