Nicotine Replacement Therapy and Cardiovascular Disease

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Smoking is a well-established and important risk factor for cardiovascular disease. Cessation of smoking clearly decreases the chances of a first or subsequent cardiovascular event. Nicotine replacement therapy (NRT) is a proven adjunctive therapy to increase the probability of quitting smoking. Anecdotal reports of adverse events in patients using NRT have led some to question its safety. Is nicotine, whether in tobacco products or in NRT, the cause of the cardiovascular consequences associated with tobacco use? Is using NRT to assist with smoking cessation safer than smoking? Should health care professionals avoid recommending NRT for patients with established cardiovascular disease? This article summarizes the mechanisms of harm associated with smoking and reviews the safety of NRT in both the general population and the population with cardiovascular disease. Recommendations for NRT use are offered.


More than 40 years ago the first US Surgeon General’s report on smoking and health was released. It stated, “Cigarette smoking is a health hazard of sufficient importance in the United States to warrant appropriate remedial action.” Since the release of this document, half of all living adults who ever smoked have stopped. In addition, the smoking rate among adults declined from nearly 50% in 1965 to close to 23% in 2002.

Despite major progress, tobacco use is still the leading preventable cause of death in the United States. Almost one fourth of Americans, 46.2 million, continue to smoke. Smoking-related illnesses will affect 8.6 million people, and 440,000 will die each year as a result of tobacco use. Cigarette smoking causes an estimated 1 of 5 deaths in the United States each year. More deaths are caused each year by tobacco use than the total deaths caused by human immunodeficiency virus, illegal drug use, alcohol use, motor vehicle crashes, suicides, and homicides combined.

Smoking is a well-established risk factor for cardiovascular disease. Smokers have a 2-fold to 4-fold increased risk of coronary heart disease. Cerebrovascular accidents occur twice as often in smokers compared with nonsmokers. The incidence of peripheral arterial disease increases 10-fold in those who smoke. A multitude of studies have linked smoking cessation with reduced risk of cardiovascular events. In patients with coronary disease, smoking cessation has been shown to improve survival and decrease the incidence of myocardial infarction.

Nicotine replacement therapy (NRT) is a well-established and successful adjunctive therapy to increase the probability of quitting smoking. The nicotine patch, nicotine inhaler, and nicotine gum have been shown to approximately double long-term abstinence rates compared with placebo. Nicotine replacement therapy has greater success in combination with intense counseling. The combination of more than 1 nicotine replacement product (such as patch plus gum) has been shown to improve long-term abstinence rates compared with monotherapy.

Nicotine is known to be the addicting component of tobacco products. Is nicotine, whether in tobacco products or in NRT, the cause of the hemodynamic and cardiovascular consequences associated with long-term tobacco use? Is using NRT to assist with smoking cessation safer than smoking? Should health care professionals avoid recommending NRT for patients with established cardiovascular disease?

This article reviews and compares the mechanisms of harm associated with the use of tobacco and NRT. The safety and benefits of NRT both in the general population and in patients with cardiovascular disease are discussed and recommendations given.

MECHANISMS OF HARM WITH TOBACCO USE AND NRT

Long-term cigarette smoking is known to contribute to adverse myocardial events in several ways. Smoking causes increased platelet aggregation and thrombus formation, increased myocardial workload, and increased carbon monoxide levels, resulting in less oxygen delivered to the heart, coronary vasos constriction, and catecholamine release. Additionally, smoking causes inflammation and oxidative injury, leading to endothelial dysfunction.

Smoking is associated with thrombus formation due to increased platelet aggregation. This is thought to be an important factor in acute coronary and other arterial vascular events. Platelet activation occurs immediately after smoking a single cigarette. For long-term smokers, a substantial number of activated platelets are constantly present in the circulation. Studies of smokers who use NRT in the...
form of the gum and patch have concluded that NRT does not result in the platelet aggregation and the thrombotic effects known to be associated with smoking. Benowitz et al compared the thrombotic effect of cigarette smoking, transdermal nicotine, and placebo on platelet activation and increased plasma fibrinogen levels. They concluded that the nicotine in the transdermal patch was not responsible for platelet activation or elevated fibrinogen levels.

In otherwise healthy people, smoking a cigarette increases myocardial workload by activating the sympathetic nervous system, thus increasing heart rate, blood pressure, stroke volume, and cardiac output. Nicotine replacement therapy has been postulated to have similar effects that could result in an increase in myocardial oxygen consumption and the possibility of ischemia in patients with cardiovascular disease. Several studies of nicotine gum and patch therapy indicate that these drugs, when used in recommended dosages, have less sympathetic stimulatory effects than smoking in long-term smokers. Lucini et al compared the heart rate and systolic blood pressure response to smoking, nicotine patch therapy, and placebo patch. They found that cigarette smoking had the most significant effect on both heart rate and blood pressure. Nicotine patch therapy had autonomic effects greater than the placebo patch; however, it produced only minor disturbances in autonomic cardiac control. Blann et al analyzed the influence of smoking and transdermal nicotine on blood pressure and hemato logic and coagulation indices in a group of 18 smokers without known cardiac disease as they attempted to stop smoking. They found that oral and/or transdermal nicotine did not influence blood pressure or hemato logical and coagulation indices. Tzivoni et al evaluated the effects of nicotine patch therapy in 106 patients with coronary artery disease who smoked. They found no aggravation of myocardial ischemia or arrhythmias in these patients.

Carbon monoxide is present in the inhaled component of cigarettes. It is thought to be harmful in part because it reduces available myocardial oxygen. The increase in carbon monoxide levels may possibly contribute to an increased potential for arrhythmias by inducing myocardial ischemia. Mall et al concluded that higher levels of carboxyhemoglobin were associated with a worsening course of acute ischemic heart conditions, even when nicotine from cigarette smoking was no longer present (measured 6 hours after hospital admission). Carbon monoxide levels are not affected by NRT.

Cigarette smoking results in coronary vasoconstriction and decreases in coronary blood flow in patients with coronary artery stenosis. The nicotine component of cigarettes has been suggested to cause coronary vasoconstriction. Studies of nicotine gum and nasal spray have not supported these assumptions in smokers. Nitenberg and Antony found no change in cardiac vessel dimensions in former smokers with coronary artery disease when nicotine gum was chewed. Keeley et al found that additional nicotine in the form of nicotine nasal spray did not further increase myocardial ischemia in long-term cigarette smokers undergoing cardiac catheterization for evaluation of chest pain.

Nicotine-induced sympathetic stimulation may result in myocardial ischemia and arrhythmia potentiation. Nicotine causes catecholamine release and increased heart rate and blood pressure that may result in myocardial ischemia, especially if coronary stenosis is present. Several authors have analyzed the autonomic effects of transdermal administration of nicotine in long-term smokers and found that nicotine patch therapy produced only minor disturbances of autonomic cardiac control. The previously cited single-blind, crossover, placebo-controlled study by Lucini et al found that high-dose transdermal nicotine along with cigarette smoking had no additional adverse effects on heart rate, blood pressure, fibrinogen levels, or lipid profiles in long-term smokers. These parameters were similar between doses of transdermal nicotine ranging from 21 to 63 mg and smoking alone. Transdermal nicotine at the 21-mg dose had less immediate hemodynamic effects and little or no procoagulant effect compared with smoking. The cardiovascular effects of nicotine seem to be less pronounced in long-term smokers as a result of apparent development of tolerance.

Nicotine patch therapy may actually decrease exercise-induced ischemia in smokers with coronary artery disease. Mahmarian et al analyzed the effects of nicotine patch therapy in a group of smokers who completed stress tests. This cohort continued to smoke while using the nicotine patch. The investigators measured exercise-induced myocardial ischemia in 40 heavy smokers (more than 1 pack per day) with coronary artery disease who had greater than 5% exercise-induced reversible perfusion defects at baseline. They observed serial changes in total and ischemic myocardial perfusion defect size at baseline, while patients were smoking, and when using treatment with 14- or 21-mg nicotine patches. Use of the nicotine patch was found to result in reduced exercise-induced ischemia, despite significantly higher serum nicotine levels. Smoking cessation using the nicotine patch correlated to increased time to exercise-induced electrocardiographic ischemia.

Inflammation and oxidative injury are emerging as mechanisms in the initiation and propagation of the atherosclerotic process. A recently published population-based, cross-sectional study showed that male smokers had higher white blood cell counts, fibrinogen levels, plasma viscosity, and high-sensitivity C-reactive protein levels than patients who had never smoked. In that study, the only
significant marker of inflammation in female smokers was an elevated white blood cell count. However, others have shown elevated levels of inflammatory markers in female smokers compared with nonsmoking women. There is also evidence that smoking increases vascular production of free radicals, such as superoxide. These react with nitric oxide to decrease its availability, thereby impairing endothelium-dependent vasodilation and promoting other processes that accelerate atherosclerosis. Whether NRT contributes to endothelial dysfunction by these mechanisms is unknown.

CONCERNS ABOUT NRT RISK

Case reports published in the early 1990s generated concern about NRT safety and suggested a possible causal relationship between NRT and vascular events. Soon after the nicotine patch was approved as an agent to assist with smoking cessation, an article that linked the nicotine patch with cardiovascular risk was published in the Wall Street Journal. This report cited 5 people who experienced cardiac events allegedly associated with combining 2 “high nicotine products.” Since the Wall Street Journal publication, other case reports published as recently as 2001 have implicated NRT as the possible cause of cardiac and other vascular untoward events. These events included acute myocardial infarction in patients with no prior cardiac history or significant risk factors besides tobacco use, coronary spasm, aortic dissection, vasculitis, intracranial vasospasm, and intracerebral hemorrhage.

When evaluating these anecdotal reports, it is important to understand that smokers, whether using NRT or not, have an increased risk compared with nonsmokers of all the cardiovascular events reported. Randomized controlled studies have failed to support the association between nicotine patch therapy and acute cardiovascular events, even in patients who continue to smoke. This “rumor” of causality related to NRT and cardiovascular events continues to be present in the public and in the medical community.

SAFETY OF NRT IN SMOKERS WITHOUT KNOWN CARDIOVASCULAR DISEASE

What is known about the safety of NRT? Nicotine replacement products have been researched extensively and have been found to be safe and effective pharmacological support for tobacco dependence. A meta-analysis of 34 randomized controlled trials of tobacco cessation with NRT included 28 trials that specifically excluded participants with cardiovascular disease or risk factors. The authors concluded that there was no difference in cardiovascular complications between smokers who were using nicotine patches (n=5501) and those who received placebo patches (n=3752). However, the number of cardiovascular events in that study was low because of the population studied. An extensive population-based, case-control study also found no association between over-the-counter nicotine patch use and an increased risk of myocardial infarction. A small group of nicotine patch users in that study continued to smoke but had no increased risk of myocardial infarction.

SAFETY OF NRT IN SMOKERS WITH KNOWN CARDIOVASCULAR DISEASE

Many studies evaluating the safety and efficacy of NRT have excluded patients with cardiovascular disease. Two major studies have included participants with cardiovascular diagnoses and found no increased risk of cardiovascular disease in smokers who used NRT. The Working Group for the Study of Transdermal Nicotine in Patients With Coronary Artery Disease (n=156) and a study by Joseph et al (n=584) determined there was no significant increase in cardiovascular events in 2 high-risk populations with cardiac disease when nicotine patch users were compared with placebo patch users. These landmark studies excluded patients with symptoms of acute coronary syndrome within 12 weeks of randomization and 2 weeks of randomization, respectively. These findings contributed to the recommendation from the 2000 Clinical Practice Guidelines to use nicotine replacement products with caution among particular cardiovascular patient groups: those “in the immediate (within 2 weeks) postmyocardial infarction period, those with serious arrhythmias, and those with serious or worsening angina pectoris.” A continuing question remains concerning the safety of nicotine replacement when used during the first several weeks after an acute coronary event. No large randomized controlled trials have included this patient population. However, no clinical evidence exists that the use of NRT is detrimental in this setting.

RECOMMENDATIONS FOR SMOKING CESSATION USING NRT

The 2000 Clinical Practice Guidelines for treating tobacco use and dependency are the cornerstone for approaching tobacco cessation in clinical practice. Key recommendations for clinicians include the use of the “5 A’s,” designed to be used with smokers who are willing to quit, and the “5 R’s,” an intervention designed to motivate smokers who are not currently willing to quit smoking. Clinical smoking cessation interventions include the following suggested approaches.
TABLE 1. Nicotine Replacement Therapy*

<table>
<thead>
<tr>
<th>Pharmacotherapy</th>
<th>Dose</th>
<th>Administration</th>
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<tbody>
<tr>
<td>Nicotine transdermal patch</td>
<td>7, 14, 21 mg/24 h or</td>
<td>Highest dose daily for 6 wk, then taper. Rotate application sites; avoid hairy areas, open sores, rashes, or bruises</td>
</tr>
<tr>
<td>(Nicoderm CQ, Nicotrol)</td>
<td>5, 10, 15 mg/16 h, OTC</td>
<td>One piece every 1-2 h for 6 wk, then taper. Chew and moisten, then park in buccal mucosa</td>
</tr>
<tr>
<td>Nicotine gum</td>
<td>2, 4 mg, OTC</td>
<td>One piece every 1-2 h for 6 wk, then taper. Moisten, then park in buccal mucosa</td>
</tr>
<tr>
<td>(Nicorette)</td>
<td></td>
<td>Six to 16 cartridges inhaled daily for 6-12 wk, then taper. Puff frequently for 20 min per cartridge</td>
</tr>
<tr>
<td>Nicotine lozenges (Commit)</td>
<td>2, 4 mg, OTC</td>
<td>One piece every 1-2 h for 6 wk, then taper. Moisten, then park in buccal mucosa</td>
</tr>
<tr>
<td>Nicotine inhaler (Nicotrol)</td>
<td>2 mg per cartridge, prescription</td>
<td>One to 2 sprays in each nostril every hour for 8 wk, then taper</td>
</tr>
<tr>
<td>Nicotine nasal spray (Nicotrol NS)</td>
<td>0.5 mg per spray, prescription</td>
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*Nicotine replacement should be dosed at the same level as the patient’s tobacco nicotine intake: 1 cigarette equals an average of 1 mg of nicotine, 1 dip of chewing tobacco equals 3 to 4 cigarettes, and 1 cigar equals 20 cigarettes. Patients should be instructed not to smoke while using nicotine replacement therapy. If relapse occurs, the process should be reinitiated with assessment of relapse cause, establishment of a new quit date, and reevaluation of pharmacological therapy and overall plan. OTC = over the counter.

THE 5 A’S

ASK each patient about smoking and tobacco use at each visit.

ADVISE with a strong clear message to quit tobacco use. Inform, support, and recommend interventions based on an individual’s stage of readiness to quit tobacco use.

ASSESS willingness to quit. Provide motivational intervention (use the “5 R’s” as given subsequently).

ASSIST with a plan to quit using tobacco products. This includes setting a quit date, identifying behavioral assistance and interpersonal support, and recommending pharmacotherapy. Counseling and behavioral therapies are noted to be especially effective and should be used in all patients attempting to quit tobacco use. Be supportive—“We can help you quit.”

ARRANGE for follow-up (telephone call, letter, office visit).

THE 5 R’S

RELEVANCE: Discuss the impact of tobacco use on health and family and the associated social stigma. Help the patient understand why quitting would be personally important.

RISKS: Discuss negative tobacco consequences. Have the patient identify negative health consequences or risks that are personally important.

REWARDS: Discuss benefits of tobacco cessation (health, financial, energy level increase, recovery, role model).

ROADBLOCKS: Ask about barriers to quitting. “What is the one thing that keeps you from quitting?”

REPETITION: Address cessation at each visit. Always remember that this is a process and that your patient can learn from each experience of quitting.

Current recommendations for NRT use are given in Table 1.

Research supports a strong dose-response relationship between the intensity of tobacco dependence counseling and its effectiveness. Most states have toll-free tobacco quit lines that provide education or brief telephone counseling and follow-up, as well as referral to local tobacco cessation support services. Smoking cessation education and support are available through the American Lung Association, American Cancer Association, and local groups sponsored by health care organizations. Comprehensive residential programs for tobacco cessation services are also available at some specialty centers.

In the recent 2004 update of ST-elevation myocardial infarction guidelines, the American College of Cardiology and the American Heart Association recommend pharmacotherapy, including NRT in selected patients, along with counseling and formal cessation programs for patients recovering from ST-elevation myocardial infarction at the time of hospital discharge if blood pressure and heart rate are stable. These guidelines recognize that the nicotine replacement in the form of gum and patches may be preferable to cigarette smoking for those who experience withdrawal symptoms after hospitalization. However, the routine use of NRT during hospitalization of smokers with ST-elevation myocardial infarction is not recommended. No data regarding the safety of this practice yet exist.

CONCLUSIONS

Nicotine replacement therapy is a proven effective pharmacotherapy for smoking cessation. Anecdotal reports of adverse cardiac and vascular consequences resulting from the use of nicotine replacement products have led to cautious use or avoidance in the cardiovascular disease population. People with cardiovascular disease who continue to smoke have an increased risk of myocardial infarction, cerebrovascular accident, and other serious vascular events.
Studies have indicated no increase in cardiovascular events in those who use NRT compared with those who continue to smoke. The benefit of NRT to enhance efforts to quit smoking successfully is clear and convincing, and NRT is even more effective if used in conjunction with other cessation approaches. This proven pharmacotherapy as an adjunctive to brief smoking cessation counseling should be considered in this high-risk group of patients.

REFERENCES