Recent developments in smoking cessation

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Abstract

Smoking cessation substantially reduces the risk of cardiovascular disease in the prevention of primary and secondary cardiovascular events. Current first-line therapies include nicotine replacement therapy and bupropion, that approximately double a smoker's chances of long-term success. Both therapies are safe in patients with cardiovascular disease. Novel treatments include rimonabant, nicotine vaccines and varenicline. To date, varenicline, an $\alpha 4\beta 2$ nicotinic acetylcholine receptor partial agonist has been approved for smoking cessation and has been shown to be efficacious and well tolerated in clinical studies conducted in healthy smokers.

Key words: smoking cessation, tobacco dependence, varenicline.

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Epidemiology and consequences of smoking in relation to CVD risk

The link between smoking and cardiovascular disease was initially proposed to explain the marked rise in the incidence of coronary heart disease in smokers after World War I. Since then, a wealth of data has shown that smoking predisposes to virtually every clinical manifestation of cardiovascular disease including myocardial infarction (MI) and other acute coronary syndromes, stable angina, sudden death, ischaemic and haemorrhagic stroke, aortic aneurysm and peripheral vascular disease. The Framingham Heart Study demonstrated that men and women who had never smoked lived 6.2 and 4.9 years longer, respectively, free of cardiovascular disease than cigarette smokers.[1] Among smokers with a history of cardiovascular disease, men and women who had never smoked lived 2.4 and 2.7 years longer, respectively, than smokers.[1] These differences are the result of the increased rate of cardiovascular disease, the increased rate of mortality when cardiovascular disease is established and the higher rate of mortality from non-cardiovascular diseases associated with smoking.

Smoking interacts synergistically with blood lipid levels resulting in markedly increased rates of cardiovascular disease in populations with high cholesterol levels.[2] The recent INTERHEART study demonstrated that the risk of acute MI associated with smoking is consistent across a wide range of populations with diverse lifestyles and socioeconomic development.[3] This risk is closely related to the number of cigarettes smoked, even at low smoking levels.[3] Previous studies have shown that the risk of fatal and non-fatal coronary artery disease is doubled among very light smokers of one to four cigarettes a day, especially in women.[4] Smoking may be relatively more damaging for women than for men.[5] Smoking cigarettes with filters or low-tar cigarettes does not ameliorate the harm because smokers obtain their preferred amount of nicotine (and accompanying carbon monoxide and pro-oxidant gases) by taking more frequent and deeper puffs, or by blocking the ventilation holes in the filter.

In terms of attributable risk, the impact of smoking on coronary artery disease is most marked in young and middle-aged individuals. In smokers younger than 50 years, about one-half of non-fatal MI is due to smoking.[6] Attributable risk decreases in older age groups and about one-fifth of non-fatal MIs are attributable to smoking in men and women aged 60–64 years.[3] Smoking cessation, even at the age of 60 years or later, reduces cardiovascular risk substantially.[3] Cohort studies have generally

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shown that most of the drop in the excess risk of coronary artery disease mortality among former smokers occurs in the first two to three years of cessation. Thereafter, the rate of decline slows and it may take up to 10 to 15 years for former smokers to reach the same risk level as that of lifelong non-smokers. In patients with coronary artery disease, stopping smoking is associated with an estimated 36% reduction in mortality compared with continuing smokers.[7] Such a large decrease in risk is similar to that observed with statin therapy. It occurs on top of such therapy[8] and is extremely cost-effective.[9]

Currently available therapies

The chief obstacle to quitting smoking is the smoker's dependence on tobacco. Though about one-half of smokers say that they wish to quit within a foreseeable timeframe, most quit attempts do not succeed for more than a few days. Among smokers quitting on their own, less than 5% succeed in remaining smoke free for 12 months. Structured behavioural or motivational support programmes boost quit rates significantly. Nicotine replacement therapy (NRT) in its various forms (gum, patch, nasal spray, inhaler, lozenges and sublingual tablets) and bupropion enhance quit rates further. These medications approximately double the smoker's chances of success whether used independently or as part of a formal quit programme. The most substantial quit rate is achieved by combining medication and some form of behavioural support. NRT and bupropion are recommended by clinical practice guidelines as first-line treatments.

Most forms of NRT are easily available over the counter. NRT should be used at regular intervals and also to ameliorate acute craving. NRT products are safe, have almost no contraindications, and may be taken by patients with cardiovascular disease.[10] While NRT is usually started on the quit date or the night before in the case of the patch, efficacy may be enhanced by starting the patch before the quit date.[11]

Bupropion is an antidepressant that was serendipitously found to reduce smoking. Bupropion increases noradrenaline and dopamine levels in the central nervous system but its precise mode of action in aiding smoking cessation has not been clarified. Bupropion was more effective than the nicotine patch in one study[12] but, overall, its effectiveness is about the same as that of NRT.[13,14] As many as one-third of smokers interested in using bupropion may have contraindications or conditions that limit its use.[15] A target quit date is set at eight to 13 days after the start of treatment to allow steady state blood levels to be achieved. The dose should be limited to 150 mg daily, rather than 150 mg twice daily, in the elderly and also in individuals using medications with conditions that lower the seizure threshold. The main drawback of bupropion is a very low risk of seizure of one per 1,000, similar to that of other antidepressants in its class. There is also a risk of angioedema or psychosis. Bupropion blunts post-cessation weight gain during its use and is safe in patients with stable cardiovascular disease.[16]

Another antidepressant that has been used for smoking cessation is nortryptiline. Nortryptiline is a noradrenergic tricyclic antidepressant that is considered a second-line intervention because of its side effects.

New treatments for tobacco addiction

Rimonabant

Chronic use of nicotine seems to overactivate the endocannabinoid system.[17] Blocking the system with a cannabinoid receptor antagonist could potentially inhibit nicotine's stimulation of reward circuits associated with limbic dopaminergic transmission. Findings in rats that were trained to self-administer nicotine were consistent with this concept.[18] In a phase III clinical trial, smokers wishing to quit were randomised to 5 mg/day or 20 mg/day of rimonabant or placebo. Abstinence from smoking during the final four weeks of the treatment period was boosted from ~16% in the placebo and low-dose rimonabant groups to ~28% in the 20 mg/day rimonabant group.[19] No long-term abstinence rates have been published Rimonabant is only licensed for the treatment of obesity in Europe and the US and was not approved for smoking cessation by the US Food and Drugs Administration (FDA). Rimonabant may be a useful approach to managing post-cessation weight gain.[19]

Nicotine vaccines

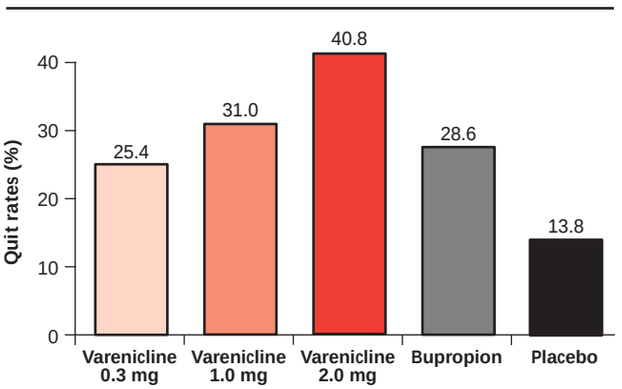
Nicotine vaccines may prevent nicotine in cigarette smoke from attaching to brain receptors.[20] Current vaccines do not induce long-lasting antibody titres and are not likely to be available for some time.

Varenicline

Varenicline is an orally administered $\alpha4\beta2$ nicotinic acetylcholine receptor partial agonist that was expressly developed by scientists at Pfizer Inc. to treat nicotine addiction.[21] The $\alpha4\beta2$ receptors are necessary for nicotine dependence to develop.[22,23] The binding of varenicline to these receptors may limit the reinforcing effects of nicotine on brain reward pathways and activate dopaminergic neurons in the ventral tegmental area to a lesser degree than nicotine. The agonist effect of varenicline on dopamine release is about 35–60% of the comparative nicotine response.[21] These effects have been shown to translate into changes in animal behaviour. Varenicline significantly reduced nicotine intake in rats trained to self-administer nicotine under a fixed ratio schedule, at doses that did not decrease food-maintained control responding. Results from nicotine self-administration tests under a progressive ratio schedule, which require an animal to work harder for each successive nicotine infusion and is considered an index of the drug's reinforcing properties, suggest that varenicline is a less efficacious reinforcer than nicotine, possibly because of its partial agonist properties.[24]

Preclinical data have now been extended to a series of studies conducted among smokers who were ready to make a quit attempt. In a phase II study healthy smokers were randomised evenly to varenicline 0.3 mg once daily, 1.0 mg once daily or 1.0 mg twice daily for six weeks plus one week of placebo, 150 mg sustained release bupropion twice daily or to placebo for seven weeks.[25] During the last four weeks of treatment, continuous

Figure 1. Continuous quit rates during the last four weeks of treatment in a seven-week study with different therapies for smoking cessation. Varenicline treatment was discontinued after six weeks and replaced by placebo. Based on reference 25



quit rates were 25.4%, 31.0%, 40.8%, 28.6% and 13.8% in the varenicline 0.3 mg, 1.0 mg, 2.0 mg, bupropion and placebo groups, respectively, demonstrating a clear dose response of varenicline on quit rates (figure 1). After one year, the 1.0 mg twice-daily dose of varenicline retained its advantage over placebo. This dose of varenicline significantly reduced the urge to smoke and the craving for a cigarette. In subjects who were still smoking the reinforcing effects of cigarettes (including enjoyment of respiratory tract symptoms) were decreased with varenicline compared to placebo. There was a dose-related increase in nausea, insomnia, abnormal dreams and taste perversion in varenicline-treated subjects but the frequency of discontinuations due to adverse events was not dose related, and was lower than among bupropion-treated subjects. Another trial was designed to study the effect of dose titration on tolerance.[26] In this trial, the quit rates were again clearly dose related but reports of nausea were lower for the titrated versus the non-titrated dosing.

The effect of varenicline on cessation rates compared to placebo and bupropion was further evaluated in two identical phase III studies.[27,28] In each study, over 1,000 smokers were randomised to varenicline 1.0 mg twice daily after titration, bupropion 150 mg twice daily after titration, or to placebo for 12 weeks. Eligible subjects were 18 to 75 years of age, smoked 10 or more cigarettes daily and were motivated to quit. The study protocol excluded individuals with contraindications to bupropion, chronic diseases, alcohol or drug abuse or dependency, uncontrolled hypertension, or with prior exposure to bupropion or varenicline. In both studies, varenicline proved to be superior to placebo and to bupropion at the week 9–12 continuous abstinence end point (i.e. not a single puff of a cigarette allowed) and to placebo at the week 9–52 continuous abstinence end point. In one study, varenicline was superior to bupropion at the week 9–52 end point,[28] while in the other study, this comparison did not achieve statistical significance.[27] Bupropion showed its expected advantage to placebo.[27,28] Nausea was the most commonly reported adverse event for varenicline and was reported by almost 30% of subjects. Its severity was mostly mild or moderate and was of limited duration. Study drug discontinuations due to adverse events were 8–9% for varenicline, 11–15% for bupropion and 7–9% for placebo. Adverse events responsible for discontinuation of active treatments were nausea for varenicline (2–3% of subjects) and insomnia for bupropion (2–3% of subjects). A safety study has shown that the administration of varenicline for up to one year was generally as well tolerated as in shorter term studies.[29]

A further study addressed the question of whether extended (maintenance) use of varenicline helped smokers who had quit (during a 12-week course of open-label varenicline) to stay abstinent from smoking.[30] Almost two-thirds of subjects that entered this trial did quit during week 12 or longer and were eligible for randomisation to a further 12 weeks of varenicline or to placebo. About 44% versus 37% of subjects that received varenicline or placebo, respectively, were continuously abstinent after one year. Here, as in previous studies,[27,28] varenicline reduced the urge to smoke and the craving for cigarettes. The effect of varenicline on other withdrawal symptoms was less consistent. It is particularly noteworthy that in several studies, the point prevalence quit rate (i.e. abstinence from smoking during the past week) increased slightly during the first few weeks of treatment[26-30] perhaps because varenicline prevents the reinforcing effects of a lapse to smoking. No adverse cardiovascular effects of varenicline were reported and vital signs were unchanged during treatment. The effect of varenicline on post-cessation weight gain is similar to placebo.

Key messages

- Current medical therapies for smoking cessation – nicotine replacement therapy and bupropion – approximately double the odds of success in a given quit attempt
- Varenicline is a new treatment for nicotine addiction that targets the nicotine receptor in the brain
- Varenicline has no contraindications, is well tolerated, and may be more effective than bupropion

Conclusion

The addictiveness of nicotine delivered in cigarettes, together with a host of psychological and social cues to smoke, hamper the attempts of smokers to quit despite clear benefits. NRT in various forms and bupropion are the only medical treatments to date.

Varenicline is a novel non-nicotine medication with a defined mode of action that has recently received approval by the European Medicines Evaluation Agency (EMEA) and the US FDA.

It is now available on perscription in the UK. Varenicline seems to be more efficacious than bupropion, and in contrast to bupropion, has no contraindications or serious side effects. Studies, to date, indicate no cardiovascular safety concerns. Many smokers have tried current medications and the availability of a novel prescription medication provides physicians with the opportunity of offering smokers medical and motivational support towards a new quit attempt. Assessment and prescription by a physician and follow-up are integral parts of a medical model of smoking cessation treatment.[31]

Conflict of interest

ST has received honoraria for lectures and/or consulting and research grants from Pfizer Inc, GlaxoSmithKline and Novartis.

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