OPINION

Smokeless Tobacco as a Nicotine Delivery Device: Harm or Harm Reduction?

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Smokeless tobacco (ST) delivers nicotine in doses similar to those received in cigarette smoking but does not expose the user to the toxic combustion gases and particles that are responsible for most tobacco-induced disease. This Opinion piece discusses the controversies pertaining to ST and health, the pros and cons of ST in harm reduction, and progress in treatment for those who would like to quit ST use.

Tobacco use can be considered a form of drug self-administration. The drug is nicotine, which sustains tobacco use and in many cases results in highly compulsive use. Tobacco products differ in their drug delivery characteristics and in the toxicity of the delivery systems. Cigarette smoking delivers nicotine rapidly, achieving high concentrations in arterial blood in a manner that optimizes reinforcement and self-administration. Smoking also exposes the user to high concentrations of toxic combustion products. ST delivers nicotine more slowly than smoking, results in lower peak arterial nicotine levels, and does not expose users to combustion gases and particles (**Figure 1**).

The implications of ST use for public health are a topic of debate among tobacco scientists and health-care professionals. On the one hand, ST use can be addictive and has been associated with an increased risk of oral disease, pancreatic cancer, and reproductive problems. Treatment of ST addiction has been problematic, with most clinical trials of pharmacotherapy producing disappointing results. On the other hand, because ST use does not expose the user to most of the combustion products generated by cigarette smoking, there is a far lower risk of cancer, cardiovascular disease, and lung disease with ST use compared with cigarette smoking. Some have advocated the use of ST as a source of nicotine to substitute for cigarettes so as to reduce the harm of smoking, and ST use has been suggested as an aid in smoking cessation.

The ST used in the United States and Europe is primarily oral snuff, which is moist ground tobacco, sometimes packaged in sachets like small tea bags, that is placed between the lips and gums. Nicotine is absorbed through the oral mucous membranes. Chewing tobacco, which consists of shredded tobacco, is a form of ST that is less widely used than oral snuff. More recently, ST has been marketed in the United States as compressed tablets or lozenges. (Other forms of ST are used in other parts of the world but are not discussed here because of space limitations.) The constituents of ST products vary—for example, in levels of carcinogenic nitrosamines as well as other carcinogens and tumor promoters. Because it is difficult to generalize about constituents, one must be product-specific when considering evidence about ST use and disease risk.

In the United States, about 3% of adults use ST, with rates as high as 7% in subgroups such as American Indians and Alaskan natives. ST use is common among high school boys and is often used in association with athletic activities such as baseball. The use of oral snuff (called "snus") is quite high in some countries; in Sweden and Norway, the prevalence of use by young men is as high as 30%.

ST contains nicotine in high concentrations and delivers daily systemic doses of nicotine similar to those obtained from cigarette smoking. ST also contains carcinogenic tobacco-specific nitrosamines, with levels varying by product. Swedish snus contains lower levels of nitrosamines than many US products. Levels of the carcinogenic nitrosamine NNAL in the urine of ST users in the United States are on average as high as or higher than those in cigarette smokers. Low levels of other combustion products (e.g., polycyclic aromatic hydrocarbons) generated during fire curing of tobacco and other potential toxins (e.g., arsenic, cadmium, and lead) are also present in ST.

Epidemiological studies of ST use and disease have yielded quite different results, depending on the product and the population studied. Many studies have shown an association between ST use and oral-cavity disease, including caries, periodontal disease, and oral cancer. Oral cancer was a particularly common problem in the early twentieth century in the southeastern United States, as well as India and other countries where

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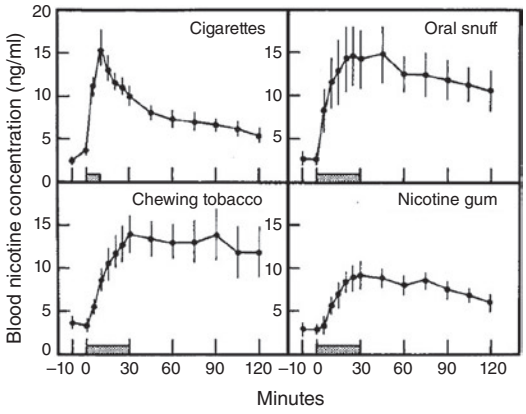

Figure 1 Mean (±SEM) blood concentrations of nicotine in 10 subjects who smoked cigarettes for 9 minutes (1 1/3 cigarettes), and for 30 minutes used oral snuff (2.5 g), used chewing tobacco (mean, 7.9 g), and chewed nicotine gum (two 2-mg pieces). Shaded bars above the time axis indicate the period of exposure to tobacco or nicotine gum. Reprinted from ref. 6 with permission.

tobacco is chewed as part of betel quid. Studies of cancer risk related to Swedish snus—one of the cleanest products, with relatively low nitrosamine levels—show an increased risk of pancreatic and, possibly, esophageal cancer but not of oral or other cancers. The risk of pancreatic cancer with ST use is considerably lower than that associated with cigarette smoking. Associations between ST use and cardiovascular disease also vary according to product and population.[1] Most studies in Sweden show little or no increased risk of cardiovascular disease. However, studies performed in the United States in the 1970s as well as in other countries show an increased risk of myocardial infarction and stroke in ST users. Increased cardiovascular risk has not been seen in more recent US studies.

Research on ST use and cardiovascular disease and cancer has been an informative way to probe the role of nicotine in causing these diseases. Because ST users take in as much nicotine as cigarette smokers but have much lower rates of cardiovascular disease, it can be concluded that nicotine plays a minor role in causing cardiovascular disease. Cardiovascular disease from tobacco use appears to be related primarily to combustion products, including particulates and other oxidant chemicals. Likewise, the absence of increased cancer risk (other than pancreatic) in Swedish snus users argues against a role of nicotine in causing or promoting cancers in general. It is quite clear that, although ST may be associated with some risk of cancer and cardiovascular disease, the risks are far lower than those associated with cigarette smoking.

Data from Sweden, where a large percentage of young men use snus and the prevalence of smoking is lower than in other European countries, demonstrate markedly lower rates of lung cancer compared with populations in other countries. This has been a basis for the proposition that substituting ST for cigarette smoking could reduce harm in people who are addicted to nicotine and cannot stop its use. Observational studies from Scandinavia have also found that ST is used by many to aid in smoking cessation.

Although ST use increases the risk of some cancers, oral disease, disorders of pregnancy, and possibly cardiovascular disease, the major argument against its use for harm reduction is that it may result in dual use of ST and cigarettes, with fewer people quitting smoking. For example, ST may be used to relieve withdrawal symptoms when smokers are unable to smoke because of workplace or other restrictions, reducing the discomfort that would otherwise have prompted them to quit smoking. Another argument is that ST users who are able to reduce their cigarette consumption by this practice may believe that they are significantly reducing their smoking-related disease risk, when in fact that is not the case. Furthermore, there is evidence that ST use among US adolescents is a strong risk factor for becoming an adult smoker. A recent analysis modeling the benefit versus harm for the US population suggests that adoption of ST would not in the long term reduce harm for the population.[2] Although anecdotally ST helps smokers quit, one controlled clinical trial found no long-term benefit for quitting.[3] Therefore, at present there appears to be—at least at the population level in the United States—more risk than benefit in the use of ST for harm reduction or to aid in smoking cessation.

Because ST contains and delivers large amounts of nicotine, addiction to ST is a problem for many users. Treatment of ST addiction in the past has been difficult, and most clinical trials have shown a low level of success. In general, efficacy studies (controlled clinical trials) of nicotine-replacement therapy and bupropion have not shown benefit, although some effectiveness studies combining behavior counseling with nicotine-replacement therapy appear to be helpful.[4] Recently, a controlled clinical trial of varenicline, a nicotine receptor partial agonist, demonstrated ST cessation rates that are quite high and comparable to those seen among cigarette smokers treated with varenicline.[5] The mechanism of varenicline action is believed to include both blocking the psychoactive effects of exogenous nicotine from tobacco and providing adequate intrinsic nicotinic receptor stimulation to prevent withdrawal symptoms.

In conclusion, ST poses an interesting challenge to the tobacco control community. As a drug delivery system, ST products marketed in the United States today are not clean and pose some risk to health. On the other hand, ST products are much cleaner and less hazardous than cigarettes. ST use could reduce harm to smokers if they switched entirely to ST. This appears to be the case with snus use in Sweden. In the United States, however, there is concern that promoting ST would result in dual use of ST and cigarettes, which would not reduce harm and might increase the risks in the overall population because fewer people would quit smoking. ST is addictive, but recent advances in medication development have led to drugs such as varenicline that appear to be as effective for quitting ST use as they are in achieving smoking cessation.

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CONFLICT OF INTEREST
N.L.B. is a consultant to several pharmaceutical companies that market medications to aid in smoking cessation and has served as a paid expert witness in litigation against tobacco companies.

1. Piano, M.R. *et al.* Impact of smokeless tobacco products on cardiovascular disease: implications for policy, prevention, and treatment: a policy statement from the American Heart Association. *Circulation* **122**, 1520–1544 (2010).
2. Mejia, A.B., Ling, P.M. & Glantz, S.A. Quantifying the effects of promoting smokeless tobacco as a harm reduction strategy in the USA. *Tob. Control* **19**, 297–305 (2010).
3. Tonnesen, P., Mikkelsen, K. & Bremann, L. Smoking cessation with smokeless tobacco and group therapy: an open, randomized, controlled trial. *Nicotine Tob. Res.* **10**, 1365–1372 (2008).
4. Ebbert, J., Montori, V.M., Erwin, P.J. & Stead, L.F. Interventions for smokeless tobacco use cessation. *Cochrane Database Syst. Rev.* **2**, CD004306 (2011).
5. Fagerstrom, K., Gilljam, H., Metcalfe, M., Tonstad, S. & Messig, M. Stopping smokeless tobacco with varenicline: randomised double blind placebo controlled trial. *BMJ* **341**, c6549 (2010).
6. Benowitz, N.L., Porchet, H., Sheiner, L. & Jacob, P. III. Nicotine absorption and cardiovascular effects with smokeless tobacco use: comparison with cigarettes and nicotine gum. *Clin. Pharmacol. Ther.* **44**, 24 (1988).

The Impact of Pharmacogenomics on the Management of Cardiac Disease

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Pharmacogenomics promises to help maximize efficacy and minimize adverse drug reactions. It could have a significant impact on the treatment of cardiovascular disease, the leading cause of death in the United States. The past decade has seen pharmacogenomics move from study of a candidate gene to genome-wide approaches, with the development of a series of pharmacogenetic tests. However, many barriers need to be overcome for cardiovascular pharmacogenomics to have its promised clinical impact.

Significant progress has been made in the development of pharmacogenetic tests for drugs used to treat common cardiovascular diseases such as coronary artery disease, congestive heart failure, and atrial fibrillation. Here we outline the trials that have provided evidence in support of these tests and the challenges involved in implementing them in clinical practice.

Treatment of coronary artery disease: statins and clopidogrel

Statin therapy. Statins, which prevent cardiovascular events and stroke in patients with coronary disease, are prescribed for millions of patients. Statin use in the Prediction of Muscular Risk in Observational Conditions study was limited by the development of myalgias in 11% of patients and resulted in discontinuation of therapy in 4%. A genome-wide association study was performed to identify genetic variation associated with the development of myopathy using DNA samples from the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine, a randomized trial comparing high-dose (80 mg) versus low-dose (20 mg) simvastatin in patients with a history of myocardial infarction.[1] Patients homozygous or heterozygous for rs4363657—a single-nucleotide polymorphism in the *SLCO1B1* gene, which encodes a hepatic statin transporter, OATP1B1—had a 16.9- and 4.5-fold increased risk for rhabdomyolysis and myopathy, respectively. Because of this increased risk of myopathy or fatal rhabdomyolysis with 80 mg simvastatin, the US Food and Drug Administration (FDA) recently recommended that the 80-mg dose be restricted to patients who have been taking it for 12 months or longer because most patients develop this adverse response early in the therapy. Conceivably, with preemptive genetic testing, patients at greatest risk for myopathy could be identified before statin therapy and treated with alternative "muscle-safe" statins such as fluvastatin or pravastatin. Such a genotype-based approach has not yet been tested prospectively, and it might be difficult to conduct such a trial given the relatively low incidence of serious statin-dependent muscle damage.

Recently, genetic variation in the *CLMN* and *APOC1* genes has been reported to be related to statin-induced reduction of total cholesterol and low-density lipoprotein cholesterol levels, but the magnitude of this effect is small and these markers are not useful clinically because lipid profiles can be easily measured and statin dose can be titrated to meet national guidelines. A pharmacogenetic test that would help identify individuals who would benefit from statin therapy independent of effect on lipid levels might be useful. The Trp719Arg polymorphism in kinesin-like protein 6 (KIF6) has been considered promising for this purpose. However, even though several small studies reported that carriers of the *KIF6* allele encoding Arg719 had increased risk for coronary artery events and benefited

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