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Emerging Nicotine Delivery Products
Implications for Public Health

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Abstract

The idea of clean nicotine delivery systems that would satisfy nicotine craving and promote smoking cessation has been considered as a possible public health tool for many years. Nicotine medications have been useful for smoking cessation but have not found widespread popularity among smokers, perhaps because of slow nicotine delivery and other sensory characteristics that differ from cigarettes. Traditional smokeless tobacco delivers as much nicotine as cigarettes and has been advocated for harm reduction but contains carcinogenic nitrosamines and has not been proven to promote cessation. Furthermore, there is concern that dual use of smokeless tobacco and cigarettes may inhibit quitting smoking. Newer oral dissolvable tobacco products contain lower levels of toxicants than other smokeless tobacco but also deliver much less nicotine and have not been popular with consumers. Electronic cigarettes that aerosolize nicotine without generating toxic tobacco combustion products have become quite popular and hold promise as a way to attract smokers away from cigarettes, although efficacy in promoting smoking cessation has not yet been demonstrated. There are concerns about safety of long-term use, and there is evidence that youth, including nonsmokers, are taking up e-cigarette use. E-cigarettes are marketed for use when one cannot smoke conventional cigarettes, and such use might result in more persistent cigarette smoking. Although their benefits and risks are being vigorously debated, e-cigarettes or other clean nicotine delivery devices could play an important role as an adjunct to a U.S. Food and Drug Administration regulatory intervention to make cigarettes less addictive and in this context could contribute to the end of cigarette smoking and smoking-induced disease.

Keywords: nicotine; cigarettes; smoking; smokeless tobacco; electronic cigarettes; FDA regulation

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The devastating worldwide health effects of cigarette smoking have been discussed elsewhere in this issue of the *Journal*. Nicotine is the addictive principle in tobacco and is responsible for compulsive cigarette smoking (1). Cigarette smoking is the most highly addictive form of nicotine self-administration. Cigarette smoke exposes smokers to high concentrations of toxic combustion products that are responsible for most of the disease caused by tobacco. Nicotine may have adverse effects on the cardiovascular system and may be harmful to fetal brain and lung development during pregnancy, but the direct risks of nicotine appear to be far less than those of cigarette smoking (2).

The goal of tobacco control is to reduce and eventually eliminate disability and death caused by tobacco use. Clearly, the most effective way to do this is to get current smokers to quit and prevent nonsmokers from starting. However, because smoking is highly addictive, most smokers, despite wanting to quit, have difficulty doing so. The questions of how to get more smokers to quit and how to reduce harm among those who continue to smoke have been the subjects of public health debate for many years. For a number of years, tobacco and health researchers and policy makers considered the possibility of clean nicotine delivery devices that would satisfy nicotine craving and addiction in smokers, allowing them to stop smoking cigarettes and thus avoid most if not all of the harm from cigarette smoking (3). The idea has been considered both in the context of medicinal nicotine preparations and tobacco-based reduced-risk nicotine delivery products.

Nature of Nicotine Addiction

Nicotine establishes and maintains tobacco addiction by complex actions that affect the neurochemistry of the brain (1). Nicotine from

cigarette smoke is rapidly absorbed in the lungs, from which it rapidly passes into the brain. The rapidity of absorption is an important determinant of the addictiveness of a drug, and cigarette smoking is the most rapid method of nicotine delivery. Nicotine exerts its effects by binding to nicotinic cholinergic receptors in the brain. Nicotine affects a number of neurotransmitter systems, including the dopamine system, which is critical in experiencing pleasure. Nicotine results in positive psychological effects including pleasure, arousal, and mood modulation.

With chronic nicotine exposure, as is the case with addicted smokers, neuroadaptation occurs, such that more nicotine is required to deliver the same neurochemical effect. As the brain becomes tolerant, nicotine is needed to maintain normal brain functioning. In this context, stopping smoking is associated with deficient neurotransmitter release and associated withdrawal symptoms, including irritability, anxiety, problems getting along with family and friends, difficulty concentrating, increased hunger and eating, and weight gain. Nicotine addiction is thus sustained by a combination of positive effects related to pleasure and arousal and the need to continue to take nicotine to avoid the unpleasant effects of nicotine withdrawal.

In addition to the pharmacological aspects of nicotine addiction, conditioning also plays an important role in tobacco addiction. Smoking often becomes associated with specific behaviors, such as drinking a cup of coffee, alcohol consumption, talking on the phone, driving a car, and/or after meals. Through conditioning these behaviors become cues for smoking and contribute to maintained smoking. Smoking also facilitates nicotine dependence through sensorimotor factors associated with the act of smoking. The factors include the smoking process and the smell, taste, and feel of the cigarette smoke. Denicotinized cigarettes can produce some smoking satisfaction and can reduce cigarette craving. Given that nicotine is the essential element of addiction to tobacco but that most of the harm to health comes from combustion of tobacco, it is logical to consider the use of noncombusted sources of nicotine as way to reduce the harm from cigarette smoking.

Potentially Reduced-Harm Nicotine Delivery Products

As described above, cigarette smoke delivers nicotine rapidly to the bloodstream, achieving high concentrations in arterial blood in a manner that optimizes reinforcement and self-administration. Thus far no medicinal nicotine devices match the rapid nicotine delivery characteristics of cigarette smoking; only 25% of smokers use nicotine medications when they try to quit smoking, and most fail (4).

On the other hand, a number of potentially reduced-harm nicotine delivery products have been introduced to the market in recent years. These include oral tobacco products, such as snus and dissolvable tobacco products, and more recently electronic nicotine delivery systems (more popularly known as electronic cigarettes, or e-cigarettes). The implications of the use of oral tobacco products and e-cigarettes for public health, a topic of debate among tobacco scientists and health-care professionals, is the subject of this review.

Traditional Smokeless Tobacco Products

Traditional smokeless tobacco use delivers daily systemic doses of nicotine similar to those obtained from cigarette smoking (5). The smokeless tobacco most widely used in the United States and Europe is oral snuff, which is moist ground tobacco, sometimes packaged in a small sachet like a tea bag, that is placed between the lips and gum. Chewing tobacco, consisting of shredded tobacco, is also used in the United States but less than oral snuff. The constituents of smokeless tobacco products vary in levels of carcinogenic nitrosamines as well as other carcinogens and tumor promoters (6). Because the constituents of different oral products vary, one must be product-specific when considering evidence relating smokeless tobacco and disease risk.

In the United States, about 3% of adults use smokeless tobacco, with higher rates among American Indians and Alaskan natives (7). The prevalence of use of oral snuff, known as snus, in Sweden is approximately 20% in men and 8% in women (8). The use of smokeless tobacco in general has historically been associated with diseases of the oral cavity, oral cancer, pancreatic cancer, cardiovascular disease, and reproductive problems. However, there have been changes in smokeless tobacco in some countries, with manufacturing of products that are much lower in nitrosamines and other carcinogens compared with older products.

The epidemiology of Swedish snus is informative with respect to understanding pathophysiology and for public health recommendations, because Swedish snus delivers high levels of nicotine but contains lower levels of carcinogenic nitrosamines than most other smokeless tobacco products (6, 9). Lower nitrosamine levels are believed to be the result of pasteurization of tobacco used in Swedish snus, whereas most conventional smokeless tobacco products are fermented, resulting in higher levels of nitrite and nitrosamines (10). Studies of cancer risk in Sweden and Norway show that the use of snus is associated with an increased risk of pancreatic and possibly esophageal cancer but not oral or other cancers (11). The relative risk of pancreatic cancer with ever use of snus compared with never using any tobacco is 2.0, compared with 2.8 for cigarette smoking, and is likely a result of exposure to tobacco-specific nitrosamines (12). Because so many Swedish men use snus and do not smoke cigarettes, the prevalence of cigarette smoking is lower in Swedish men compared with men in other European countries, and the lung cancer incidence is remarkably lower as well (11). Most studies in Sweden show little or no increased risk in cardiovascular disease, although increased risk of cardiovascular disease, including acute myocardial infarction and stroke, has been associated with the use of other smokeless tobacco products in other countries (7).

Because the risks of traditional smokeless tobacco are much lower than those of cigarette smoking, smokeless tobacco has been proposed as a way to help decrease cigarette consumption, thereby reducing the harm from cigarette smoking in those who cannot stop smoking, and as an aid to smoking cessation (13). Although the use of smokeless tobacco is not harmless, it is certainly far less harmful than cigarette smoking. The major argument against the use of smokeless tobacco for harm reduction is that it may promote dual use of smokeless tobacco and cigarettes, resulting in fewer people quitting smoking (14). For example, smokeless tobacco may be used to relieve withdrawal symptoms when smokers are not permitted to smoke because of workplace or other clean air restrictions, reducing the discomfort that would otherwise have prompted them to

quit smoking. Another argument is that smokeless tobacco 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 this may not be the case. Furthermore, there is some evidence (although conflicting) that smokeless tobacco among U.S. adolescents is a strong risk factor for becoming an adult smoker, although smokeless tobacco does not appear to be a gateway to smoking in Sweden (15, 16). A recent analysis modeling the benefit versus harm for smokeless tobacco use in the U.S. population suggests that because of dual use with persistence of cigarette smoking, the adoption of smokeless tobacco would not in the long term reduce harm for the population (14). Although anecdotally smokeless tobacco helps some smokers quit, one controlled clinical trial found short-term but no long-term benefits for quitting (17). Therefore, at present there appears to be, at least at the population level in the United States, more risk than benefit in the promotion of conventional smokeless tobacco for harm reduction or to aid smoking cessation.

Newer Oral Tobacco Products

Recently, new oral tobacco products have been marketed in the United States. These include snus products, such as Camel, Marlboro, and Skoal snus, and dissolvable tobacco products, such as Stonewall, Ariva, and Camel Orbs, sticks, and strips, and Marlboro and Skoal sticks (9, 18). Like the Scandinavian products, U.S. snus products contain substantially lower levels of tobacco-specific nitrosamines than traditional smokeless tobacco products (19). Dissolvable tobacco products are finely ground tobacco compressed into sticks, strips, and tablets (orbs) that dissolve in the mouth and do not require spitting. These products contain even lower levels of nitrosamines than snus (20). The nicotine delivery of U.S. snus and dissolvables is substantially lower and results in lower plasma nicotine concentrations in users of these products compared with users of traditional smokeless tobacco; use of these products has small effects on withdrawal symptoms in abstinent smokers (20). Although there is general awareness of the availability of snus products in the United States, product use remains relatively low (21). The dissolvable products were found not to be popular in the marketplace, and several products have been withdrawn. Most likely the marketplace failure of dissolvable products is due to poor nicotine delivery, which did not satisfy the cravings of addicted smokers.

Electronic Cigarettes

Although oral nicotine products have not done well in the marketplace, the use of e-cigarettes has exploded. Electronic cigarettes heat a nicotine solution to generate an aerosol that is inhaled, without the combustion of tobacco and generation of toxic combustion products. E-cigarettes were first introduced in the United States in 2007, and use has increased exponentially every year. In 2012 in the United States, 11.4% of smokers report ever use of these cigarettes and 4.1% use in the past 30 days (22). Data from the 2012 National Youth Tobacco Survey show that recent use of electronic cigarettes rose in middle school students from 0.6% in 2011 to 1.1% in 2012 and in high school students from 1.5 to 2.8% (23). Although the vast majority of children and adolescents who have tried e-cigarettes were cigarette smokers, a substantial number had never smoked cigarettes. Whether youth who experiment with e-cigarettes become regular users or become tobacco cigarette smokers is unknown at this time.

E-cigarettes consist of a cartridge containing a liquid (propylene glycol, sometimes combined with glycerine, nicotine, and flavorings), a heating element, a lithium battery, and a microchip. Some devices look like conventional cigarettes and are disposable; others resemble pens or cigars and have replaceable or refillable tanks. More than 400 different e-cigarettes are currently marketed. Initially e-cigarettes were manufactured by small companies that did not also manufacture cigarettes. Now major tobacco companies have entered the marketplace. Lorillard has a large percent of the market with its Blu e-cigarette, and other major tobacco companies have begun marketing e-cigarettes as well. The marketing of e-cigarettes has been vigorous and has emphasized harm-reduction beliefs (24). Thus, e-cigarettes are marketed with claims of health benefit compared with smoking tobacco cigarettes, for reducing and quitting smoking, for smoking without generating irritating and harmful secondhand smoke, and for using when a person cannot smoke cigarettes. Marketing uses models and celebrities to convey images of the product as glamorous and modern.

There is currently considerable debate in the public health community about the safety and benefits versus risks of e-cigarettes. All agree that e-cigarettes would be a health benefit if the population of conventional cigarette smokers all switched to e-cigarettes and stopped smoking cigarettes entirely. There are anecdotal reports of smokers quitting smoking using e-cigarettes, and one controlled clinical trial showed noninferiority of e-cigarettes compared with nicotine patches for smoking cessation (25). This trial was conducted by telephone quit lines with minimal counseling and with e-cigarettes that delivered nicotine poorly; the quit rates in this trial were low. Population survey data do not show that people who have used e-cigarettes are more likely to quit than those who have not (26). Many e-cigarette users report smoking fewer cigarettes per day while using e-cigarettes, but the health benefits of such reduction are not clear, and there is concern that the availability of e-cigarettes when one cannot smoke conventional cigarettes may impede quitting, resulting in more smokers and more population harm.

There are also concerns about the potential toxicity of e-cigarettes, as reviewed elsewhere in this issue. The e-cigarettes that were marketed initially were contaminated with tobacco-specific nitrosamines and alkaloids other than nicotine, which were extracted along with nicotine from tobacco. Some more recently marketed products do not have such contamination. Propylene glycol in aerosol form can be a pulmonary irritant and increases dynamic airway resistance (27). E-cigarette use could be detrimental to people with asthma and chronic obstructive pulmonary disease. E-cigarettes generate particles of a size similar to cigarette smoke particles, and there are concerns that particles *per se* may have adverse health effects (28, 29). Nicotine itself has some potentially deleterious effects on cardiovascular hemodynamics (increased heart rate and blood pressure), may impair endothelial function, and may promote insulin resistance with a possible increased risk of type 2 diabetes, but its

effects are certainly much less than those of the combustion products in cigarette smoke (2). The most important potential population harm may be the renormalization of cigarette smoking behavior, resulting in more youth initiation and fewer adults quitting smoking. Some e-cigarettes look like traditional cigarettes, and their widespread use would suggest that smoking behavior is socially acceptable. Currently, e-cigarette advertising is unregulated and includes the use of young models and celebrities to convey images of the products as glamorous and modern. As mentioned previously, there are concerns that uptake of e-cigarette use by youth may lead to greater tobacco cigarette initiation.

The public health benefit of electronic cigarettes competing with conventional cigarettes in the free marketplace, as is the environment around most of the world at present, is uncertain. The U.S. Food and Drug Administration has exerted regulatory authority over e-cigarettes and is expected to issue regulations on the product in the near future. Such regulations could, and it is hoped will, ensure relative direct safety of the products and restrict advertising and other promotions to minors. Possibly in the context of free market competition, smokers would find e-cigarettes more attractive than cigarette smoking (for health and other reasons), and many would use them to quit smoking. On the other hand, the permissive availability of e-cigarettes could backfire, resulting in a situation in which there is an increase in nicotine addiction without a reduction of overall tobacco use.

Electronic Nicotine Delivery Devices as Part of a Comprehensive Nicotine Regulatory Strategy

One can also envision a broader public health strategy that combines cigarette regulation, including regulation of cigarette characteristics and pricing, with the permissive regulation of e-cigarettes or other electronic nicotine devices that are satisfying to smokers. In 1994, the idea of reducing the nicotine content of cigarettes to make cigarettes less addictive was proposed (30). In 2009, the U.S. Food and Drug Administration gained regulatory authority over tobacco, which includes the authority to reduce nicotine in cigarettes to make them less addictive, so long as the nicotine level is not reduced to zero (31). The idea of a nicotine reduction regulatory policy would be to mandate nicotine reduction in all manufactured cigarettes, as well as roll-your-own tobacco and other smoked tobacco products, so that they would not sustain addiction. Research is ongoing on the safety and effects of smoking behavior of reduced nicotine content cigarettes (32, 33). If a reduced nicotine content regulatory strategy becomes policy, cigarettes will become less addictive due to limited nicotine availability, and therefore less attractive to the smoker. If at the same time electronic cigarettes or other noncombusted nicotine delivery devices were made widely available, it could help the cigarette smoker to transfer their nicotine addiction from tobacco to a cleaner form of nicotine delivery. The movement from cigarette smoking to cleaner forms of nicotine could be facilitated by differential taxation. The result could be prevention of most cigarette-induced disease. Whether society would be accepting of recreational nicotine addiction if there were minimal health consequences from such addiction is unknown at this time. But if the result would be the termination of the epidemic of cigarette-induced disease, refusing such an alternative would be difficult.

These are exciting and challenging times for tobacco researchers and policy makers, because of the possibility that tobacco-related disease might be eliminated in the next generation. Modeling the health effects of reducing the nicotine content of cigarettes to nonaddictive levels, Tengs and colleagues concluded, "Policy makers would be hard-pressed to identify another domestic public health intervention, short of historical sanitation efforts, that has offered this magnitude of benefit to the population" (34). Our understanding of tobacco use and nicotine addiction, and the possibility of applying addiction science to eliminate cigarette smoking, is a result of 50 years of science that was kicked off with the 1964 Surgeon General's Report. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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