Circulation

AHA POLICY STATEMENT

Impact of Smokeless Oral Nicotine Products on Cardiovascular Disease: Implications for Policy, Prevention, and Treatment: A Policy Statement From the American Heart Association

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ABSTRACT: Smokeless oral nicotine products are addictive, and their use has potential adverse effects on some but not all biomarkers of cardiovascular risk. The use of some types of these products, for instance, is associated with an increased mortality risk in those with ischemic heart or cerebrovascular disease. Similarly, smokeless tobacco has the potential to increase the risk of oral cancer, but the risks depend on the chemical composition of the product. The market of smokeless oral nicotine products has transformed since the last American Heart Association smokeless tobacco policy statement. Several varieties of tobacco-free oral nicotine products—including oral nicotine pouches; nontherapeutic nicotine gums, lozenges, and tablets; and nicotine gummies—have rapidly proliferated. The sales of oral nicotine pouches, in particular, have increased substantially; however, no data are available on their cardiovascular or health risks. In addition, synthetic (compared with tobacco-derived) nicotine has been used in some brands of oral nicotine products, but its cardiovascular and health effects have been inadequately studied. Robust public policy levers are identified to support ending addiction to all commercial tobacco products. Critical components and policy initiatives include clinicians emphasizing the prevention of tobacco product initiation and supporting cessation with established pharmacological and behavioral tobacco dependence treatment therapies as primary goals for achieving an end to commercial tobacco and nicotine addiction.

Key Words: AHA Scientific Statements ■ cardiovascular diseases ■ epidemiology ■ health policy ■ nicotine ■ risk factors ■ tobacco, smokeless

This policy statement updates the 2010 American Heart Association policy statement on smokeless tobacco products to reflect the rapid proliferation of new noncombustible products in the marketplace, especially oral nicotine pouches, including those containing synthetic nicotine.[1,2] Objectives of this policy statement are (1) to review and summarize the chemical composition of smokeless oral nicotine products, including newer synthetic nicotine products; (2) to describe and discuss use patterns among youth and adults and across geography, sex, gender, race, and ethnicity; (3) to review potential cardiovascular and oral effects of smokeless oral nicotine product use; and (4) to summarize implications of use for our policy work toward ending tobacco and nicotine addiction in the United States. This policy statement does not address combustible products, noncombustible products such electronic cigarettes (e-cigarettes), or approved therapeutic use of nicotine such as nicotine replacement therapy.

In national surveillance data, smokeless tobacco products were reclassified in 2023 as smokeless oral nicotine products to reflect the proliferation of new oral nicotine products.[3] Smokeless oral nicotine products include smokeless tobacco (chewing tobacco, snuff, dip, or snus), nicotine pouches, and other oral nicotine products (lozenges, discs, tablets, gums, dissolvable tobacco

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products, and other products).[3] Smokeless oral nicotine products vary widely in composition around the world. Product composition and concomitant use of different types of nicotine products influence the level of risk of dependence and health risk associated with product use.

In the United States, the prevalence of smokeless oral nicotine product (primarily smokeless tobacco) use has remained relatively stable across recent years. In the 2021 National Health Interview Survey, 2.1% of adults ≥18 years of age (5.2 million) reported current (every day or some days) smokeless oral nicotine product use[4] compared with 2.3% in 2020.[5] Newer categories of smokeless oral nicotine products, marketed as tobacco-free products, are gaining popularity, particularly among youth[3,6–8] and young adults.[9,10] Among youth (6th–12th grade) with current (past 30 days) use of any tobacco product, nicotine pouch (tobacco-derived and synthetic nicotine) use increased from 1.1% (280 000 students) to 1.5% (400 000 students) between 2022 and 2023.[3,6] Furthermore, among those who are current and former smokers and those who use e-cigarettes, nicotine pouches are most popular among individuals 18 to 24 years of age (2.3% past 30-day use) compared with other age groups,[9] and the unit sales numbers have increased steadily since 2016.[11] In 2023, although e-cigarettes were still the most used tobacco product among middle and high school students (7.7%, 2.13 million), nicotine pouches were behind cigarettes and cigars at 1.5%, followed by smokeless tobacco (1.2%) and other oral nicotine products (1.2%), which include lozenges, discs, tablets, gum, and other dissolvable tobacco products.[3] Some of these emerging oral nicotine products contain synthetic nicotine instead of the tobacco-derived nicotine used in conventional tobacco products.

Synthetic nicotine is not derived from tobacco, and it was not clear that the US Food and Drug Administration (FDA) had regulatory authority over synthetic nicotine until Congress explicitly granted that authority in March 2022 with H.R. 2471, the Consolidated Appropriations Act.[12] According to this law, synthetic nicotine or nontobacco nicotine products were required to submit premarket tobacco applications to the FDA, and those applications are being reviewed. Under this authority, the FDA has issued warning letters to manufacturers and retailers for selling synthetic nicotine products that have not received FDA authorization, but many products remain on the market illegally.[13]

More research is needed on the health risks associated with use of the recently introduced types of smokeless oral nicotine products. It is important that concomitant use of tobacco-based and synthetic nicotine products be assessed. Data on the relative cardiovascular disease (CVD) risk of different smokeless oral nicotine products are limited and complicated because risk is a function of toxicological characteristic and use patterns. Although there are no safe tobacco products, a continuum of risk across tobacco and oral nicotine products exists, with the greatest risk associated with combustible products such as cigarettes and cigars.

SMOKELESS ORAL NICOTINE PRODUCTS

Categories of Products

Throughout this policy statement, we use terms delineating tobacco-containing products from nicotine-containing products to avoid potential confusion caused by imprecise or inconsistent terms.[14] Table 1 lists relevant smokeless oral nicotine products by category.

Chewing tobacco leaves are cured, may be flavored or sweetened, and come as loose leaves, a plug, a twist, or a roll that is placed between the cheek and teeth row and requires spitting. Nicotine absorption, as in other oral products, is across the buccal mucosa.

Dissolvable tobacco products consist of finely ground tobacco pressed into various shapes such as lozenges, strips, sticks, and pellets that do not require spitting.[15,16] Dissolvable tobacco products are used and marketed as alternatives to combustible tobacco products, especially in situations when an individual is unable to smoke (eg, schools, planes, hospitals).[16] These products are not

Table 1. Smokeless Oral Nicotine Products Available in the United States

Category and product	Definition
Tobacco containing	
Chewing tobacco/spit	Oral tobacco-containing product that is manufactured to be chewed
Dissolvable tobacco	Oral tobacco-containing product that dissolves in the mouth
Oral snuff/dip	Oral tobacco-containing product that is composed mainly or exclusively of moist, ground, or powdered tobacco that is processed to make it suitable for use by a person placing it in the mouth between the gum and the cheek
Nasal snuff	Smokeless oral nicotine-containing product that is formed of dry finely ground tobacco and is ingested by a person into the nasal cavity
Snus	Oral tobacco product that is composed of dry tobacco that is placed between the upper lip and gum for extended periods; snus does not typically result in the need for spitting
Tobacco derived and synthetic	
Pouches	Small fiber pouch containing nicotine, flavorings, sweeteners, and plant-based fibers that is placed between the upper lip and gum
Gums	Flavored chewing gum containing nicotine
Lozenges	Flavored lozenge containing nicotine that dissolves in the mouth
Tablets	Flavored tablet containing nicotine that dissolves under the tongue
Gummies	Flavored chewable gummy candies containing nicotine

approved as smoking cessation therapies and, in fact, have the potential for promoting dual use with combustible tobacco products.[16,17] However, since 2013, these products are no longer commercially available in the United States.

Snuff is noncombustible finely ground tobacco, which is available moist or dry and loose or in pouches. Moist snuff (ie, dip) is cured, fermented tobacco that is pinched and placed in between the cheek and gum and requires spitting. Dry snuff is fine-cured tobacco powder that is inhaled through the nose. Snuff products are marketed as smokeless tobacco products, not as smoking cessation therapies. However, one moist snuff product, Copenhagen Classic Snuff (US Smokeless Tobacco Company), has been designated by the FDA as a modified-risk tobacco product in 2023.[18] This designation indicates that switching completely to this product from smoking tobacco may reduce the risk of lung cancer.[19,20] Modified-risk tobacco product status can be granted only to a single specific product, not an entire class of tobacco products.

Snus is a type of moist snuff that is often packaged in small teabag-like pouches that are placed between the upper cheek and gums and, unlike snuff, do not require spitting. Several snus products were authorized by the FDA in 2019 as modified-risk tobacco products[20] because they may be less harmful to health when used instead of combustible cigarettes. The safety and effectiveness of oral nicotine pouches as a risk reduction approach or quit therapy need further research. General Snus (Swedish Match USA, Inc; undergoing the renewal process in 2024) and Camel Snus (R.J. Reynolds Tobacco Company) have been designated by the FDA as modified-risk tobacco products.[20]

Oral nicotine pouches emerged on the US market in 2016. They are pouches prefilled with either tobacco-derived or synthetic nicotine mixed with flavorings (eg, mint, fruit) and other fillers.[21,22] Like snus, oral nicotine pouches do not require spitting.[21,22] Pouches are placed between the upper lip and gum, and the nicotine that is released is absorbed into the bloodstream through the buccal mucosa over 30 to 60 minutes per use.[22] Oral nicotine pouches differ from snus in that they do not contain leaf tobacco.[21] Like snus, however, they are marketed as an alternative, tobacco-free, and safer product than combustible cigarettes.[21,23] The safety and effectiveness of oral nicotine pouches as a harm reduction approach or quit therapy have not been established, but on the basis of the FDA authorization of reduced risk for certain snus products, it is likely that nicotine pouches that contain fewer toxicants have the potential to reduce tobacco-related harm if someone who smokes switches completely.

Nicotine gummies contain nicotine in the form of a flavored gummy candy, ranging in nicotine concentration between 1 and 6 mg per gummy. Because of their candy-like appearance with appealing flavors with colorful packaging, these products are particularly dangerous for children. Depending on the child's weight, exposure of 1 to 14 mg nicotine in a child <5 years of age can lead to toxic events ranging from nausea, vomiting, and abdominal pain to seizure, coma, and death.[24,25] Of note, nicotine gummies are not approved by the FDA as a form of nicotine replacement therapy or as a method to stop smoking. In August 2022, the FDA sent a warning letter to one manufacturer of nicotine gummies because they were marketing the product as tobacco-free but did not submit a premarket tobacco product application.[26]

CHEMICAL COMPOSITION AND PHARMACOLOGY OF ORAL NICOTINE PRODUCTS

Chemical Composition

Tobacco-Derived Nicotine Products

According to the FDA, smokeless tobacco contains a mix of 4000 chemicals, including ≥30 linked to cancer.[27] The chemical compounds identified in these products have been classified broadly into tobacco alkaloids, tobacco-specific nitrosamines, volatile N-nitrosamines, N-nitrosamino acids, polycyclic aromatic hydrocarbons, radionucleotides, pesticide residues, humectants, alfatoxins, and mycotoxins.[28] Tobacco-specific nitrosamines such as N′-nitrosonornicotine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and polycyclic aromatic hydrocarbons such as benzo[a]pyrene (B[a]P), radionuclides, and alfatoxins have been classified as potent carcinogens by the International Agency for Research on Cancer.[28] Nicotine, the predominant tobacco alkaloid and precursor of tobacco-specific nitrosamines, is also the cause of the addictiveness associated with any form of tobacco use.[28] Other chemicals identified include the heavy metals cadmium, lead, and nickel, as well as arsenic, a chemical used in insecticides, and formaldehyde. One must use caution, however, when extrapolating from one smokeless tobacco-derived product to another because various products are different and vary considerably in composition, toxicant profiles, and associated health risk, related primarily to differences in tobacco production, curing, processing, and storage.[29,30]

The Smokeless Tobacco Chemical Database has identified a total of 233 known compounds from 82 different products used internationally, of which 98% have known toxic physiochemical properties and 30% (69 compounds) are considered carcinogenic by the International Agency for Research on Cancer.[28] Of 69 classified compounds, 7 compounds (formaldehyde, beryllium, arsenic, cadmium, N-nitrosonornicotine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, and

Benzo[a]pyrene) were classified as carcinogenic to humans (Figure 1).[28]

Synthetic Nicotine Products

Synthetic nicotine, also called tobacco-free nicotine or nontobacco nicotine,[31] is currently being used in e-cigarettes, nicotine pouches, and moist snuff products. Because nicotine exists as a chiral molecule with 2 stereoisomers, (S)-nicotine and (R)-nicotine, tobacco leaf contains almost exclusively (S)-nicotine. Early methods to synthesize nicotine produced an equal mixture of the (S)-nicotine and (R)-nicotine, but more recently, manufacturers have developed methods to refine the synthetic mixture to create different ratios of the isomers and even products that are similar to tobacco-derived (S)-nicotine.[2,32–35] Nonetheless, the term tobacco-free can be confusing and ambiguous for the consumer. Technically, this is a broad term encompassing synthetic nicotine and nicotine derived from other nightshade family plant sources such as tomato and eggplant. Some companies may be using this label inaccurately, describing their brands as tobacco-free but actually using a highly purified form of tobacco-derived nicotine, or merely inaccurately, labeling standard tobacco-derived nicotine.[36]

Although various tobacco-free oral nicotine pouches have entered the US market, little is known about the long-term safety and the pharmacological and metabolic effects in humans. Within the nose, mouth, and throat, nicotine may act on not only nicotinic acetylcholine receptors but also olfactory receptors and transient receptor potential (TRP) ankyrin1, melastatin 4, and melastatin 5, which contribute to the chemosensory effects of nicotine.[37] The TRP ankyrin1 channel, in particular, has been identified as potential target for treatment for tobacco and nicotine dependence.[38] Compared with (S)-nicotine, (R)-nicotine is a less potent (≈10-fold) agonist of nicotine receptors and does not induce weight loss in animal studies; however, both stereoisomers interfere with the production of certain lipid mediators involved in the regulation of inflammation and have similar effects on the TRP ankyrin1 receptor.[21,37,39–41] In addition, animal models have suggested that exposure to (R)-nicotine upregulates nicotine receptor binding sites similar to exposure to (S)-nicotine,[42,43] which may have further implications for nicotine dependence. Manufacturers and vendors of tobacco-free nicotine claim that their products are virtually tasteless, odorless nicotine without the residual impurities of tobacco-derived nicotine and, as a result of specific ratios of the R to S isomers, could potentially offer nicotine use at satisfying but nonaddictive or less addictive levels.[44,45] At least 1 recent analysis of 48 packages from 22 brands (purchased in Germany) of nicotine pouches found 186 substances, in addition to nicotine, that included sweeteners, humectants, acidity regulators, aroma substances, and fillers.[46] Furthermore, many of these ingredients are classified as hazardous, are not authorized as food flavorings, or are classified as possible carcinogens.[46] Data suggest that young adults who are male and have past use of smokeless tobacco are more likely to be susceptible to or to have attested to the use of tobacco-free nicotine pouches.[47–49] Further research is needed to determine whether synthetic nicotine products are more or less addictive than their tobacco-derived nicotine product counterparts.

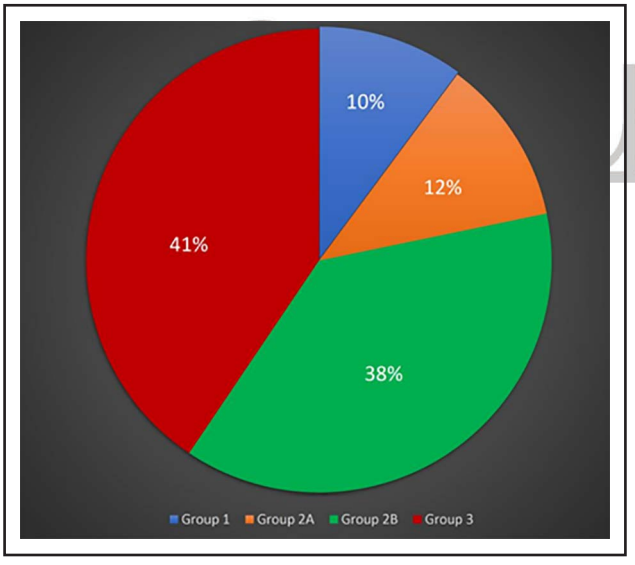

Figure 1. Percentages of carcinogens in smokeless tobacco products (n=82) per International Agency for Research on Cancer classifications.

Group 1, carcinogenic to humans; group 2A, probably carcinogenic to humans; group 2B, possibly carcinogenic to humans; and group 3, not classifiable as to its carcinogenicity to humans. Reprinted from Kaur et al.[28] Copyright © 2019 The Authors. Published on behalf of the Authors, by Springer Nature. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited. Available at https://nature.com/articles/s41598-019-43559-y

Pharmacology of Nicotine

General Pharmacology

Nicotine is the proximate cause of all tobacco-induced disease because it drives dependence and compulsive use. However, most of the harm from tobacco use results from inhalation of tobacco combustion products, which delivers high levels of oxidizing chemicals, numerous toxic volatile organic compounds, and carbon monoxide. Because oral nicotine products do not expose users to combustion toxins, an important question is the intrinsic toxicity of nicotine. Nevertheless, most smokeless oral nicotine products, except those containing pure nicotine, contain various chemicals, including various carcinogens (discussed previously), that may impart disease risk; therefore, it cannot be assumed that the risks of oral nicotine products could be attributed wholly to nicotine.

When ingested or inhaled, nicotine acts on nicotinic cholinergic receptors, which are endogenous receptors for the actions of acetylcholine.[50] Nicotinic receptors are present throughout the body, including in the cardiovascular system. The major pharmacological effect of nicotine is activation of the sympathetic nervous system by both neuronal release of norepinephrine and systemic release of epinephrine. Nicotine acutely increases heart rate and blood pressure and constricts blood vessels in the skin and diseased coronary arteries. Sympathetic neural activation results in reduced heart rate variability and an increase in arterial stiffness. Nicotine can also induce nonneuronal effects, including impaired endothelial function, as demonstrated by reduced flow-mediated dilation. Reduced heart rate variability, arterial stiffness, and endothelial dysfunction are robust markers of cardiovascular risk; however, it is unclear how acute changes in these responses due to the sympathetic effects of nicotine relate to long-term CVD risk.[51]

In addition to the hemodynamic effects, nicotine-mediated sympathetic stimulation activates lipolysis and induces insulin resistance, which can increase the risk of developing type 2 diabetes.[50] Nicotine exposure also reduces high-density lipoprotein cholesterol, leading to a more atherogenic lipid profile.[50] Furthermore, the actions of nicotine on the release of catecholamines may lower the threshold for arrhythmias, elevating mortality risk under proarrhythmic conditions such as myocardial ischemia.[50] Nicotine augments angiogenesis in animal models, although the relevance of this observation to human disease is not yet clear.[50]

Pharmacokinetic Considerations

Nicotine that is inhaled is absorbed quickly into the bloodstream, resulting in high concentrations of nicotine in arterial blood and various body organs. Nicotine levels decline quickly between cigarettes, although with consistent smoking, nicotine levels in the body increase throughout the day. Compared with inhalation, nicotine absorption from smokeless oral nicotine products is more gradual, resulting in lower peak nicotine blood levels and a longer time to peak concentration, depending on how long the product is held in the mouth.[51] With consistent use of smokeless tobacco, blood nicotine levels rise and fall throughout the day, similar to what is seen with cigarette smoking.[52]

The rate and, to some extent, the route of oral absorption of nicotine depend in part on the pH of the product.[32] Un-ionized nicotine is readily absorbed through mucous membranes such as the buccal mucosa, but ionized nicotine is not. At high pH, more nicotine is un-ionized; therefore, more nicotine is absorbed across mucous membranes more quickly. At a lower pH, less nicotine is absorbed buccally, and more of the nicotine is swallowed and absorbed through the gastrointestinal tract, after which nicotine undergoes first-pass metabolism in the liver. The bioavailability of swallowed nicotine is between 30% and 40%.[42] The industry's own documents detail the "graduation program" whereby tobacco companies market smokeless oral nicotine products with different pHs such that youth who start can use lower pH products with slower nicotine delivery and then graduate over time to higher pH products for faster nicotine delivery.[53]

The pharmacodynamics of nicotine are also important considerations in understanding risk of oral compared with inhaled nicotine. The faster the rate of rise is, the greater the subjective and cardiovascular effects are. Another important pharmacodynamic phenomenon is the development of tolerance. Sustained exposure of nicotinic receptor results in the development of acute tolerance, although the tolerance to some effects is partial. For example, with sustained nicotine exposure, resting heart rate remains significantly higher than in those who do not use nicotine.[54] On the other hand, the acute effect of nicotine exposure from smokeless tobacco on blood pressure is between 5 and 10 mm Hg,[47] whereas with daily use, there is a smaller average increase of <5 mm Hg.[50] The implications of slower absorption of nicotine from oral nicotine products may be less pronounced cardiovascular effects than those from smoking.

Nicotine Addiction

Noncombustible smokeless oral nicotine products, including oral nicotine pouches, snuff, and snus, continue to emerge as alternatives to combustible tobacco products. Although the FDA Center for Tobacco Products has regulatory authority over tobacco products and many are marketed as an alternative to combustible tobacco products, they are not regulated as drugs and thus do not have well-established clinical trial–level data to establish their safety and effectiveness for treatment of tobacco and nicotine dependence.[55,56] The potential for ongoing nicotine addiction is associated with the use of these products in that they tend to deliver substantial amounts of nicotine and are often used in addition to combustible cigarettes or other tobacco products, contributing to dual use.[57] Last, because of the discreet nature of use, these products tend to be attractive to adolescents and young adults, thereby increasing the risk of dependence, addiction, and harm.[7,8,58,59]

EPIDEMIOLOGY OF SMOKELESS ORAL NICOTINE PRODUCT USE

According to data from the 2022 National Survey on Drug Use and Health, 63.9 million people in the United States attested to using some form of tobacco or nicotine product in the past month, of whom 6.1 million

reported using conventional smokeless oral nicotine products (snuff, dip, chewing tobacco, or snus) within the past month (Figure 2).[60]

Conventional Smokeless Oral Nicotine Products Used in the United States

Table 2 depicts the prevalence of use of conventional smokeless oral nicotine products in the United States broken down by demographic characteristics. These products are currently (past 30 days) used by ≈5.2 million adults ≥18 years of age (2.1%)[4] and by 330 000 middle and high school students (1.2%).[3] Although smokeless tobacco is used at higher rates by adults than by youth, rates are comparable for adults up to 65 years of age. Likewise, the prevalence of conventional smokeless tobacco use does not differ significantly by income or education level.[65,66] In contrast, smokeless tobacco is used at consistently higher rates by male than female individuals and by those who identify as non-Hispanic White than any other race and ethnicity for both youth[3] and adult[4,63,64] samples. Use of these products is also historically greater in rural than urban areas and in the South and Midwest regions of the United States relative to the West and Northeast regions.[4] As for use by sexual identity status, conventional smokeless tobacco use is higher among adults identifying as heterosexual than those identifying as a sexual or gender minority.[4,61,63] However, this pattern may apply only to men. For women, those identifying as lesbian report higher rates of smokeless tobacco use than heterosexuals.[62] At least 1 study suggests that ever-use of smokeless tobacco is more likely among youth who identify as transgender than those who identify as non-transgender.[61]

Novel Smokeless Oral Nicotine Products Use in the United States

Table 3 shows prevalence of use of novel oral nicotine products in the United States by demographic characteristics. Among adults who report ever-use of a tobacco or e-cigarette product, ever-use of novel oral nicotine products ranges from 3.0% to 16.4%, and current (past 30-day) use ranges from 0.9% to 3.0%.[9,27] For adults from younger age groups specifically (ie, ≈18–40 years of age), the rates of ever-use and current use are as high as 39.0% and 28.5%, respectively.[67,68] Rates for youth are 2.3% to 3.1% for ever-use and 1.2% to 1.8% for current use of these products.[3,65,67] As with the use of conventional smokeless oral nicotine products, ever-use and current use of novel products are more common among male than female adolescents[3,65] and adults.[9,66,67] Generally, use of these products is most common among younger adults (eg, 18–40 years of age) relative to older adults or youth.[9,66,67] As for use by race and ethnicity, use of smokeless oral nicotine products is higher among non-Hispanic White youth and adults,[3,67] or there is no differences between groups.[9,66] No data are available on the prevalence of these products among those identifying as a gender or sexual minority.

International Prevalence of Smokeless Oral Nicotine Product Use

Recent work describes global use of conventional smokeless oral nicotine products in any form from 2010 to 2019 for youth (12–16 years of age).[69] Across all 138 countries that were included, current use of smokeless tobacco was reported by 4.4% (Table 4). When considered by region, use rates are highest in Southeast

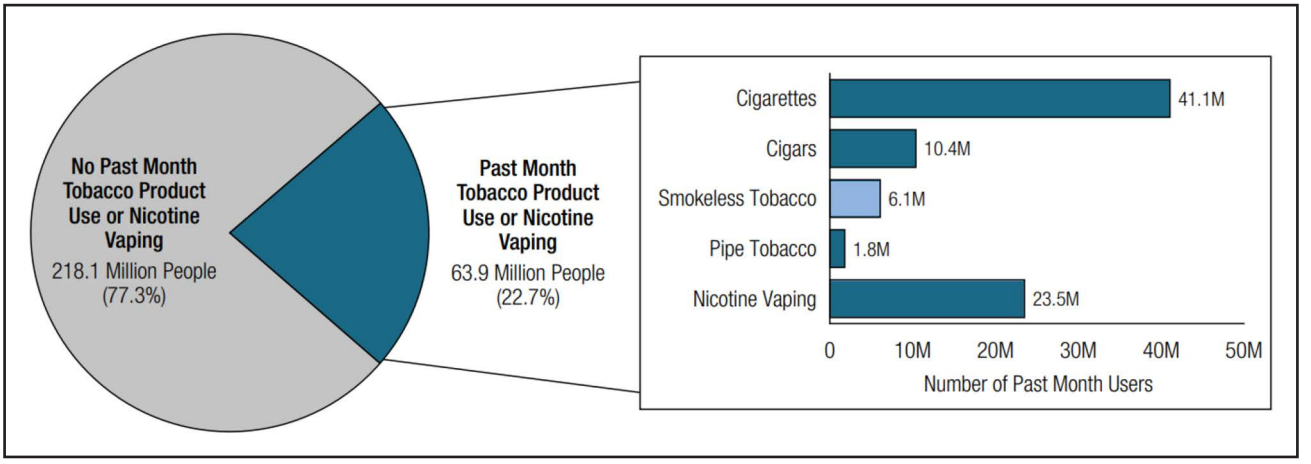

Figure 2. Past-month tobacco use and nicotine vaping among people ≥12 years of age, 2020.
The estimated numbers of current (past-month) users of different tobacco products or nicotine vaping are not mutually exclusive because people could have used >1 type of tobacco product or used tobacco products and vaped nicotine in the past month. Adapted from: Substance Abuse and Mental Health Services Administration.[60] *Key Substance Use and mental health indicators in the United States: Results From the 2020 National Survey on Drug Use and Health*. Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. HHS Publication No. PEP21-07-01-003, NSDUH Series H-56. Retrieved from https://samhsa.gov/data/

Table 2. Current (Past 30 day) and Ever-Use of Conventional Smokeless Oral Nicotine Products Among Youth and Adults in the United States

	Johnson et al[61]		Birdsey et al[3]		Delahanty et al[62]		Azagba et al[63]	Zavala-Arciniega et al[64]	Cornelius et al[4]	
Data source	PATH, 2015–2016		NYTS, 2023		TFL, 2016		BRFSS, 2014–2017	TUS-CPS, 2018–2019	NHIS, 2021	
Age range, y	14–17		Middle and high school students		18–24		≥18	≥18	≥18	
	Current	Ever	Current	Ever	Current	Ever	Current	Current		Current
Overall, y			1.5	2.4						2.1
Age, %										
18–34 y								1.7	18–24 y	1.4
35–54 y								1.8	25–44 y	2.5
≥55 y								0.9	45–64 y	2.8
									≥65 y	0.9
Sex, %										
Male			2.1	2.7				2.9		4.2
Female			0.8	2.3				0.1		0.2
Gender, %										
Transgender	5.7	21.5								
Non-transgender	1.6	6.0								
Cisgender male gay					5.5	14.5				
Cisgender male bisexual					1.9	16.3				
Cisgender female gay					3.4	14.8				
Cisgender female bisexual					0.1	9.1				
Gender minority					2.7	13.6				
Sexual orientation, %										
Heterosexual/straight							3.5			2.2
Lesbian/gay/bisexual										1.2
Lesbian/gay							2.5			
Bisexual							3.2			
Other							3.7			
Race and ethnicity, %										
Non-Hispanic White			1.2	2.9				2.0		2.9
Non-Hispanic Black								0.4		0.9
Non-Hispanic Asian										0.3
Non-Hispanic AI/AN										
Non-Hispanic other								0.8%		1.2
Other										
Hispanic			1.6	2.5				0.3		0.8
US Census region, %*										
South										2.3
Midwest										3.2
Northeast										1.2
West										1.6

(*Continued*)

Table 2. Continued

	Johnson et al[61]		Birdsey et al[3]		Delahanty et al[62]		Azagba et al[63]	Zavala-Arciniega et al[64]	Cornelius et al[4]	
Metropolitan statistical area, %†										
Urban										1.8
Rural										4.5

PATH wave 3 includes chewing tobacco, snuff, dip, spit, or snus; current use defined as any use in past 30 d.[61] NYTS includes chewing tobacco, snuff, dip, or snus; ever use defined as ever using the product; current use defined as use on ≥1 d in past 30 d.[3] TFL sample: individuals identifying as sexual minority; includes chewing tobacco, snuff, dip, or snus; current use defined as use on ≥1 d in past 30 d.[62] BRFSS includes chewing tobacco, snuff, or snus; current use defined as using every day or some days.[63] TUS-CPS includes chewing tobacco, snuff, dip, spit, or dissolvable; current use defined as using every day or some days.[64] NHIS includes chewing tobacco, snuff, dip, snus, or dissolvable; current use defined as using at least once in lifetime and now using every day or some days.[4]

AI/AN indicates American Indian/Alaska Native; BRFSS, Behavioral Risk Factor Surveillance System; NHIS, National Health Interview Survey; NYTS, National Youth Tobacco Survey; PATH, Population Assessment of Tobacco and Health; TFL, This Free Life; and TUS-CPS, Tobacco Use Supplement to the Current Population Survey.

*Northeast: Connecticut, Maine, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Vermont. Midwest: Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, and Wisconsin. South: Alabama, Arkansas, Delaware, District of Columbia, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, and West Virginia. West: Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, and Wyoming.

†Metropolitan statistical area: urban=large central metropolitan, large fringe metropolitan, medium metropolitan, and small metropolitan; rural=nonmetropolitan.

Asia, Africa, and the Eastern Mediterranean and lowest in the Americas, Europe, and Western Pacific.[69] In addition, overall rates were higher for boys than girls and for older than younger youth (15–16 versus 12–14 years of age, respectively; similar to what has been previously reported[72]). These patterns are supported by other work that examined smokeless tobacco use in 82 middle- and low-income countries among those ≥15 years of age (Table 4).[70] That is, rates of current smokeless tobacco use were 7.7% overall, were higher for men than women, and were higher in Southeast Asia than all other regions.[70] However, the most popular smokeless tobacco product used by men was chewing tobacco, whereas that used by women was betel nut (with or without tobacco) and oral snuff.[70] Smokeless tobacco use also was higher in rural than in urban areas, and use generally increased with increasing age but decreased with increasing income and education levels (Table 4).[70] Also notable is that snus pouches are highly popular in Norway and Sweden, where the product originated.[73–75] In fact, rates of snus use surpass those for cigarette smoking among men in these countries.[74,75] Notably, these products can differ dramatically from country to country. Different additives are used to increase product appeal to specific groups, and we have limited knowledge about the toxicities of many of these additives.

SMOKELESS ORAL NICOTINE PRODUCT USE AND CVD AND OTHER HEALTH IMPACTS

Cardiovascular Effects of Smokeless Oral Nicotine Products

The cardiovascular effects of smokeless tobacco use were reviewed in detail in the 2010 American Heart Association scientific statement "Impact of Smokeless Tobacco Products on Cardiovascular Disease: Implications for Policy, Prevention, and Treatment."[1] The evidence at that time was that cardiovascular risks with smokeless tobacco use are lower compared with cigarette smoking, but there were still cardiovascular risks. Long-term smokeless tobacco use was associated with a modest increase in risk of fatal myocardial infarction (MI) and stroke.[1] Some smokeless tobacco products contain sodium as part of the sodium bicarbonate buffer or glycyrrhizic acid derived from licorice flavoring. Ingestion of either in high doses may result in hypertension. Most of the epidemiological studies on smokeless tobacco and CVD came from Sweden, where the use of snus is common among men. Moreover, the international INTERHEART study, which examined smokeless tobacco use from a number of countries from around the world, found an association between smokeless tobacco use and the risk of acute MI.[76] The inconsistent findings may be due to differences in smokeless tobacco products, patterns and intensity of use, or research designs.

Several epidemiological studies on smokeless tobacco and CVD have been published since the last American Heart Association scientific statement. Most studies have been conducted in Sweden, where 20% of men use snus, a moist-tobacco, low-nitrosamine product that is regulated by the government, and in the United States, where fewer adults use smokeless tobacco and many types of smokeless products are currently in the market without authorization. Pooled analyses of prospective cohort studies in Sweden have confirmed an increased short-term risk of mortality resulting from MI and stroke but no increased risk of acute MI or stroke.[77,78] One study found that among those who use snus who were hospitalized with acute MI, those who quit snus use had a lower mortality in a 2-year follow-up compared with those who continued snus use.[79] Increased mortality in people with underlying coronary heart disease could be related to the arrhythmogenic effects of nicotine in the context of recurrent acute ischemia. A study of those using snus who underwent percutaneous coronary

Table 3. Current (Past 30 day) and Ever-Use of Novel Smokeless Oral Nicotine Products Among Youth and Adults in the United States

	Birdsey et al[3]				Schneller et al[65]			Couch et al[66]			Felicione et al[9]			Sparrock et al[67]		
Data Source	NYTS, 2023				ITC-Youth, 2019–2021			Online, 2021			ITC-4CV3, 2020			CaC-TUS, 2021		
Age range, y	Middle and high school students				16–19			14–20			≥18			≥21		
	Current (other)	Ever (other)	Current (pouches)	Ever (pouches)		Current	Ever		Current	Ever		Current	Ever		Current	Ever
Overall, %	1.2	3.0	1.5	2.3		1.8	4.1		13.5	36.4		0.9	3.0		3.0	16.4
Age, %																
					16 y	1.3	2.9	14–17 y	10.2	29.7	18–24 y	2.3	7.2	18–30 y	4.2	20.8
					17 y	1.4	2.9	18–20 y	14.7	39.0	25–39 y	1.5	4.4	31–45 y	5.1	26.0
					18 y	2.2	4.8				40–54 y	0.3	1.9	46–60 y	0.9	6.2
					19 y	2.3	5.7				≥55 y	0.0	0.4	≥61 y	0.1	6.2
Sex, %																
Male	1.2	3.2	2.1	3.0		2.3	4.9					1.1	4.2		3.8	18.6
Female	1.1	2.7	0.8	1.7		1.3	3.2					0.5	1.3		1.7	13.1
Gender, %																
Men									18.7	45.9						
Women									11.1	32.0						
Other									10.5	34.2						
Race and ethnicity, %																
Non-Hispanic White	1.2	3.2	1.4	3.0		1.8	4.0		11.8	34.4	White	0.8	2.9		2.7	16.8
Non-Hispanic Black	0.5	1.7				2.3	5.2		15.9	36.8	Non-White*	0.8	3.0		4.0	13.4
Non-Hispanic Asian									13.3	40.0					5.7	20.9
Non-Hispanic AI/AN		4.9														
Other		4.2				1.8	3.7		15.4	37.0					0.0	29.0
Hispanic	1.5	3.5	1.9	2.0		1.9	4.4		16.5	41.0					3.0	14.1
Urbanicity, %†																
Small city															2.4	16.6
Suburban															3.0	15.8
Small town															1.6	18.1
Rural															2.9	15.0
Big city															5.0	19.1

NYTS includes lozenges, discs, tablets, gums, and dissolvables ("other") or includes nicotine pouches ("pouches"); ever-use defined as ever using the product; current use defined as use on ≥1 d in the past 30 d.[3] ITC-Youth: data collapsed across 2019 to 2022; includes nicotine pouches; ever-use defined as ever using the product; current use defined as use on ≥1 d in past 30 d.[65] Participant sample consists of ever-users of electronic cigarettes; includes pouches and nontherapeutic lozenges or gum; ever-use defined as ever using the product; current use defined as use on ≥1 d in the past 30 d.[66] ITC-4CV3 sample: current or former cigarette smokers or electronic cigarette users; includes oral nicotine tobacco-free pouches or pods; ever-use defined as ever using the product; current use defined as use on ≥1 d in past 30 d.[9] CaC-TUS sample: recent former or current tobacco product users; includes nicotine pouches; ever used defined as used product but not at time of survey; current use defined as used product at least some days at time of survey.[67]

AI/AN indicates American Indian/Alaska Native; CaC-TUS, COVID-19 and Commercial Tobacco Use Study; ITC-4CV3, International Tobacco Control Four Country Smoking and Vaping Survey, Wave 3; ITC-Youth, International Tobacco Control Policy Evaluation Youth Tobacco and Vaping; and NYTS, National Youth Tobacco Survey.

*Non-White includes non-Hispanic Black, non-Hispanic other, non-Hispanic multiple races, and Hispanic.

†Not defined.

intervention found that snus use on admission was not associated with a composite outcome of all-cause mortality, new coronary revascularization, or new hospitalization for heart failure, but continuing compared with quitting snus use was associated with a shorter time to a subsequent percutaneous coronary intervention.[80] Another cohort study found that snus use was associated with increased hospitalization for heart failure, including nonischemic heart failure.[81] In contrast, another large Swedish population-based cohort study found no association with MI, heart failure, atrial fibrillation, aortic valve stenosis, abdominal aortic aneurysm, stroke, or CVD mortality but did find an increased risk of stroke in those who used snus and who had never smoked.[82] Another large Swedish cohort analysis found that compared with those who never used tobacco, those who used snus exclusively had a small but significant increase in cardiovascular mortality and a small increase in overall mortality.[83]

Table 4. Current (Past 30 day) Use of Smokeless Oral Tobacco Products Among Youth and Adults Across the Globe

	Yang et al,[69] %				Theilmann et al,[70] %				GBD,[71] %			
Data source	GYTS and NYTS, 2010–2019				2015–2020				GBD Study, 2019			
Age range	12–16 y				≥15 y				≥15 y			
		Overall	Boys vs girls	12–14 y vs 15–16 y		Overall	Male	Female		Overall	Male	Female
	WHO region											
	Africa	5.4	6.5	4.9	Global	7.7	11.1	4.8	Global	4.7	6.6	2.9
			4.3	6.1	Afghanistan	19.3			Bangladesh		22.0	25.4
	Americas	3.2	4.4	3.0	Algeria	8.9			Bhutan		27.2	14.2
			2.0	3.6	Bangladesh	27.5			Cambodia		1.7	12.8
	Eastern Mediterranean	4.8	6.7	4.5	Bhutan	14.6			India		26.0	11.5
			2.7	5.3	India	21.4			Madagascar		17.0	6.4
	Europe	2.7	3.4	2.1	Madagascar	13.7			Marshall Islands		10.4	4.1
			1.9	3.6	Myanmar	29.3			Myanmar		14.2	6.5
	Southeast Asia	6.1	7.4	5.0	Nepal	18.3			Nepal		39.2	8.2
			4.5	9.2	Tajikistan	10.2			Pakistan		14.0	4.9
	Western Pacific	2.0	2.4	1.8	Timor-Leste	9.2			Palau		25.8	24.4
			1.7	2.5					Sri Lanka		13.6	5.2
									Yemen		10.7	4.4

GYTS and NYTS: 138 countries; includes chewing tobacco, snuff, dip, gutka; current use defined as any use in past 30 d.[69] Seventy-two low- and middle-income countries; includes chewing tobacco, oral/nasal snuff, betel nut with or without tobacco; current use defined differently across surveys; countries depicted represent those with the highest rates of smokeless oral tobacco use.[70] GBD Study includes chewing tobacco; current use defined as daily or occasional use in past 30 d or as defined by a given survey; countries depicted represent those with the highest rates of smokeless oral tobacco use.[71]

GBD indicates Global Burden of Diseases, Injuries, and Risk Factors; GYTS, Global Youth Tobacco Survey; NYTS, National Youth Tobacco Survey; and WHO, World Health Organization.

Epidemiological studies in the United States have also shown increased risk of mortality from heart disease and increased risk of heart disease and stroke in those who use smokeless tobacco.[84,85] However, an analysis of PATH study (Population Assessment of Tobacco and Health) data found no greater self-reported history of MI, heart failure, or stroke in those who use smokeless tobacco compared with those who never used tobacco.[86] A recent US cohort study found that smokeless tobacco use increased the risk of incident peripheral arterial disease,[87] but a large Swedish cohort study found no association with peripheral arterial disease,[88] and another Swedish study found no association between snus and abdominal aortic aneurysm.[82] Many of these studies did not control for intensity of use.

Several cardiovascular risk factors have been explored among those who use smokeless tobacco (United States) or snus (Sweden). Biomarker studies in the United States report no association of biomarkers of cardiovascular harm in those who use smokeless tobacco,[89,90] and in Sweden, no evidence was found of higher vascular intima-media thickness in the carotid and femoral arteries, a noninvasive measure of atherosclerosis.[91] An analysis of NHANES (National Health and Nutrition Examination Survey) data from 2003 to 2018 found a substantial association of hypertension, higher cholesterol levels, and obesity among those in the United States who use smokeless tobacco compared with those who do not.[92] However, a Swedish snus cohort study found no relationship between snus use and metabolic syndrome.[93] Another large Swedish cohort study found that those who use snus had higher high-density lipoprotein cholesterol and triglyceride concentrations but similar non–high-density lipoprotein cholesterol levels compared with those who do not use tobacco.[94] Limited evidence suggests an association of a dose response with smokeless tobacco use and an increased risk of type 2 diabetes, but this relationship needs further study.[95]

In summary, most Swedish epidemiological studies have found evidence of increased fatal MI and stroke but no evidence of accelerated CVD and stroke among those who use snus compared with those who do not use tobacco. Risk factors for CVD among those who use snus were more prevalent in the US compared with the Swedish studies. Whether these differences relate to differences in the smokeless tobacco products or are due to differences in potential confounders (eg, diet, exercise, education, income, or concurrent other tobacco use) is unclear. In studies that did report an increased risk of CVD in those using smokeless tobacco, nearly all found that the magnitude of risk is much less than among those who smoke cigarettes. Smokeless oral

nicotine product use has potential adverse effects on some but not all biomarkers of CVD risk. Smokeless oral nicotine product use does not appear to accelerate atherogenesis but does appear to be associated with an increased mortality risk in those with ischemic heart or cerebrovascular disease. No data are available on the cardiovascular or health risks of oral nicotine pouches, but the lack of data of these newer products does not mean they are safe. These newer products are still too new and study windows are too short to understand their cardiovascular risk.

Smokeless Tobacco and Oral Cancer

Because of the prolonged exposure and absorption of chemicals, particularly the potent carcinogens N'-nitrosonornicotine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, through the oral mucosa, oral cancer is a major health concern for some but not all smokeless tobacco products.[96] A global systematic review and meta-analysis of studies from 4 World Health Organization regions (Southeast Asia region, Eastern Mediterranean Region, Europe, and region of Americas [North and South]) demonstrated a significant positive association between smokeless tobacco product use (comparing ever-users with never-users) and the risk of oral cancer, with risks varying according to geographic region and product type.[97] Increased odds of oral cancer were observed in Southeast Asia region countries, likely influenced by betel quid use (odds ratio, 4.44 [95% CI, 3.51–5.61]) compared with American regions where the association was nonsignificant (odds ratio, 4.72 [95% CI, 0.66–33.62]).[97] Similar studies show that associations vary by geographic region. A more recent review of systematic reviews showed that although there is an association between smokeless tobacco use and oral cancer for the global population (relative risk, 3.53 [95% CI, 2.76–4.51]), there was a much lower association with oral cancer in the American regions (relative risk, 1.37 [95% CI, 0.80–2.36]).[98]

Unlike findings showing no oral cancer risk from use of snus products from Nordic countries, findings from a meta-analysis of epidemiological studies show that the use of smokeless tobacco in the United States is associated with increased risk of oral cancer (relative risk, 2.6 [95% CI, 1.3–5.2].[99] A pooled analysis of 11 US studies found an increased risk for cancers of the oral cavity for ever-use (versus never-use) of snuff (odds ratio, 3.01 [95% CI, 1.63–5.55]) and tobacco chewing (1.81 [95% CI, 1.04–3.17]).[100] It is noteworthy that many meta-analyses included individuals who reported use of high-nitrosamine smokeless tobacco products from many years in the past. These differences need to be considered carefully when extrapolating to oral cancer effects among individuals reporting use of currently available products with lower nitrosamine levels. In contrast, according to nationally representative data from the US PATH study waves 1 through 5 (2013–2019), smokeless tobacco use (excluding snus) and snus use (only snus pouches use at waves 1–3 and any snus use at wave 4) were not associated with incidence of precancerous oral lesions (adjusted hazard ratio, 1.66 [95% CI, 0.90–3.07] and 0.73 [95% CI, 0.16–3.41], respectively).[101]

The majority of Swedish studies show no association between Swedish snus use and incidence of oral cancer.[102–106] According to a recent pooled analysis of 9 Swedish cohort studies, Swedish snus ever-use (versus never-use) was not associated with oral cancer (adjusted hazard ratio, 0.90 [95% CI, 0.74–1.09]).[102] Another Swedish study showed no increase in the incidence of oral cancer among those who ever used snus compared with those who never used tobacco.[103] In contrast, a population-based prospective study among male Swedish individuals found a significant increase in incidence of combined oral and pharyngeal cancer among those using snus daily (hazard ratio, 3.1 [95% CI, 1.5–6.6]) but not an increased incidence of cancer overall.[106]

In summary, smokeless tobacco has the potential to increase risk of oral cancer, but the risks depend on the chemical composition of the product. Low-nitrosamine Nordic smokeless tobacco appears to pose little or no risk, whereas some US smokeless tobacco products and many smokeless tobacco products from other countries in the world are strongly associated with oral cancer. No data are available on cancer risk from oral nicotine pouch products, but with absent or trace amounts of nitrosamines,[107] the risk is expected to be low.

MARKETING, MESSAGING, AND SALES

In the United States, industry spending on advertising and promotion of smokeless oral nicotine products between 2020 and 2021 was more than $1 billion.[108] For 2021, Table 5 summarizes the smokeless oral nicotine products sales, advertising, and promotional expenditures stratified by tobacco type, and Table 6 summarizes smokeless oral nicotine product advertising and promotional expenditures by category.[108] Changes in advertising and promotional expenditures varied by marketing strategy and channel. For traditional channels such as magazines, the advertising expenditure was $8.1 million in 2021, an increase from $7.8 million in 2020. Point-of-sale advertising decreased from $18.9 million in 2020 to $18.8 million in 2021.[108] In 2021, companies reported spending $308.2 million on price discounts (payments made to reduce the price of smokeless oral nicotine products to consumers) paid to retailers and $81.3 million on price discounts paid to wholesalers.[108] Retail and wholesale price discounts were the 2 largest expenditure categories in 2021, representing a combined 67.7% of total expenditures (53.6% and 14.1%, respectively).[108] For digital marketing, expenditure was $3.6 million on

Table 5. Smokeless Oral Nicotine Products Sales and Advertising by Tobacco Type for 2021

Tobacco type	Pounds sold	Dollar sales/ revenue	Advertising and promotional expenditures, $
Loose-leaf chewing tobacco	13 789 478	222 679 034	5 825 000
Plug/twist chewing tobacco	227 531	13 204 915	174 000
Scotch/dry snuff	567 269	48 310 169	569 000
Moist snuff	105 733 097	4 486 792 750	538 065 000
Snus	1 640 503	187 128 785	12 533 000

Data from the US Federal Data Commission.[108]

company websites, $4.6 million on internet advertising, excluding company websites, and $169 000 on social media advertising.[108]

Marketing Strategies

Advertising of smokeless oral nicotine products is prohibited through experiential marketing (except on adult-only premises) and on radio, magazines, newspapers, television, and billboards (including signs and placards in areas/shopping malls). In recent years, marketing has evolved beyond these traditional, prohibited strategies to include targeted digital marketing through access to consumer data.[109,110] The FDA also prohibited providing free samples of any tobacco products in 2017.[109,111]

Digital marketing channels are increasingly being used to market smokeless oral nicotine products, including smartphone-optimized websites, mobile applications (apps), social media, and social media influencers, including microblogging sites, brand ambassadors, endorsements, and testimonials.[110,112] Digital marketing has largely been unregulated, with social media companies being responsible for self-regulating tobacco advertisements. Most social media platforms have policies prohibiting tobacco marketing; however, such self-regulation appears not to be enforced because tobacco brands have a widespread presence on social media platforms.

The FDA requires tracking dissemination of digital tobacco product promotion to audiences <18 years of age and requires that social media influencers and brand ambassadors label their digital content with the tobacco brand sponsor.[113,114] However, the larger digital marketing of smokeless oral nicotine products remains unregulated[115]; hence, the vast majority of digital marketing is fully visible to adolescents and young adults.

Table 6. Smokeless Oral Nicotine Products Advertising and Promotional Expenditures by Category for 2019 to 2021

Advertisement type	2019, $	2020, $	2021, $
Magazines	6 124 000	7 754 000	8 067 000
Outdoor	438 000	186 000	114 000
Point of sale	19 316 000	18 851 000	18 832 000
Direct mail	3 290 000	2 719 000	1 794 000
Price discounts–retailers	285 604 000	296 588 000	308 240 000
Sampling	720 000	210 000	499 000
Coupons	39 743 000	41 108 000	33 403 000
Company websites	4 990 000	3 456 000	3 604 000
Internet–other	1 698 000	4 585 000	4,552 000
Social media	316 000	256 000	169 000
Sporting events	943 000	377 000	21 000
Other*	32 074 000	24 840 000	32 168 000
Total	576 054 000	567 262 000	575 010 000

*Advertising and promotional expenditures not covered by another category. To the extent that third-party agency fees relating to smokeless oral nicotine product advertising, merchandising, or promotion cannot be divided according to the materials to which they relate, they should be reported in this category.

Data from the US Federal Data Commission.[108]

The Role of Flavors

As with other tobacco products, flavors play a key role in supporting initiation and continued use of smokeless oral nicotine products.[116–118] An estimated 70.1% of US youth who were current users of smokeless tobacco reported using flavored products (61.6% for oral nicotine pouches) in 2021.[116] Among adults who use smokeless tobacco, 45.9% reported using flavored products in 2014 to 2015, and those who used flavored smokeless tobacco had lower odds of cessation 2 years later.[119] In addition to masking the taste and oral sensations of nicotine, flavors can be used to lower the pH of smokeless oral nicotine products, making them more appealing to new users.[120] Mint flavors are the most popular across smokeless oral nicotine products, with wintergreen being especially popular for moist snuff.[121] Wintergreen flavoring carries properties that are useful from marketing and product perspectives. The tobacco industry noted that wintergreen flavors connoted increased "strength" of the product.[121] The chemical used primarily for imparting wintergreen flavoring, methyl salicylate, has analgesic and antimicrobial properties, which the industry noted further reduced the harshness of using smokeless oral nicotine products and mitigated formation of tobacco-specific nitrosamines during storage in tobacco-based products, respectively.[120]

Equity and Industry Targeting

Historically, the industry has targeted male individuals, individuals in rural areas, and groups with lower socioeconomic indicators with smokeless tobacco product marketing.[122–125] For conventional smokeless tobacco products such as moist snuff, this trend continues, with advertisements relying on masculine, outdoor, hunting,

"everyman," and blue-collar themes.[109,122–126] Low-income households are also more likely to receive direct mail advertisements and coupons for smokeless tobacco products.[127,128] Advertisements for smokeless tobacco additionally tend to resonate with Appalachian and other groups' values by portraying themes of toughness and masculinity.[125,129] For pouched smokeless oral nicotine products (eg, pouched snus, moist snuff, and oral nicotine pouches), the industry has attempted to extend reach to different groups, including women, people of color, and sexual and gender minoritized communities.[130,131]

IMPLICATIONS FOR THESE PRODUCTS IN THE REGULATORY AND POLICY LANDSCAPE

The American Heart Association is committed to ending addiction to all commercial tobacco products, including those with synthetic nicotine, in the United States and globally with robust evidence-based public policies that include smokeless oral nicotine products.[55] In real terms, achieving this endgame will be a progressive effort getting to <5% tobacco use prevalence across the US population in every state across all demographics by 2035, prioritizing <5% prevalence of combustible tobacco use by 2030, and continuing to ensure that other products do not addict the next generation of youth and adolescents.[55] Table 7 summarizes the public policy solutions that will guide the organization's advocacy efforts around smokeless oral nicotine products. Tobacco excise taxes remain one of the leading evidence-based strategies[133] to discourage tobacco product use, and the resulting revenue must be used by states to support programs to treat tobacco and nicotine addiction. All characterizing flavors, including mint, menthol, synthetic coolants, and sweeteners, should be eliminated from all tobacco products, including smokeless oral nicotine products, because of their appeal to youth. Massachusetts'[134] and California's[135] comprehensive flavor restriction legislation, as well as worldwide efforts around ending commercial tobacco product addiction, offers models for continued action in the United States. To increase the effectiveness of flavor restrictions, the FDA should continue to require all companies to present a comprehensive list of their ingredients and more information on the purpose of their inclusion. In 2016 to 2017, the FDA started the process to establish a product standard for N′-nitrosonornicotine levels in smokeless tobacco products, but this lingered and has not moved forward.[136] Plain packaging and prohibition of text, imagery, or color that implies a flavor should be implemented to decrease the appeal of smokeless oral tobacco products to youth. Robust regulatory policy should be developed and enforced around digital marketing and advertising, especially on social media where youth obtain much of their information. Last, restrictions on tobacco retail outlets through zoning laws are an emerging promising strategy for reducing youth initiation and tobacco use.

In addition to public policy solutions, organizational and systems-level policies are important for creating environments that are free from commercial tobacco product use. In professional sports, for example, the use of the oral nicotine pouch products has proliferated as a way to enhance performance and to use discreetly in tobacco-free environments.[137,138] This is a concerning role modeling for young fans and youth sports organizations.[138] Organizations should advocate for and enforce comprehensive tobacco-free policies.

A challenge to these public health policies is the tobacco industry's continued efforts to evade FDA and state regulations. The tobacco industry chemistry projects are designed for the purpose of increasing addiction and bypassing regulations. The previously mentioned synthetic cooling agents were developed to reduce the harshness, irritation, and bitterness of tobacco and nicotine. Because these chemicals are odorless, they are not likely to be classified as characterizing flavors, but at least 1 analysis found the concentration of these coolants in e-cigarettes at levels that could pose health risks to consumers.[139] Newer to the market are nicotine analogs, one of which has been growing in popularity in e-cigarette products. Products containing 6-methyl nicotine are being marketed as being premarket tobacco application exempt, and the chemical manufacturer of 6-methyl nicotine states that it is not subject to FDA regulation as a tobacco product.[140] At least 1 website of a product indicates that it provides the same effects as nicotine and may be addictive.[140] It is incumbent on the FDA to provide regulatory guidance and classification of these chemicals. The American Heart Association and its partners will continue to monitor and address industry behavior that is attempting to evade regulation.

CONCLUSIONS

The prevalence of conventional smokeless oral nicotine product use has remained stable across recent years. However, newer categories of oral nicotine products, especially the nicotine pouches, are increasing in use, particularly among youth and young adults. The FDA has the authority to regulate newer oral nicotine products and should do so more quickly by prohibiting the sale of unauthorized tobacco products.

Smokeless oral nicotine product use has potential adverse effects on some but not all biomarkers of CVD risk. Although pooled studies from Sweden showed no increased risk of CVD, many studies in the United States and elsewhere did find a positive association with an increased mortality risk in those with ischemic heart or cerebrovascular disease. It seems that the use of snus

Table 7. Public Policy Levers

Policy lever	AHA position
Tax policies	Tobacco excise taxes are a leading evidence-based strategy for reducing tobacco use and uptake. Smokeless oral nicotine products should be included in excise taxes. Any variation of excise taxes across product categories should be based on the latest evidence base for population health impact and risk of youth uptake and initiation.
Tobacco 21	The AHA advocates for comprehensive implementation of Tobacco 21 laws that include all tobacco products and are enforced with an equity focus.
Flavoring restrictions	The AHA's position at this time is that the FDA should eliminate the use of all characterizing flavors other than tobacco in all tobacco products. This should explicitly include sweeteners and coolants and other ingredients that provide sensory effect (coolants, sweeteners). The removal of these flavor ingredients from all tobacco products is essential for reducing their appeal to youth. Controversy arises because, although there is no experimental evidence to support the view that flavors help adults switch from combustible to noncombustible tobacco products or to quit tobacco altogether, individual reports suggest that for some adults flavors are appealing. However, maintaining flavors to attract adults who smoke increases the risk of these products becoming available to youth and young adults, with new evidence indicating that ≈75% of current (past 30 d) e-cigarette users 18–20 y of age have never used a combustible product.[132] The FDA should continue to require all companies to present a comprehensive list of their ingredients and require more information on the purpose of their inclusion. Text, signs, symbols, terms, or imagery that implies flavor, including concept flavors, should be prohibited. Mint, menthol, and coolants: Mint, menthol, and coolants increase the palatability of tobacco products and contribute to inequities in tobacco use and related harms. Hence, mint, menthol, and coolants should be included in characterizing flavor restrictions from smokeless oral nicotine products. Sweeteners: Emerging evidence also suggests that sweeteners in tobacco products may play a role in increasing the appeal of the product; this evidence suggests that the FDA should also consider the inclusion of high-intensity sweeteners in its definition of characterizing flavors. This should be accompanied by research aimed at studying the role of flavors in enhancing adult cessation and the toxicity of flavor additives. This research and surveillance will be required to determine any negative effects on the efficacy of cessation with new approaches developed to counteract them if found.
Synthetic nicotine	Synthetic nicotine may be as addictive as nicotine derived from tobacco. The FDA now has the authority to regulate products with synthetic nicotine and should do so by addressing nicotine marketing, advertising, nicotine concentration, flavorings, and other aspects of regulatory oversight.
Nicotine concentration levels	The AHA supports lowering nicotine concentrations to minimally addictive levels in all combustible tobacco products to reduce tobacco-related mortality. Research favors doing this quickly rather than a stepwise reduction over time. This will likely be most successful if nicotine is available in noncombustible forms as nicotine replacement to reduce withdrawal symptoms as those who smoke adjust. Any nicotine reduction strategy should consider the relationship with switching and dual use. In addition, FDA action should be taken to ensure that further changes are not made by industry to reduced-nicotine products to retain their appeal such as altering other ingredients or flavors. Over the long term, subsequent research is needed to determine how nicotine levels should be addressed in noncombustible tobacco products to achieve an end to tobacco product addiction.
Tobacco-free environments	Comprehensive tobacco-free policies in public places such as government buildings, schools, casinos, health systems, and restaurants should include smokeless oral tobacco products. This is important for role modeling to youth and for creating spaces that support healthy living.
FDA regulation	There should be robust FDA regulation of the manufacture, import, packaging, labeling, advertising, promotion, distribution of, and chemical makeup and nicotine concentrations in smokeless and oral tobacco products. There also needs to be more robust enforcement of FDA regulation.
Comprehensive tobacco cessation	Those who use smokeless oral nicotine products should be offered all comprehensive tobacco cessation therapies, including counseling and pharmacotherapy. Anyone using tobacco products should have access to comprehensive cessation services with no copay. Tobacco excise tax revenue and other appropriations should be used by states to fund tobacco prevention and cessation programs with some dedicated emphasis on youth. A large-scale real-world study is needed to compare the effectiveness of numerous cessation options, including FDA-approved cessation therapies, with products such as oral nicotine pouches to assess efficacy in helping people on their journey to quit their tobacco and nicotine addiction. This study could be funded by PCORI, by a federal funding mechanism, or through private/public research partnership. If efficacious for cessation, industry would take these products through regulation by the FDA's Center for Drug Evaluation and Research.
Regulation for marketing, advertising, and digital media	The AHA supports robust regulation restricting all tobacco marketing and advertising to youth, including the use of television, radio, and print ads and commercials; celebrity endorsement; social media influencers; movie placements; price promotions; free sampling; branded events; and nontobacco merchandise. Regulatory restrictions on tobacco marketing should be applied to and enforced on digital media where youth and young adults obtain much of their information and are exposed to tobacco product advertising. Existing requirements of warning label statements covering at least 20% of print ad space should be extended to social media posts by industry and their influencers. Advertising by smokeless oral tobacco product brands on social media should also be closely scrutinized for claims of modified risk that have not undergone FDA review through the modified-risk tobacco product application process. The FDA has already granted modified-risk tobacco product designation to several smokeless tobacco products, including Swedish Match and Copenhagen Classic Snuff. The use of appropriate hashtags and statements of sponsorship as outlined by the FTC should be required in all digital media advertising by brands and social media influencers.
Tobacco control and prevention funding	States should optimize their tobacco control and prevention program funding to CDC-recommended levels and incorporate technical assistance, programming, education, cessation services, countermarketing strategies, and resources addressing smokeless oral nicotine products use.

(*Continued*)

Table 7. Continued

Policy lever	AHA position
Warning labels	The AHA supports the FDA in requiring immediate implementation of impactful, evidence-based graphic warning labels on all tobacco products in the United States once the legal challenges initiated by the industry are resolved. Because of final resolution of the federal government's long-running civil racketeering lawsuit against the largest US cigarette companies, the defendants are now required to display signs in retail stores that have contracts with them featuring corrective statements about the health effects and addictiveness of smoking. The AHA and its national partners will monitor this placement and any effect on tobacco use prevalence overall.
Plain packaging	The AHA supports plain packaging for all tobacco products in the United States in accordance with the provisions on packaging and labeling for tobacco products outlined by the WHO Framework Convention on Tobacco Control Article 11. Plain packaging requirements should include size and dimension restrictions, use of a uniform color, and specific formatting requirements for the brand and variant names.
Retail strategies	The AHA supports exploration of retail strategies to reduce all tobacco product use in the United States. There are 3 primary policy approaches to addressing tobacco retail strategies: (1) restrict the location of tobacco retail outlets away from each other and away from youth-serving institutions, other related organizations, and colleges and universities; (2) reduce the quantity of tobacco retail outlets with a purposeful equity goal of addressing density across different jurisdictions; and (3) restrict the eligibility to sell, including completely ending sales in local jurisdictions, limiting sales to adult-only, tobacco-only shops, and maintaining tobacco-free pharmacies and other health-related retailers. Each of these strategies has shown potentially significant public health and equity impact, and the effect is amplified when the strategies are combined.
PUP laws	PUP laws criminalize and punish youth for buying, possessing, and using tobacco products (including smokeless oral nicotine products), which can include penalties, fines, and detainment. Tobacco use and possession should not be criminalized. The AHA believes that PUP laws should be reformed so that the penalty is on retailers who sell to those who are underage.
Global Tobacco Pact (WHO)	The AHA supports coordinated, collaborative tobacco endgame efforts among dedicated global health networks, the WHO, governmental agencies, individuals, and nongovernmental organizations around a unified policy framework that minimizes the devastating impact of tobacco product use in populations at high risk around the world. Industry should not respond to robust regulation in the United States by increasing export of these deleterious products to other parts of the globe, especially to low- and middle- income countries.

AHA indicates American Heart Association; CDC, Centers for Disease Control and Prevention; e-cigarette, electronic cigarette; FDA, US Food and Drug Administration; FTC, Federal Trade Commission; PCORI, Patient-Centered Outcomes Research Institute; PUP, purchasing, use, and possession; and WHO, World Health Organization.

in Sweden carries a different cardiovascular risk than the use of other smokeless oral nicotine products around the world. Smokeless oral nicotine products also have the potential to increase the risk of oral cancer, with risks dependent on the chemical composition of the specific product used and the frequency of use.

Smokeless oral nicotine products are addictive, and their use has harmful effects on health. Further research is needed (1) to evaluate factors associated with the initiation and use of smokeless oral nicotine products, including novel synthetic nicotine products; (2) to determine how addictive the novel smokeless oral nicotine products are for youth and adults; (3) to determine the influence of smokeless oral nicotine products on continued tobacco use, including dual use or poly-use; (4) to evaluate the health impact of long-term use on population health; (5) to understand use patterns in youth and adults; and (6) to develop and test strategies, including public health messaging and policy approaches, to reduce the use of smokeless oral nicotine products. On the basis of the findings reviewed in this policy statement, clinicians should continue to screen for all nicotine use in all patients. Although smokeless oral products are harmful to health, data from Sweden indicate that the use of low-nitrosamine, government-regulated snus is far less detrimental than cigarette smoking.[78–82] Several such low-nitrosamine snus products have been authorized by the FDA as modified-risk products, indicating that switching completely from cigarettes to these products will reduce risk, progression, and adverse outcomes of tobacco-related disease.

Clinicians should encourage patients to first consider established pharmacological and behavioral therapies to treat tobacco and nicotine addiction[55,141] and should be prepared to counsel their youth and adolescent patients to avoid or quit the use of all tobacco and nicotine products altogether.[55] Clinicians might support the use of smokeless oral nicotine products for those patients who are unable or unwilling to use FDA-approved smoking cessation treatments to stop the use of combustible products but need to stress the importance of a complete transition and emphasize that the goal is cessation of all nicotine products.[55,141] Clinicians should also educate their patients that although smokeless oral nicotine products may be less toxic than combustible products, they may still have adverse effects on cardiovascular health and overall health if used long term.[55] There is a need for a large-scale real-world evidence trial to compare products in the marketplace, including nicotine pouches, with FDA-approved cessation therapies to address nicotine dependence and to assess efficacy in helping those who use tobacco and nicotine to quit. However, unlike currently approved nicotine replacement therapy products, oral nicotine pouches are manufactured for addiction as commercial tobacco products and would likely have to be modified to be approved and marketed as cessation therapy. Clinicians should emphasize the prevention of tobacco and nicotine product initiation and treat tobacco and nicotine dependence as primary goals for achieving an end to commercial tobacco and nicotine addiction. Last, implementation of a robust policy strategy is crucial

to support ending addiction to all commercial tobacco products, including those with synthetic nicotine.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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Disclosures

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*Modest.

†Significant.

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*Modest.

†Significant.

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