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Cardiovascular Effects of Pharmacologic Therapies for Smoking Cessation

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Abstract

Tobacco dependence is a potent risk factor for cardiovascular (CV) diseases and despite known harms of smoking and benefits associated with smoking cessation, approximately 20% of the adult population with CV diseases or hypertension continue to smoke. Extensive research has demonstrated that nicotine replacement, varenicline, and bupropion sustained-release are superior to placebo for short- and intermediate-term smoking cessation. Due to their mechanisms of action, some smoking cessation therapies have been thought to have the potential to increase CV risk, particularly if the pharmacotherapies are taken while individuals are still smoking. Hence, we have analytically reviewed the literature describing the CV effects of therapies for smoking cessation, particularly as they apply to patients with CV disease.

Keywords

smoking cessation; cardiovascular diseases; tobacco use cessation products; varenicline; bupropion; nicotine replacement

INTRODUCTION

Tobacco dependence is a potent risk factor for cardiovascular (CV) diseases, including coronary heart disease, peripheral vascular disease (PVD), stroke, and aortic abdominal aneurysm.[1] Despite known harms of smoking and benefits associated with quitting, approximately 20% of the adult population with CV diseases or hypertension (HTN) continue to smoke.[2]

National practice guidelines recommend seven pharmacotherapies to aid in quitting, including five nicotine replacement (NRT) therapies, bupropion sustained-release (SR), and

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varenicline (Table 1).[3] Extensive research has demonstrated these therapies to be superior to placebo for short- and intermediate-term smoking cessation.[3] More recently, trials have been conducted in patients with CV disease, to evaluate the benefit- risk profiles.[4–6] Due to their mechanisms of action, some smoking cessation therapies may have the potential to increase CV risk, particularly if patients who still smoke. This review analyzes CV effects of smoking cessation therapies, particularly in patients with CV disease.

NICOTINE REPLACEMENT THERAPY

Mechanisms for Cardiovascular Adverse Effects

Nicotine replacement therapy (NRT) represents a cornerstone of managing tobacco dependence although quit rates on NRT are disappointing (19–27%).[3] Shortly after approval by the FDA in the mid-1980's, reports of atrial fibrillation, myocardial infarction, and stroke associated with NRT use began to surface.[7–9] Subsequently, substantive research was undertaken to characterize the impact of nicotine and NRT on the CV system. Smoking increases CV event risk and through nicotine, increases sympathetic nervous system activity and prothrombosis.[10–13] This results in hemodynamic effects of increased heart rate, blood pressure (BP), and myocardial contractility.[14]

Clinical Data Evaluating Cardiovascular Effects of Nicotine Replacement Therapies

Numerous clinical studies have investigated the CV effects of NRT.[15–27] Some studies show important increases in heart rate (10–15 beats/minute) and BP (5–10 mmHg systolic) following NRT use [15,20,25–27] while others show no effect.[16,17,19,21,23] Zevin and colleagues showed that escalating doses of nicotine patches (21, 42, and 63 mg/24 hours) had no effect on circadian variations of heart rate or BP patterns versus placebo in 12 healthy male smokers.[19] Use of nasal NRT showed a similar pattern compared with cigarette smoking.[23] Tanus-Santos and colleagues reported increases in mean arterial pressure and heart rate with nicotine patches (21 mg/24 hours) in nonsmokers and normotensive smokers, but not in hypertensive smokers.[21] Similar findings of increases in BP and heart rate after dosing of nasal NRT products or gum in healthy, nonsmoking patients have been seen.[15,20]

One explanation for these discordant hemodynamic findings may be that particularly heavy smokers might develop tolerance to the pressor effects of nicotine, resulting in no effects on hemodynamic markers.[28] In addition, while nicotine is a relatively short-acting pressor agent, it is offset by the vasodilatory effects of its major metabolite cotinine, leading to mixed effects on BP.[14] Yugar-Toledo and colleagues showed that the use of nicotine patches (21 mg/24 hours) in heavy smokers who interrupt tobacco consumption slightly increased BP in the early morning and attenuated the reductions in nocturnal pressure compared with placebo.[25] These effects may be related to endothelial dysfunction and require additional study to determine their association to clinical events.

A population-based, case-control study of 3,643 patients at high risk showed no association between nicotine patch use and first myocardial infarction.[29] Moreover, a meta-analysis of 34 randomized controlled trials showed no increase in the risk of myocardial infarction, stroke, palpitations, angina, arrhythmia, or hypertension in nicotine- versus placebo-treated patients.[30] Crude event rates ranged from 0.3–3% in the nicotine group and 0–2% in the placebo group. These investigations suggest that NRT is generally safe for use in smokers wishing to abstain.

Use of Nicotine Replacement Therapy in Patients with Cardiovascular Disease

Given the concerns of NRT safety, a few large clinical trials aimed to evaluate whether NRT is safe in patients with CV disease.[4,5] The Working Group for the Study of Transdermal

Nicotine in Patients with Coronary Artery Disease conducted a 5-week, randomized, double-blind trial of 156 patients with coronary disease who smoked at least 1 pack per day.[4] Patients were randomized to receive nicotine patches (14 to 21 mg/24 hours) or placebo in addition to weekly counseling sessions. There were no differences in the frequencies of angina, arrhythmias, or ST-segment depression (via 24-hour ECGs) between the groups, although smoking cessation was achieved more frequently in the NRT group.

Joseph and colleagues randomized 584 patients from 10 Veterans Affairs hospitals at least 45 years of age who smoked at least 15 cigarettes per day and had a history of CV disease to receive either nicotine patches (7–21 mg/24 hours) or placebo for 10 weeks, with patients monitored for 14 weeks.[5] The primary composite endpoint (death, myocardial infarction, cardiac arrest, and hospitalization due to angina, arrhythmia, or heart failure) occurred in 5.4% of patients receiving NRT and 7.9% of patients receiving placebo, a non-significant difference (p=0.23). Similarly, secondary endpoints, including all-cause hospitalizations and outpatient visits for increased severity of heart disease symptoms, did not differ between groups (p=0.37).

Similar trends have been seen in recent studies. Meine and colleagues showed no difference in 7-day, 30-day, or 1-year mortality between nicotine patch users and nonusers who were admitted for unstable angina or non-ST-segment myocardial infarction.[31] Wolf and colleagues also showed no association between NRT and risk of adverse CV events in the first year following an acute coronary event in a database study of 663 smokers.[32]

The impact of NRT on myocardial ischemia has been evaluated in patients with CV disease. Mahmarian and colleagues assessed the effects of nicotine patches (14 or 21 mg/24 hours) on exercise-induced myocardial ischemia in 40 patients with coronary artery disease who smoked ≥ 1 pack per day and had an abnormal exercise thallium-201 single-photon emission computed tomography.[18] Patients using both the 14 and 21 mg nicotine patches saw significant reductions in total perfusion defect size from baseline versus placebo ($p<0.001$ for both) despite having higher serum nicotine levels ($p<0.001$). NRT also significantly increased the time to exercise-induced ECG ischemia ($p<0.01$).

BUPROPION Sustained-Release

Bupropion SR (Zyban®) was approved for tobacco dependence in 1997 as the first non-nicotine option, although previously available for the treatment of depression. While the mechanism for smoking cessation remains unclear, the drug inhibits the reuptake of norepinephrine and dopamine.[33] Nicotine stimulates the mesolimbic system and the dopamine reward pathway to promote and reinforce the behaviors of smoking; it is thought that bupropion may interfere with this pathway.[34] Although the main side effect of concern with bupropion is a dose-related risk of seizures, CV side effects, mainly HTN, have been reported regardless of pre-existing HTN.[33] The proposed mechanism of action for increasing BP is the effect bupropion has on the reuptake of norepinephrine.

Clinical Data Evaluating Cardiovascular Effects of Bupropion Sustained-Release Therapy

Due to the history of tricyclic antidepressants' propensity to cause adverse cardiac effects, when bupropion became available as an antidepressant several studies evaluated its CV effects particularly on cardiac function and conduction.[35–37] In an initial small study by Roose et al, bupropion (average dose, 445 mg/day) did not significantly impact left ventricular (LV) ejection fraction in a cross-over trial of 10 patients with depression and LV dysfunction.[35] In a follow-up study by the same investigators, 36 patients with heart failure, ventricular premature depolarizations, or bundle branch block were evaluated with bupropion (average 442mg/day) on pulse, ejection fraction, or the PR or QRS intervals.[36]

No significant functional, conduction complications or higher degrees of AV block were noted although patients with baseline ventricular premature depolarizations had a significant reduction in the number of premature depolarizations compared with baseline (−140±144, p<0.0005). The drug was discontinued in five patients, four of which were cardiac in nature including an increase in BP, orthostatic hypotension, and a change in anginal pattern. In an analysis of a series of trials conducted in over 500 patients with depression, bupropion SR 100–400mg daily had no clinically important effects on BP or heart rate compared to placebo.[37] Eight serious adverse events occurred, including HTN in a placebo patient and chest pain in a bupropion patient. One study compared the hemodynamic effects of short term (7 days) bupropion (150mg daily for 6 days then 300mg once), NRT (21mg/day), the combination, or control.[27] Statistically significant increases in systolic blood pressure (SBP) and diastolic blood pressure (DBP) were noted comparing bupropion, NRT, or the combination to control. The maximal increases in the SBP were 17 mmHg, 25 mmHg, and 23 mmHg in the bupropion, NRT, and combination groups respectively while maximal increases in the DBP were 12 mmHg, 11 mmHg, and 11 mmHg in the bupropion, NRT and combination groups respectively. In the control group, the maximal increases in SBP and DBP were 23 mmHg and 11 mmHg, respectively.

Clinical Data Evaluating Use of Bupropion SR for Smoking Cessation in Patients With Cardiovascular Disease

The use of bupropion SR for smoking cessation has been evaluated in several trials in patients with CV disease.[38–40] Rigotti and colleagues performed a randomized trial in 248 smokers hospitalized for acute coronary syndromes, coronary revascularization, or other CV conditions in patients with related coronary artery disease.[38] No differences in BP were seen at 12 weeks compared to placebo nor were there new cases of BP levels >160/100 mmHg and the rate of adverse CV events were similar in both groups. In the intent-to-treat population, CV events were not significantly different at 12 months (Table 2). However a post-hoc analysis of CV events in patients who completed 12 weeks of therapy showed that while 30-day rates did not differ significantly between groups, CV events were greater following 12 months of observation [incidence rate ratio 3.12, 95% confidence interval (CI) 1.01 to 9.65]. The second RCT evaluated 157 smokers hospitalized for acute coronary syndrome, although the trial was stopped early due to a lack of efficacy.[40] At 1-year, there were no deaths and when comparing bupropion to placebo, the percent of patients re-hospitalized (36% vs. 39%), who had a myocardial infarction (3% vs. 1%), acute coronary syndrome (3% vs. 7%) or chest pain (15% vs. 19%) did not differ significantly.

Two trials have evaluated bupropion in the outpatient setting with a CV focus.[39,41] Thase and colleagues evaluated 300 smokers with untreated stage 1 HTN, other CV disorders were excluded. Both SBP and DBP decreased from baseline to day 28 in all treatment groups (bupropion SR 150mg daily, 150 mg twice daily, 200 mg twice daily and placebo) and there were no significant differences in the proportion of patients who experienced a clinically significant increase in BP or change in 24 hour ambulatory BP. A small but significant difference in heart rate occurred on bupropion SR 400mg versus placebo, (difference of 2.9 beats/min, p=0.004). In a large trial by Tonstad and colleagues, 629 smokers with myocardial infarction or interventional cardiac procedures >3 months ago, stable angina, PVD, or heart failure were evaluated on bupropion SR and placebo.[39] Subjects with HTN were allowed to participate if the baseline BPs were <160/100 mmHg. A greater proportion of patients in the bupropion group reported CV adverse events compared to those on placebo (8% vs. 4%), including angina, HTN, and palpitations. There were no significant changes in BP or heart rate.

VARENICLINE

Varenicline, approved in 2006, is a partial and highly selective agonist of the alpha-4-beta-2 nicotinic acetylcholine receptors, which attenuates nicotine withdrawal symptoms while inhibiting the surge of dopamine release. This dopamine suge is believed to reinforce the behavior of smoking.[42,43] Varenicline is also a potent and full agonist at the alpha-7 subunit and a partial agonist at the alpha-3-beta-4 subunit of nicotine acetylcholine receptors.[44] Activity at these subunits may contribute to the CV effects of this drug through parasympathetic and sympathetic stimulation of cardiac neurons, leading to changes in BP, heart rate, cardiac contractility, and myocardial ischemia.[11,45,46]

Clinical Data Evaluating Cardiovascular Effects of Varenicline

One cross-over trial evaluated the effect of varenicline on heart rate variability using time variables on the R-R interval and a ratio to measure sympathovagal balance to quantify autonomic nervous system control of the heart.[45] Thirty healthy subjects (15 smokers and 15 non-smokers) were randomly assigned to receive a single dose of varenicline 2 mg or placebo. Varenicline did not impact any of the variables in the group of smokers ($p>0.05$ for all); in non-smokers there was an increase in sympathetic activity following the dose of varenicline. The authors suggest that down regulation of nicotine receptors and low affinity for the alpha-3-beta-4 and alpha-7 subunits could explain why the same effect was not observed in smokers.

Major clinical trials that have evaluated varenicline for smoking cessation have not routinely reported CV outcomes. Amongst the most common adverse events reported, CV type events were not listed.[47,48] Within two trials, cases of serious CV adverse events were rare and reported as atrial fibrillation, possible stroke, chest pain, and acute coronary syndrome.[47,48] One trial evaluating 24 weeks of varenicline therapy reported that there were no changes in BP from baseline compared with placebo and while the mean pulse remained similar in the varenicline group, it decreased by 2 beat per minute in the placebo group.[49]

Clinical Data Evaluating Use of Varenicline for Smoking Cessation in Patients with Cardiovascular Disease

Varenicline was evaluated in a randomized trial of 714 smokers with stable CV disease (a history of myocardial infarction, coronary revascularization, angina pectoris, peripheral arterial vascular disease, stroke, or transient ischemic attack).[6] There was a 0.5 mmHg increase in SBP on varenicline and no changes in DBP and heart rate between the groups. The number of patients with an adjudicated CV event or death did not differ significantly between groups. The proportion of patients with CV events was numerically higher in those who received varenicline compared to placebo [myocardial infarction 2.0% versus 0.9%, coronary revascularization 2.3% versus 0.9%, newly diagnosed PVD or treatment for PVD 1.4% versus 0.9%].

In June of 2011, the FDA issued a safety communication warning healthcare professionals that varenicline may be associated with a small increased risk of certain CV events in patients with CV disease based on the trial by Rigotti and colleagues.[6,50] The FDA called for the manufacturer to conduct a meta-analysis of placebo-controlled trials to further evaluate such risks and since, two independent meta-analyses have been published.[51,52] Although neither sought to exclude trials evaluating patients with CV disease, the analysis by Singh and colleagues was predominately of trials excluding patients with CV disease.[51] Results of the meta-analysis suggest an increased risk of any ischemic or arrhythmic adverse CV events in patients treated with varenicline compared with placebo [Peto's odds ratio 1.72, 95% CI 1.09 to 2.71]. The analysis by Prochaska and colleagues included RCTs of

varenicline compared with inactive controls for smoking cessation, including events on-treatment and up to 30 days after discontinuation.[52] The primary outcome was the same as in Singh et al. defined as any ischemic or arrhythmic adverse CV event (myocardial infarction, unstable angina, coronary revascularization, coronary artery disease, arrhythmias, transient ischemic attacks, stroke, sudden death or CV-related death, and congestive heart failure) reported during the trial. A total of 22 trials with over 9,000 patients were included and 13 of the trials included patients with a history of or current CV disease or a prior CV event. The absolute difference in risk for the primary outcome did not reach statistical significance [risk difference = 0.27%, 95% CI −0.10% to 0.63%]. The authors concluded that given the larger number of participants evaluated, their analysis had high power to detect differences, and have excluded a difference in risk larger than 0.63%.

Clinical Perspectives

The benefits of quitting smoking are substantial, and despite this, patients with CV conditions continue to smoke. Effective therapies to aid in smoking cessation are available, and are recommended by practice guidelines.[3] The concern of adverse CV effects from these therapies is appropriate, particularly in patients with existing CV disease. Fortunately drug-related risks are likely short-term, while the patient is taking therapy. However, the benefits derived from a successful quit attempt are life-long. Age may also play a role as it is plausible to believe that quitting at a younger age may be associated with greater health benefits which further outweigh small risks associated with drug therapy. In addition, to truly determine the CV risks associated with the drug therapies would require adjustment for adherence and smoking status while on therapy, since patients who continue to smoke while on therapy have continued risk due to smoking status.

Based on pharmacologic mechanisms, deleterious CV effects are possible through use of the NRT. While clinical studies have not demonstrated harm in patients with CV disease, they may be underpowered to do so. Similarly, bupropion has been shown to increase BP, yet has not been shown to increase CV risk in patients with CV disease when used in studies up to 3 months. Given the lack of clinical outcomes data suggesting harm in patients with CV disease, if risk does exist, it is likely small and outweighed by the benefits of smoking cessation. In the one randomized trial which specifically evaluated varenicline in patients with CV disease, an increase in major adverse cardiovascular events (MACE) was not observed. While this trial was fairly large, it was also not powered to detect small differences in MACE. Subsequent meta-analyses provide conflicting data: one analysis suggests that patients without CV diseases might have an increase in CV risk[51] whereas a second meta-analysis, which included patients with CV disorders, showed no difference in CV events[52]. Therefore, the safety of varenicline in patients with CV disease has yet to be definitively established.

While there is a lack of definitive information on the CV safety of NRT, bupropion and varenicline, they all improve smoking quit rates. Furthermore, since these treatments are prescribed for 3 months or less and double or triple the rate of smoking cessation compared to placebo in the short- and intermediate-term, it is clinically appropriate to utilize these pharmacologic therapies in patients with stable CV disease who wish to quit smoking.

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Table 1

Food and Drug Administration Approved Therapies for Smoking Cessation

Therapy	Mechanism of Action	Suggested dosing
Nicotine patch	Nicotine agonist	For >10 cigarettes/day: 21 mg/24 hour for 6 to 8 weeks then decrease to 14 mg/24 hour for 2 to 4 weeks then decrease to 7 mg/24 hour for two to four weeks For ≤10 cigarettes/day: 14 mg/24 hour for 1 to 6 weeks then decrease to 7 mg/24 hour for 2 to 4 weeks
Nicotine lozenge		For patients who smoke their 1st cigarette within 30 min of awakening: 4 mg lozenge; Others: 2 mg lozenge 1 lozenge every 1 to 2 h in weeks 1 to 6 then 1 lozenge every 2 to 4 h in weeks 7 to 9 then 1 lozenge every 4 to 8 h in weeks 10 to 12
Nicotine gum		For ≥ 25 cigarettes/day: 4 mg gum; For < 25 cigarettes/day: 2 mg gum 1 piece every 1 to 2 hour in weeks 1 to 6 then 1 piece every 2 to 4 hour in weeks 7 to 9 then 1 piece every 4 to 8 hour in weeks 10 to 12
Nicotine nasal spray (Nicotrol NS)		1 or 2 0.5 mg doses per hour, increasing as needed for symptom relief for 3 to 6 months. Minimum of 8 doses and maximum of 40 doses per day.
Nicotine oral inhaler (Nicotrol)		6 to 16 10 mg cartridges/day for up to 6 months with taper over the last 3 months.
Bupropion SR (Zyban)	Inhibits reuptake of NE and DA	Begin 1 to 2 weeks before quit date with 150 mg daily for 3 days then increase to 150 mg twice daily 7–12 weeks
Varenicline (Chantix)	Selective agonist of the alpha-4-beta-2 nicotinic acetylcholine receptors	Begin 1 week before quit date. Take 0.5 mg daily on days 1–3 and 0.5 mg twice daily on days 4 to 7 and then take 1mg twice daily thereafter for 12 weeks. Additional 12 weeks suggested for those who are successful with initial course.

DA = dopamine; mg = milligrams; NE = norepinephrine

Table 2

Comparison of Cardiovascular Outcomes in Clinical Studies of Bupropion and Varenicline

Study	Population characteristics (N)	Intervention	Outcome studied	Results
Bupropion				
Rigotti, 2006[38]	Smokers hospitalized for acute coronary syndromes, coronary revascularization, or other CV conditions in patients with related coronary artery disease (n=248)	Bupropion 300 mg daily or placebo for 12 weeks	CV death, nonfatal MI, unstable angina, stroke, hospitalization for CHF, or coronary revascularization at 12 months	Incident rate ratio 1.56 (0.90 to 2.72)
Varenicline				
Singh, 2011[51]	Current tobacco users of adult age, regardless of CV history (n=8216)	Varenicline compared to placebo	MI, unstable angina, coronary revascularization, CAD, arrhythmias, TIA, stroke, sudden death or CV-related death, and CHF during the trial	Peto's odds ratio 1.72 (95% CI, 1.09 to 2.71)]
Prochaska, 2012[52]	Current tobacco users of adult age, regardless of CV history (n=9232)	Varenicline compared to inactive control	MI, unstable angina, coronary revascularization, CAD, arrhythmias, TIA, stroke, sudden death or CV-related death, and CHF during the trial	Risk difference 0.27% (95% CI, −0.10% to 0.63%)]

CAD = coronary artery disease; CHF = congestive heart failure; CI = confidence interval; CV = cardiovascular; MI = myocardial infarction; TIA = transient ischemic attack