



Public Health Implications of Smokeless Tobacco Use as a Harm Reduction Strategy

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Harm reduction strategies involve promoting a product that has adverse health consequences as a substitute for one that has more severe adverse health consequences. Smokeless tobacco low in nitrosamine content offers potential benefits in reducing smoking prevalence rates. Possible harm arises from the potential for such products to serve as a gateway to more harmful tobacco products, public misinterpretation of “less harmful” as “safe,” distraction from the public health goal of tobacco elimination, and ethical issues involved in advising those marketing these harmful products. We offer a research agenda to provide a stronger basis for evaluating the risks and benefits of smokeless tobacco as a means of reducing the adverse health effects of tobacco. (*Am J Public Health*. 2006;96:1934–1939. doi:10.2105/AJPH.2005.075499)

THE USE OF TOBACCO

products, especially cigarettes, results in exposure to hundreds of chemicals, many of which have adverse health consequences. The primary agents of concern in smoked tobacco are polycyclic aromatic hydrocarbons, carbon monoxide, nicotine, and N-nitroso compounds, along with smaller amounts of polonium, radon,

arsenic, and cadmium. Polycyclic aromatic hydrocarbons are produced by the high temperatures reached in the burning of tobacco. N-nitroso compounds, including nitrosamines, are found in tobacco leaves themselves, may be formed to some extent during combustion, and are transported to cigarette smoke. Smoked tobacco is the most prevalent and harmful tobacco product, with overwhelming evidence showing substantially increased risks of a variety of cancers; chronic obstructive pulmonary, cardiovascular, and oral diseases; and adverse reproductive outcomes.

Recognition by leaders in some developed countries of these well-documented harmful consequences of smoking has resulted in increasingly effective actions, such as political action, taken to curtail the epidemic of tobacco-related diseases. Yet, the epidemic continues unabated and is even accelerating in many parts of the world. Tools for combating the epidemic include public policies intended to discourage tobacco use through taxation and restrictions on promotion, media campaigns designed to prevent smoking initiation and encourage cessation, individual counseling techniques¹ and medications designed to promote and maintain smoking cessation,

modification of tobacco products to reduce harmfulness, and substitution of less harmful for more harmful products (e.g., pharmaceutical nicotine for smoked tobacco).

HARM REDUCTION STRATEGIES

The underlying principle of harm reduction is that a product that has adverse health consequences is promoted as a substitute for one that has more severe adverse health consequences.² The addictive features of nicotine are central to the problem of continuing use of tobacco. Even nicotine as a pure pharmaceutical agent has short-term adverse cardiovascular effects, although it has none of the health effects associated with other agents in cigarette smoke or smokeless tobacco. Smokeless tobacco products offer a potential harm reduction strategy for which the magnitude of health risk to an individual user would be expected to fall between pharmaceutical-grade nicotine (1 of smokeless tobacco's constituents) and smoking (which includes all the toxic constituents of smokeless tobacco as well as others).

The primary agents of concern in smokeless tobacco are the strongly carcinogenic tobacco-specific nitrosamines, especially

N'-nitrosornicotine (NNN), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), and nicotine itself. Although the exact magnitude of reduction in risk gained from substituting use of smokeless tobacco (particularly a low-nitrosamine product) for cigarette smoking is not easily quantified, a panel of experts estimated reductions in total mortality in the range of 90% to 95%.³ Despite such a large estimated benefit relative to smoking, important scientific and ethical questions arise.

Use of high-dose methadone maintenance treatment among heroin addicts has remained controversial despite 40 years of clear clinical evidence that it is moderately effective in rehabilitating opiate injection drug users and preventing the spread of HIV/AIDS. The price of this harm reduction is acceptance of continued addiction to a narcotic. Similar questions have been raised with regard to needle exchange programs designed to prevent the spread of HIV/AIDS among injection drug users. Parallel concerns arise with the substitution of less harmful for more harmful tobacco products: might this practice “sanitize” or even unintentionally initiate the harmful behavior? Does accommodating the harmful behavior suggest that society now condones or



accepts it, discouraging more definitive solutions?

In Sweden the widespread use of Swedish snuff, called *snus*, a moist smokeless tobacco product placed under the upper lip, has been viewed as a possible model for successful harm reduction,^{4,5} although not without controversy.⁶ Sweden has achieved the lowest smoking prevalence rate in all of Europe, approximately 17% of adult men in 2000; an estimated 19% of adult men and 1% of adult women use *snus* daily.⁵ Furthermore, *snus* appears to be a component of successful smoking cessation.⁷ The low smoking prevalence rate and high rate of use of *snus* in Sweden may be related, but this association has not been established with certainty.

As recommended in the Institute of Medicine report *Clearing the Smoke*,⁸ manufacturers have now begun to develop and market tobacco products that reduce but do not eliminate exposure to tobacco-related toxicants. The report also called for consumers to be fully informed of the adverse consequences associated with these products and for surveillance to be conducted on health effects subsequent to marketing.

Star Scientific, a small tobacco company located in Chester, Va, began to market 2 smokeless tobacco products with very low levels of tobacco-specific nitrosamines and sought expert advice to better define the health risks associated with use of its products relative to smoked and conventional smokeless tobaccos. The company sought answers to the following questions: do

smokeless tobacco products pose risks to health? If so, what is the nature of these risks, are there special populations at higher risk, and how do the risks compare with those of cigarette smoking? Are there physical or chemical characteristics of specific smokeless tobacco products or different uses that influence health risks?

Star Scientific provided an unrestricted grant to Best Practice Project Management Inc, a consulting and project management company located in Bethesda, Md, to convene a consensus conference to respond to these questions. A panel was convened in May 2003 with the agreement that it would respond to the questions and would, in addition, prepare a report for publication independent of the sponsor (the present article). The panel conducted a literature search on the topic and enlisted a range of experts with and without previous experience in tobacco research as members.

EVIDENCE ON THE HEALTH EFFECTS OF SMOKELESS TOBACCO

Exposures Associated With Smokeless Tobacco

Smokeless tobacco products contain air- or fire-cured tobacco that is powdered or ground for use as nasal or oral snuff, cut and grated for use as chewing or oral snuff, or stripped and compacted for use as chewing tobacco. Such products may include sugars (sucrose, fructose, sorbitol, molasses, dried fruit), water, sodium chloride, ammonium chloride, licorice, menthol, paraffin oil, and

glycerol. Tobacco-specific nitrosamines in smokeless products are derived from leaf nitrates that were reduced to nitrites, primarily via bacterial fermentation. Nitrites and amines in the tobacco react to form nitrosamines that are clearly carcinogenic in animals and probably carcinogenic in humans.⁹ Trace metals occur at low levels and probably do not contribute to carcinogenesis in the smokeless tobacco products marketed in the United States and Sweden.¹⁰

Certain smokeless tobacco products have low levels of formaldehyde, and those that are smoke-cured also have significant amounts of polycyclic aromatic hydrocarbons, some of which, such as benzo[a]pyrene, are carcinogens.¹⁰ Swedish *snus* is composed of air-cured and fire-cured tobaccos. Since 1981, no fermentation has been used in its production, and a heating step sharply reduces microorganism content. Additives and flavors presumed to be safe are used in the process, and the net result is a product low in tobacco-specific nitrosamines (10 mg/kg or less).

The magnitude of the health risk associated with smokeless products appears to be associated with the type of tobacco and method of cultivation used. Greater potential for harm is associated with fire-curing (resulting in deposits of polycyclic aromatic hydrocarbons on the leaf), bacterial contamination, fermentation during production (which may favor the activity of microorganisms that reduce nitrates to nitrites, leading to formation of nitrosamines),¹¹ inclusion of

certain additives in Asian products (e.g., areca nuts),¹² and particular methods of product storage (some of which may promote continued bacterial formation of nitrosamines). Behavioral influences on health risks include amount of smokeless tobacco consumed and frequency of use, length of application, surface of application, oral hygiene, and rates of salivating, swallowing, and spitting. Risk associated with use may be modified by other exposures such as diet, alcohol consumption, and genetics.^{13–15}

Carcinogenicity

Evidence that smokeless tobacco, which includes moist and dry snuff, causes oral cancer in humans is persuasive, given biological plausibility, specificity for buccal mucosa and gingiva (sites of contact), and the strength and consistency of epidemiological evidence across populations and geographic locations.^{16–18} The carcinogens NNN and NNK are found in the saliva of snuff dippers, and measurements of urinary excretions of NNK metabolites have been found to be similar among users of snuff and chewing tobacco and smokers.¹⁰

Reducing the nitrosamine content of smokeless tobacco (as in *snus*) should reduce carcinogenicity. Nonetheless, nitrosamines can be produced in vivo from nicotine itself and from tobacco-specific or other amines.⁹ Reports on the carcinogenicity of *snus* in the Scandinavian and other literature^{18–22} suggest minimal risk of oral or other cancers among users. However, as is the case with any smokeless tobacco product, *snus*



contains carcinogenic nitrosamines, albeit at markedly lower levels than those found in the types of smokeless tobacco used in the United States and most other parts of the world; pharmaceutical nicotine does not contain these nitrosamines.²³

American smokeless tobaccos can be divided into chewing tobacco, moist snuff, and dry snuff. In 1 review of different types of smokeless tobacco²⁴ that evaluated 23 studies published between 1957 and 1998, no clear epidemiological evidence was uncovered that indicated chewing tobacco increases the risk of head or neck cancer. There was evidence of an increased risk of oral cancer associated with use of American dry snuff, but there were small or no clear risks of oral cancer associated with use of moist snuff, despite the presence of elevated nitrosamine levels in such products.

Cardiovascular Disease

Smokeless tobacco use produces a much slower onset and much lower peak concentration of nicotine in the blood supplying the heart and brain than does smoked tobacco, even with the same total daily dose of nicotine. Use of chewing tobacco or snuff for 30 minutes leads to a gradual rise in blood nicotine concentration followed by a sustained level of concentration that continues for up to 2 hours.^{25,26} The systemic dose from a single exposure to snuff or chewing tobacco is estimated at 2 to 3 mg.

Studies comparing cigarette smoking, snuff use, and use of chewing tobacco have demonstrated qualitatively similar effects

on the sympathetic nervous system from nicotine.²⁶ For all 3 products, the heart rate is increased, although its elevation is sharper and persists for a shorter interval with smoking than with snuff, consistent with the time course of blood concentrations. During most of the day, circadian heart rates are approximately 7 beats per minute higher among those who smoke cigarettes, chew tobacco, or use oral snuff than among those who are abstinent.

Epidemiological studies of snuff users have revealed no increased risk of myocardial infarction²⁷ or increased atherosclerosis²⁸ relative to nonusers. Although the acute nicotine-related effects of all tobacco products and pharmaceutical nicotine are essentially the same, the risk of clinically significant cardiovascular disease is clearly linked to smoking and not to use of smokeless tobacco.²⁸ Similarly, risks associated with chronic obstructive pulmonary disease are a consequence of smoking but not of smokeless tobacco use.²⁹

Oral Health Effects of Smokeless Tobacco

In addition to cancers, oral health concerns related to smokeless tobacco include leukoplakia, gingivitis, periodontitis, and dental caries as well as cosmetic concerns such as tooth staining, malodor, and tooth loss with resultant disfigurement. Leukoplakia is strongly associated with the use and placement position of smokeless tobacco and appears and disappears with changes in use.³⁰ A Swedish study of mucosal and

other leukoplakic lesions among snuff dippers showed reversible histological changes and suggested that Swedish *snus* produces less severe lesions than American snuff.³¹

Gingivitis and periodontitis are common infectious diseases in which bacteria colonize the tooth surface, with resulting gingival (gum) inflammation; recession from the tooth surface, exposing the roots; and accompanying destruction of the bony sockets of the teeth (periodontitis). Some data suggest that tobacco products adversely influence periodontitis-associated flora^{32,33} and host immune responses to inflammatory agents.³⁴ There is no evidence of an association of smokeless tobacco with recession of the gums independent of pre-existing gingivitis. However, periodontitis is clearly more rapidly destructive among smokers and perhaps among smokeless tobacco users. Periodontitis also responds more poorly to treatment in smokers.^{35,36}

One study conducted in the United States showed that caries (decay) of the root surfaces of teeth was associated with use of chewing tobacco but not snuff.³⁷ Amount of decay was associated with intensity and duration of use and was probably a function of the high levels of sugar contained in chewing tobacco products.

Reproductive Health

The primary reproductive health concern with smokeless tobacco is nicotine itself, which has vasoconstrictive effects that can have an adverse influence on fetal growth and development. In

rodents, nicotine exposure during pregnancy resulted in reduced birthweights, increased fetal mortality, abnormal bone development, and reduced activity levels.³⁸ Among smokers, carbon monoxide also contributes to adverse effects on growth and brain development.^{38,39}

One study focusing on infant birthweight suggested that women given nicotine patches usually continued to smoke but smoked less, and those who smoked less had improved birthweights.⁴⁰ Few studies of reproductive health among women who use smokeless tobacco are available from Western countries, because historically not many women of reproductive age have used such products. Some research has been conducted in India among women using chewing tobacco; although these studies are of limited relevance because of the differences between that country's products and those used in the United States and Sweden, there were indications of increases in stillbirths⁴¹ and reductions in birthweights among the participants.^{41,42} A more recent study of Swedish *snus* users revealed decreases in birthweights and increased risks of preterm delivery (relative risk [RR]=1.6) and preeclampsia (RR=1.6)⁴³; these results call for corroboration.

PUBLIC HEALTH CONCERNS WITH SMOKELESS TOBACCO

A public health approach to tobacco addiction should include preventing initiation of



use, facilitating smoking cessation, and promoting abstinence from all tobacco products by current users. Policymakers understandably disagree on the risks and benefits of harm reduction strategies aimed at those who are unable (or unwilling) to stop using tobacco products. Any product that delivers nicotine confers health risks, yet smoked tobacco clearly confers far greater risks than smokeless tobacco. Reduction of nitrosamine levels in smokeless tobacco should markedly reduce carcinogenicity.

However, whereas scientists and public health experts acknowledge a gradient of harmfulness, the public may dichotomize products and behaviors as “harmful” or “safe.” Applying the “harmful but safer” concept to the use of smokeless tobacco in comparison with active smoking poses a challenge to health educators and advertisers. Overstatement of harm could prevent smokers from switching to smokeless tobacco.⁴⁴ Understatement of harm could lead nonusers to adopt use of smokeless tobacco. Thus, the issue is not merely whether policymakers can agree on the *potential* value of risk reduction strategies but whether, in practice, the “harmful but safer” message can be effectively conveyed to the public.

The intense promotion of smokeless tobacco products to young men is clearly intended to foster initiation of use among this population. The legitimacy of harm reduction is predicated on effective targeting of *active* smokers and users of smokeless

tobacco high in nitrosamine content. Ideally, a product should not be promoted or adopted among either nonusers of tobacco or active smokers capable of quitting. The Swedish experience indicates that *snus* does not serve as a gateway to smoking and appears to have contributed to dramatic declines in smoking as its use increased,²² but the response to such products may well differ in the United States. If it is not possible to isolate and market to the group of smokers who could benefit, there may be net harm from these products.

Given the financial incentive to market smokeless tobacco products on a wide scale, the success of a public health–based harm reduction strategy will depend in part on effective regulation. The complex regulatory environment affecting tobacco advertising and sales and the marketing of nicotine delivery products is applicable as well to the marketing of smokeless tobacco products low in nitrosamine content. Restrictions on advertising and sales to minors, reporting of constituents, and mandatory warning labels would be among the key considerations.

If a harm reduction strategy is adopted, it will require a clear definition of relative health risks associated with low-nitrosamine smokeless tobacco products, perhaps coupled with further limitations on advertising of more dangerous products. A comprehensive strategy is needed from the outset to ensure that the product is marketed solely as a harm reduction tool. The ultimate test of any regulatory approach to these new

tobacco products is its impact on public health; thus, careful documentation of patterns and consequences of use is required.

Some public health advocates note that harm reduction strategies run counter to the ultimate goal of a tobacco-free society, confusing the public health message advocating abstinence from all forms of tobacco use. Furthermore, they argue, marketing one tobacco product as a substitute for another may divert attention and resources from policies designed to discourage or eliminate use altogether. Weakening the political will to aggressively pursue such proven strategies as increasing cigarette taxes, restricting public smoking, and enforcing age restrictions on purchasing tobacco may be an unintended consequence of promotion of harm reduction. Moreover, an attractive substitute in the form of smokeless tobacco could discourage active smokers from completely discontinuing their tobacco use.

A final concern facing researchers and public health advocates is ethical: whether and how to advise those who seek to market smokeless tobacco products. Manufacturers of smokeless tobacco would clearly be seeking profits through sales of a harmful product, albeit one that may have net public health benefits. These companies need scientific expertise if they are to address health concerns, devise marketing strategies consistent with the goal of harm reduction, and monitor the effectiveness of those strategies. The long history of dishonesty by the tobacco industry and by some of the

researchers supported by that industry raises ethical concerns.

Proactively addressing the concerns expressed here should be helpful to policymakers and corporations contemplating the development and marketing of harm reduction products. If these issues can be raised objectively in advance, in an open forum, reputable scientists would have the opportunity to contribute their knowledge to policymakers, who would benefit from access to the best available information. Despite much success in eliminating tobacco use, we need more, not fewer, tools in the multifaceted effort to address this public health issue. Motivated current smokers who are unable to quit should be a specific target audience for harm reduction strategies.

As a result of the limited effectiveness of smoking cessation programs, recalcitrant smokers represent a sizable proportion of tobacco users both in the United States and around the world. Smokeless tobacco products low in nitrosamine content may represent a beneficial alternative for this group of smokers who have not been helped by other available tobacco control strategies.

QUESTIONS CONCERNING SMOKELESS TOBACCO

Questions that need to be answered about smokeless tobacco products focus on whether these products have a place in the array of tobacco control tools. We propose that the following questions be addressed in research efforts:



- How do the constituents of concern change between manufacturer and consumer? In the process of storage and distribution, chemical changes can occur that could lead to increased levels of harmful compounds,¹¹ calling for evaluation of the effects of storage time and temperature after realistic estimates of distribution and storage have been taken into account.
 - What is the dose–response relationship between specific smokeless tobacco constituents and health outcomes? Quantitative uncertainties in such relationships call for additional toxicological and epidemiological research.
 - What are the short- and long-term clinical consequences of switching from tobacco smoking to use of smokeless tobacco products? Although there are abundant data to predict physiological and clinical effects of switching, detailed studies characterizing cardiovascular, oral health, and related effects would improve the extent to which consequences of changes in patterns of tobacco use could be accurately predicted at the population level.
 - What effect does use of smokeless tobacco products have on the success of smoking cessation interventions? What is the impact of using smokeless tobacco on amount of smoking among continuing smokers? Among current smokers who are unlikely to discontinue use, how effective is smokeless tobacco relative to pharmaceutical nicotine?
 - What regulations are needed to ensure that the marketing and adoption of smokeless tobacco products yield public health benefits (i.e., helping recalcitrant smokers quit) as opposed to producing harmful outcomes (i.e., leading to use of these products by nonsmokers or those who could otherwise quit smoking)?
 - What are the demographic characteristics and tobacco use histories of those who are initiating use of smokeless tobacco? To what extent is marketing leading to initiation of smokeless tobacco use among current smokers, as intended, or adoption by nonusers, possibly even leading to the use of more dangerous smokeless tobacco products or smoking? Research is also needed to estimate the proportion of active smokers who would have quit smoking but instead switched to a less harmful smokeless tobacco product, as opposed to the proportion who would have continued smoking but switched. The proportion of current smokers who continue to smoke and simply add smokeless tobacco would be of interest as well.
- Although many important issues remain unresolved, we believe that a harm reduction strategy needs to be considered as one of the elements of a broad program aimed at tobacco control. Finally, it is our belief that an effective harm reduction strategy merits the same rigorous assessment and critical evaluation as any other policy intended to advance public health. ■

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Contributors

D. A. Savitz chaired the panel discussion on which this article was based and was the principal author of the article. R. E. Meyer, J. M. Tanzer, S. S. Mirvish, and F. Lewin participated in generating ideas, wrote sections of the article, and reviewed and edited multiple drafts of the article.

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