DISEASES AND DISORDERS

Current advances in research in treatment and recovery: Nicotine addiction

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The health harms of combusted tobacco use are undeniable. With market and regulatory pressures to reduce the harms of nicotine delivery by combustion, the tobacco product landscape has diversified to include smokeless, heated, and electronic nicotine vaping products. Products of tobacco combustion are the main cause of smoking-induced disease, and nicotine addiction sustains tobacco use. An understanding of the biology and clinical features of nicotine addiction and the conditioning of behavior that occurs via stimuli paired with frequent nicotine dosing, as with a smoked cigarette, is important for informing pharmacologic and behavioral treatment targets. We review current advances in research on nicotine addiction treatment and recovery, with a focus on conventional combustible cigarette use. Our review covers evidence-based methods to treat smoking in adults and policy approaches to prevent nicotine product initiation in youth. In closing, we discuss emerging areas of evidence and consider new directions for advancing the field.

INTRODUCTION

"*To lower nicotine too much might end up destroying the nicotine habit in a large number of consumers and prevent it from ever being acquired by new smokers.*"

– British American Tobacco Company internal document, June 1959 (*1*).

Combusted tobacco use remains a major cause of premature disability and death around the world (*2*). Cigarette smoke contains an estimated 7000 different chemical compounds, of which at least 70 are proven or suspected human carcinogens including arsenic, benzene, formaldehyde, lead, nitrosamines, and polonium 210. Tobacco smoke also contains poisonous gasses: carbon monoxide, hydrogen cyanide, butane, toluene, and ammonia. Little cigars and water pipes deliver similar toxicants.

Tobacco smoking causes about half a million U.S. deaths annually, of which 50,000 are among nonsmokers exposed to secondhand smoke (*3*, *4*). More than half of all long-term smokers die from a tobacco-caused disease, with an average loss of at least 10 years of life (*3*). Smoking causes 87% of lung cancer deaths, 61% of pulmonary disease deaths [chronic obstructive pulmonary disease (COPD) and emphysema], and one in three cancer deaths. In the 50 years following the U.S. Surgeon General's first report on tobacco (1964–2014), 20 million Americans died from smoking, and an estimated 1 billion people will die worldwide this century (*3*, *5*). For every person who dies from smoking, at least 30 people live with serious smoking-related illnesses costing >$300 billion annually, with nearly $170 billion in direct medical costs and $156 billion in lost worker productivity (*3*, *6*).

The health harms of combusted tobacco use are now undeniable (*7*). With market and regulatory pressures to reduce the harms of nicotine delivery by combustion, the tobacco product landscape has diversified (Table 1). Nicotine now comes in smokeless tobacco prepackaged pouches (i.e., snus tobacco), in electronic devices that heat nicotine to an inhalable aerosol from a plug of tobacco (i.e., heated or heat-not-burn tobacco) or from an e-liquid (nicotine vaping device; e.g., e-cigarette, vape pen, and pod), and in pharmaceutical-grade nicotine replacement therapies (NRTs) (i.e., gum, lozenge, patch, nasal spray, mouth spray, and inhaler). Cigars come in a variety of sizes down to little filtered cigars, some discernible from cigarettes only by their tobacco leaf wrapper. Despite the diversification, conventional combusted cigarettes remain, by far, the most common nicotine product used by adults in the United States and in most places globally. Worldwide, there are approximately 1 billion smokers (*5*).

While products of tobacco combustion are the main cause of smoking-induced disease, nicotine addiction sustains tobacco use (*8*). Nicotine addiction, in the form of cigarette smoking, causes more harm to public health than any other drug addiction. Reflected in the quote above, at least since the 1950s, the tobacco industry has researched and recognized, decades before it became generally understood in the scientific community, that nicotine is an addictive drug and central to their business (*9*). An understanding of the clinical features of nicotine addiction and the behavioral conditioning that occurs with frequent nicotine dosing is important for informing pharmacologic and behavioral treatment targets.

We review current advances in research on nicotine addiction treatment and recovery. The "Tobacco Product Use and Nicotine Addiction" section covers the changing landscape of nicotine products with comparison of use patterns among adults and adolescents in the United States. The pharmacology of nicotine and effects on the brain are then reviewed, with consideration of particularly vulnerable populations. The "Treating Nicotine Addiction in Adults, with a Focus on Conventional Cigarettes" section focuses on treatment of nicotine addiction with attention to counseling and behavioral approaches and cessation medications. The tobacco treatment literature is far more developed for combusted cigarettes and relatively sparse in other product areas. We focus on adults given developmental differences in adolescents' preferred nicotine product type, use patterns, addiction profile, and treatment efficacy. The tobacco treatment literature with adolescents largely consists of failed smoking cessation trials (*10*), and while youth nicotine vaping is drawing public health concern and policy attention, no study, to date, has

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Table 1. Diversity of tobacco products.

Product	Definition	Types	pH	Nicotine levels
Cigarette	Tobacco rolled in paper for smoking	A typical cigarette weighs <1 g; regular length (70 mm long), king (84 mm), 100s (100 mm), and 120s (120 mm)	Acidic, inhalable, pH 5.5–6	Average in rod, 13.5 mg (range: 11.9–14.5 mg); nicotine yield to the smoker: 1–1.5 mg/cigarette
Cigar	Air-cured, fermented tobacco wrapped in material made at least, in part, of tobacco leaf	Small filtered cigars (0.9–1.3 g tobacco), cigarillos (1.3–2.5 g tobacco), and large (premium) cigars	pH 6.5–8.0 inhalable and/or buccal depending on product pH	Nicotine content ranges from 10 to 444 mg and dependent on weight of the cigar
Blunt	Cannabis filled in a hollowed-out cigarillo shell		No pH data available	Nicotine intake much lower than from cigarette or cigar smoking, but, based on animal studies, could enhance rewarding effects of delta 9-tetrahydrocannbinaol
Smokeless tobacco	Tobacco inserted between lip and gum or snorted into the nose rather than smoked by the user	Snuff (ground tobacco), snus (ground tobacco in a tea bag–like pouch), chew (shredded tobacco)	Products range from more acidic, pH 5.2–7.1, to more alkaline for greater buccal absorption, pH 7.6–8.6	Nicotine concentrations vary, range of 0.2 to 34 mg/g, the more alkaline products are capable of delivering higher levels of nicotine
Waterpipe/Hookah	Charcoal-heated flavored tobacco passed through a water-filled chamber that cools the smoke	Water tobacco is a mixture of dried fruit, molasses and glycerin, and conventional tobacco leaf	pH 3.8–5.8	Average of 1.13 mg/g and high of 3.30 mg/g for product containing nicotine; nicotine-free for herbal (nontobacco) varieties
Heated tobacco	Electronic devices that heat reconstituted tobacco sticks treated with a glycerin humectant to deliver an aerosol	IQOS, Glo, and Ploom Tech	pH 5.5–6	Nicotine delivery can match that of conventional cigarettes
E-cigarette	Electric devices that produce an aerosol from a liquid that typically contains nicotine, propylene glycol, vegetable glycerin, and flavorings	Cigalikes/e-pens, tank systems, pods/nicotine salts (e.g., benzoate and lactate)	Free base e-liquid: alkaline, pH 7–9; nicotine salts: acidic, inhalable, pH 3.5–6.8	E-liquid nicotine content from 0 to 100 mg/ml. Nicotine delivery can match that of conventional cigarette but varies by device design (heating temperature), e-liquid nicotine content, and user behavior

evaluated an intervention to treat e-cigarette use in adolescents. The "Tobacco Control Population-Based and Policy Approaches" section gives greater attention to use in youth with review of the evidence for tobacco control policy interventions. The "Discussion: What Evidence Is Needed" section closes with discussion of emerging areas and consideration of new directions for advancing the field.

TOBACCO PRODUCT USE AND NICOTINE ADDICTION

Patterns of tobacco use in the United States

In 2017, 47.4 million U.S. adults (19%) reported every day or some day use of a tobacco product, which includes e-cigarettes (in the United Stated, electronic nicotine delivery systems are classified and regulated as tobacco products) (*11*). Among U.S. adult tobacco users, 87% (41.1 million) smoked combusted tobacco products (*11*). The prevalence of tobacco product use was 14% (34.3 million) cigarettes; 4% (9.3 million) cigars, cigarillos, and little filtered cigars; 3% (6.9 million) e-cigarettes; 2% (5.1 million) smokeless tobacco; and 1% (2.6 million) pipes, water pipes, or hookah (*11*). Among cigarette smokers, 76% smoked daily (*12*).

In contrast, among U.S. adolescents, e-cigarettes exceed conventional cigarette use. In 2018, past 30-day e-cigarette use was reported by 21% of high school (3.05 million) and 5% of middle school (570,000) students, and combustible cigarette use was reported by 8% of high school (1.1 million) and 2% of middle school (200,000) students (*13*). From 2017 to 2018, e-cigarette use increased by 78% among high school and 49% among middle school students. Preliminary U.S. data for 2019 indicate that e-cigarette use has climbed further to 27.5% among high school students with most reporting use of sweet-flavored (65.9% fruit, 38.7% candy, and 4.2% chocolate) and minty/menthol–flavored (63.9%) e-cigarette products, while use of combustible cigarettes has further declined to 5.8% (*14*). To address youth e-cigarette use, the U.S. Food and Drug Administration (FDA) is considering banning all unauthorized non–tobacco-flavored e-cigarettes.

Among adolescents who use tobacco, 7 in 10 use a flavored product (*15*). For youth, flavored tobacco products are highly appealing and

decrease perceptions of harm and addictiveness (*16*). With the explicit intent of protecting youth from smoking initiation, in 2009, the U.S. Congress banned characterizing flavors from traditional cigarettes except for menthol (*17*). The 2009 flavored cigarette ban reduced the U.S. youth smoking prevalence; however, menthol cigarette use among adolescent smokers has increased (*18*). In 2013, the FDA concluded that menthol cigarettes lead to increased smoking initiation among youth and young adults, greater addiction, and decreased success in quitting smoking (*19*). In 2017, menthol cigarettes comprised 36% of the U.S. cigarette market, the highest proportion on record (*20*).

Dual use of tobacco products is also on the rise (*21*, *22*). The most recent surveillance data show that 3.7% (9 million) of adults (*11*), 11% (1.7 million) of high school students, and 2% (270,000) of middle school students (*13*) use two or more tobacco products. The most prevalent dual tobacco combination for adults and adolescents was combustible cigarettes and e-cigarettes, followed by cigarettes and cigars for adults, and e-cigarettes and cigars for adolescents. Motivations for dual use among adults include use of smokeless tobacco and e-cigarettes in places where combustible cigarette smoking is prohibited, as a form of harm reduction, and to support quitting smoking (*23*).

While e-cigarette use may represent harm reduction for adult smokers, few would suggest a benefit of nicotine vaping in adolescence when the brain is still developing. Unknown is the extent to which e-cigarette use among youth is a fad, will lead some to long-lasting primary nicotine addiction, and/or may be a gateway to cigarette smoking. The National Academies of Sciences 2017 review concluded that there is substantial evidence that e-cigarette use increases the risk of ever smoking combustible cigarettes among youth and young adults, but whether this is trial use versus sustained use could not be determined from the literature (*24*). Two recent prospective observational studies of U.S. adolescents reported that among never smokers, e-cigarette use was significantly associated with both initiating and continuing combustible cigarette use (*25*, *26*). A potential confounder is cannabis use, which has a high concordance with e-cigarette use. A third prospective study examined the question of whether adolescents are engaging in e-cigarette trial use versus dependent use (*27*). The sample was adolescent past-month e-cigarette users reporting 10+ uses in their lifetime at baseline. At 12-month follow-up, 80% continued their e-cigarette use, daily use increased from 14.5 to 29.8%, and the adolescents tended to "graduate up" to higher–nicotine content pod-type devices such as JUUL. The youths' top e-cigarette flavor preferences—fruit, mint/menthol, and candy—remained stable over time. The adolescents' self-rated level of e-cigarette addiction correlated significantly with their level of nicotine exposure, as measured by the nicotine metabolite biomarker of urinary cotinine (*28*).

The increase in e-cigarette use in youth over the past 5 years has been mirrored by a decrease in cigarette smoking, which raises the question of whether vaping may be diverting some youth away from cigarette smoking. Whether the greater e-cigarette than conventional cigarette use among adolescents will lead to sustained population declines in adult smoking is as yet unknown.

Nicotine addiction: Definitions, biology, clinical features, and vulnerable groups

Defining nicotine addiction

In this review, we refer to the compulsive use of nicotine and tobacco products as an addiction, based on the definition provided in the 1988 U.S. Surgeon General's report, referring to "behavior of repetitively ingesting mood-altering substances by individuals" (*29*). However, it should be noted that definitions such as that from the World Health Organization (WHO) define addiction as "a behavioral pattern in which the use of a given psychoactive drug is given a sharply higher priority over other behaviors that once had a significantly higher value" (*30*). There is no question that cigarette smoking fits both definitions, but with the advent of noncombusted forms of nicotine (like e-cigarettes), which are considered to be much less harmful than cigarette smoking (but not necessarily safe), some clinicians and vapers (those who use e-cigarettes) object to the term addiction because they view pure nicotine dependence as not being detrimental to health. Thus, while we use the term addiction to refer to being unable or unwilling to stop when it is clearly in one's interest to do so, we acknowledge some controversy as to its application to noncombusted tobacco product use.

Today, the health harms of smoking are well known, and most smokers want to quit. However, most attempts to quit smoking fail. The statistics are striking: (i) 68% of smokers in the United States want to stop smoking, and 55% quit for 24 hours in a given year (many more smokers attempt to quit but are unable to make it a full day) (*31*); (ii) 60% of those who quit for a day relapse by 1 week; and (iii) only 7% of quit attempts are sustained 6 months, and 45% of those end in relapse (*31*).

Ultimately, more than 90% of smokers try to quit; most make multiple quit attempts, and about half quit smoking long term, although most do not achieve abstinence until after age 30. That most smokers attempt to quit each year and less than 4% of quit attempts are sustained long term illustrates the loss of control of drug use with addiction. Factors that influence the development and maintenance of nicotine addiction are complex and include the drug's pharmacologic effects and tobacco product design; genetics; learned factors, such as conditioning of stimuli through frequent nicotine dosing; and sociocultural exposures including family and peer use and pervasive tobacco marketing and retail availability (*8*).

Nicotine and its pharmacology

Nicotine is an alkaloid that occurs in highest concentrations in leaves of the tobacco plant (*Nicotiana tabacum*). Approximately 95% of the alkaloid content of tobacco is nicotine, along with 5% of minor alkaloids including anabasine, anatabine, and norcotinine. Easy to extract, nicotine from tobacco plants is used almost exclusively in nicotine medications and e-cigarettes.

Nicotine chemistry and pharmacokinetics. Nicotine is a tertiary amine that can exist in a charged (ionized) or uncharged (unionized) form, depending on pH. Nicotine is a weak base with a pK_a (where K_a is the acid dissociation constant) of 8.0 such that, at physiological pH (7.4), 69% is ionized and 31% is unionized. The unionized (also known as free base) form of nicotine passes readily though membranes, such as the buccal mucosa, such that the pH of smokeless tobacco influences the rate and extent of systemic nicotine absorption. The more alkaline (higher pH), the more rapidly nicotine is absorbed from smokeless tobacco. Cigarette smoke has an acidic pH of about 5.5 to 6, so little nicotine is absorbed through the mouth, while large cigars have an alkaline pH, facilitating oral absorption. The differences in pH of tobacco products depends on the strains of tobacco used and curing processes, as well as on chemicals used in processing. The pH of nicotine solutions also influences the pharmacology of e-cigarettes. The earliest forms of e-cigarette liquid (e-liquid) contained mostly nicotine in free base form (pH 7 to 9),

which results in a considerable nicotine-related harshness during inhalation. Recently, e-liquids have used nicotine salts (such as benzoate or lactate), with acidic pH (5.5), similar to that of cigarettes. This results in less irritation with inhalation and has been implicated in the current popularity of e-cigarette use in never-smoker adolescents (*32*).

When cigarette smoke is inhaled, nicotine moves quickly to the lungs, arterial blood, and the brain in only 15 to 20 s (*33*), where it exerts its addiction-related effects. Rapidity of delivery to the brain is thought to be an important factor in the abuse liability of inhaled nicotine compared to other routes of nicotine administration. The importance of rapid delivery relates to higher arterial concentrations, nearly immediate psychological effects, and the ability to titrate doses to desired effects. Higher arterial levels also allow the smoker to overcome effects of tolerance to the desired psychological effects of nicotine. Inhaled nicotine from e-cigarettes potentially carries a similar abuse liability to that of tobacco cigarettes, but empirical data, to date, suggest that it is not the case. It appears that the dependence liability of inhaled nicotine is also influenced by other constituents of tobacco smoke, such as chemicals that inhibit monoamine oxidase (MAO), an enzyme that degrades neurotransmitters released by nicotine, discussed in more detail later. Furthermore, dependence on nicotine from medications (e.g., nicotine patches, gum, and lozenge) that deliver nicotine slowly appears to be low.

On average, smokers absorb 1 to 1.5 mg of nicotine from a cigarette (*33*). Nicotine has an average half-life of 2 hours, but the half-life can be affected by genetic and environmental factors. With regular smoking, nicotine levels rise in the blood over 4 to 6 hours, plateau throughout the day, and then decline overnight. Thus, although each cigarette produces a spike of arterial nicotine with a rapid decline between cigarettes, in a regular daily smoker, the brain is exposed to nicotine for 24 hours each day. This duration of exposure has implications for the development of tolerance and withdrawal symptoms, as discussed later.

Nicotine is primarily metabolized (via oxidation) by the liver enzyme, CYP2A6 (*34*). The main proximate metabolite is cotinine, which has been widely used as a biomarker of nicotine exposure. CYP2A6 activity is strongly influenced by genetic and environmental factors. Genetic variants associated with a slow rate of nicotine metabolism are more common in people of Asian and African descent compared to Caucasians. Environmental influences on nicotine metabolism include estrogen: Premenopausal women metabolize nicotine faster than men; women taking estrogen-containing birth control pills metabolize nicotine faster than women who do not; and pregnant women metabolize nicotine fastest of all. Various foods and medications can also affect nicotine metabolism. The rate of metabolism affects smoking behavior, with faster metabolizers smoking more cigarettes per day (presumably to titrate desirable nicotine levels in blood) (*35*).

Brain mechanisms. Nicotine acts on nicotinic acetylcholine receptors (nAChRs) that are found throughout the nervous system. Acetylcholine is a neurotransmitter that acts on nearly every organ in the body, and similarly, nicotine affects nearly every organ in the body. Many subtypes of nAChRs are present in the brain. Each receptor is composed of five subunits. Eleven nAChR subunits are expressed in the brain, including α2 to α7, α9, α10, and β2 to β4 (*36*). Nicotinic receptors can be heteromeric, with α and β subunits, or homomeric, with five α7 subunits. The most abundant nAChRs in the brain are α4β2 and α7 (homomeric). The α4β2 nAChR can also contain α5 and/or α6 subunits, which alter receptor physiology and contribute to differences in susceptibility to nicotine dependence. Another widespread receptor subtype is α3β4, which mediates cardiovascular and other autonomic effects of nicotine.

When nicotine binds to the outside of a nAChR, an ion channel opens, allowing entry of calcium, sodium, or potassium ions. Initially, the receptor is activated, which is then followed by desensitization. nAChRs can exist in three conformational states: closed, in the resting state; open, allowing ion entry and membrane depolarization; and desensitized, where the receptor is unresponsive to nAChR agonists (*37*). The sensitivity to nicotine and the pharmacodynamics of response (such as duration of desensitization) vary based on the particular receptor type, which translates into differential development and time course of tolerance to different nicotine effects.

Mood, cognitive, and relaxation effects of smoking are thought to occur via nicotine's stimulation of presynaptic nAChRs (*8*). Activation of these receptors results in facilitation of release of various neurotransmitters, including (i) dopamine, which is known to signal pleasure and is released by all drugs of abuse; (ii) norepinephrine and acetylcholine, which enhance vigilance and cognitive function; (iii) glutamate, which enhances memory and learning; (iv) serotonin, which affects mood; and (v) γ-aminobutyric acid (GABA) and endorphins, which ameliorate stress and anxiety.

The neural connections involving nicotine actions are complex. Nicotine affects the mesolimbic dopamine system, which is central in the neurobiology of addiction. Nicotine binds to nAChRs in the ventral tegmental area, which then activate dopamine neurons in the nucleus accumbens. The firing of dopamine neurons is modulated by GABAergic and glutaminergic neurons such that glutaminergic neurons enhance firing, while GABAergic neurons inhibit firing. The high-affinity α4β2 nAChRs are located on the inhibitory GABAergic neurons, while the α7 nAChRs are located on the excitatory glutaminergic nAChRs. The actions of nicotine on the inhibitory GABAergic neurons desensitize rapidly, while the actions on the α7 nAChR desensitize more slowly. Thus, over time, nicotine exposure results in a greater and persistent activation of dopamine neurons, actions that may promote the rewarding effects of nicotine (*38*). Nicotine may also interact with other drugs of abuse via interactions with opioid and cannabinoid receptor pathways (*39*, *40*). The importance of various nAChR subunits has been determined using genetic knockout mice. The β2 nAChR subunit is necessary for nicotine-related reward, while the β4 subunit influences nicotine withdrawal symptoms (*41*). The α6 nAChR subunit is important in activation of dopaminergic neurons, while the α5 subunit modulates the aversive effects of nicotine (*42*). Aversion to nicotine appears to be an important determinant of dependence, as people with genetic variants of the α5 nAChR subunit associated with less aversiveness are at higher risk of nicotine dependence (*43*).

With prolonged exposure to nicotine, structural changes occur in the brain. Most notably, there is up-regulation of nAChRs, with greater density of nAChRs in many parts of the brain. This up-regulation has been thought to be a response to nAChR desensitization, but more recent studies suggest that up-regulation occurs by a chaperoning mechanism (*44*). That is, nicotine appears to bind to nAChRs in the cell to facilitate assembly and chaperoning the receptors to the cell membrane. Up-regulation of nAChRs is thought to be related to the development of physical dependence, including the withdrawal symptoms that occur when nicotine exposure stops.

Presumably, the up-regulated receptors that are inactive in the presence of nicotine become sensitive again during nicotine abstinence.

Two other neurotransmitter systems appear to play important roles in nicotine dependence. Hypocretins are neuropeptides that regulate the effects of nicotine on reward centers in the brain, found to influence nicotine self-administration in animals (*45*). The insular cortex contains a high density of hypocretin-1–containing neurons. Immediate and sustained reduction in craving and withdrawal symptoms has been observed in hospitalized smokers following stroke damage to the insular cortex compared to hospitalized smokers without brain lesions (*46*).

Tolerance develops to many of the effects of nicotine with repeated exposures. In time, the brain adapts to the persistent effects to normalize brain function and related behavior. When nicotine exposure is stopped, brain function is disrupted and put in a state of withdrawal. Nicotine withdrawal results in activation of the corticotropin-releasing factor (CRF) system involved in the hypothalamus pituitary adrenal stress response. Withdrawal symptoms, such as anxiety and stress, are thought to be mediated, at least in part, by a relative underactivity of the dopaminergic system and hyperactivity of the CRF system. Antagonists of the CRF receptor reduce the anxiogenic effects of nicotine withdrawal and reduce self-administration of nicotine in the withdrawal state (*47*).

Dependence on nicotine appears to be augmented by other chemicals in cigarette smoke. Acetaldehyde, for example, increases self-administration of nicotine in animals. Particular chemicals in cigarette smoke inhibit the activity of the enzyme MAO in the brain (*48*). MAO catalyzes the breakdown of dopamine, norepinephrine, and serotonin, which are neurotransmitters that mediate nicotine reward. In animals, administration of drugs that inhibit MAO enhances nicotine self-administration. MAO-inhibiting medications have been used to treat depression. As discussed later, people with psychiatric illness, including depression, are more likely to smoke and to be more highly dependent. One theory is that MAO inhibition from smoking may have beneficial effects in depressed smokers. However, while acute smoking abstinence is associated with depressive symptoms and anxiety, prolonged quitting generally improves mood, including among smokers with psychiatric disorders such as depression (*49*).

Clinical features of nicotine addiction

Positive psychoactive effects of nicotine include pleasure, stimulation, and mood modulation, with reduced anxiety and stress (*8*). A smoker often reports pleasure and stimulation with the first cigarette of the day, stimulation and increased concentration from smoking during repetitive tasks during the day, and relaxation at times of stress and at bedtime. However, tolerance develops to many of nicotine's effects such that even within the day, the pleasure experienced from each cigarette diminishes. As nicotine levels decline, withdrawal symptoms develop, reversing nicotine's positive effects. Thus, an abstinent smoker may feel anxious, irritable, and depressed and have problems concentrating. Hedonic dysregulation (a reduced ability to experience pleasure) may be experienced, presumably related to a relative deficiency of dopaminergic activity. Nicotine increases metabolic rate and suppresses appetite, resulting in smokers, on average, weighing less than nonsmokers. During nicotine withdrawal, smokers typically experience hunger and gain weight.

Some of the perceived benefits of nicotine are mediated by the reduction of adverse effects of nicotine withdrawal (termed negative reinforcement). Thus, the pharmacologic role of nicotine in addiction is a combination of providing positive and negative reinforcement (Fig. 1). For daily smokers, there is a daily cycle during which nicotine levels rise in the blood, substantial tolerance develops during the day, and smoking occurs to relieve withdrawal symptoms. Some highly addicted smokers wake at night to smoke because of withdrawal symptoms. In contrast, some light and intermittent smokers smoke in response to particular cues, without experiencing withdrawal symptoms, and are thought to smoke just for positive reinforcement.

Nicotine dependence severity is best measured by the number of cigarettes smoked per day and the time to first cigarette upon wakening. The two items make up the heaviness of smoking index (HSI) (*50*). Number of cigarettes smoked per day is a measure of both daily nicotine intake and the frequency of nicotine self-administration.

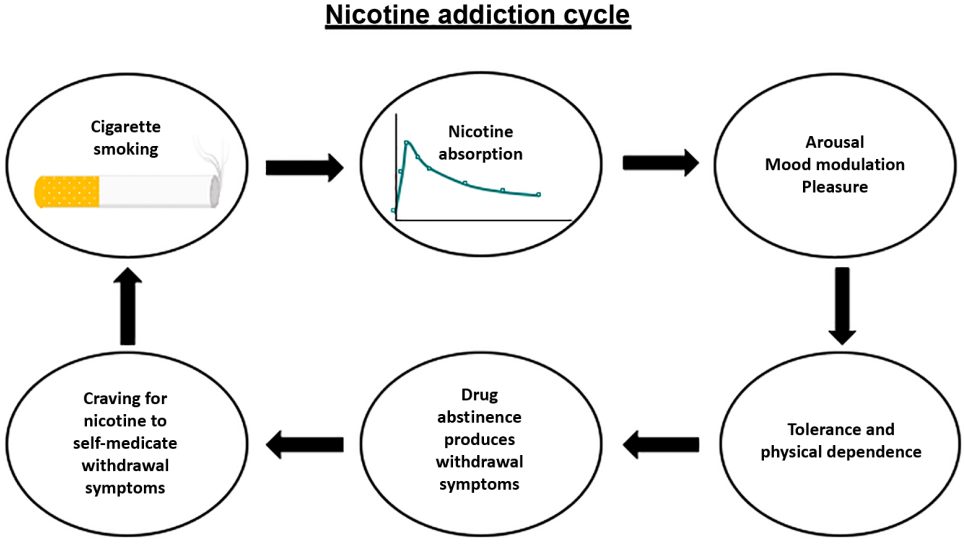

Fig. 1. The nicotine addiction cycle.

Time to first cigarette is a measure of physical dependence and the intensity of withdrawal symptoms after overnight abstinence. The two HSI items significantly correlate with biomarkers of tobacco exposure, accounting for 20 to 30% of the variance in measures of alveolar carbon monoxide, nicotine, and urinary cotinine (*50*). Research conducted by Altria with funding from Philip Morris USA concluded that the HSI items were the most important factors correlating with biomarkers of exposure (*51*). The HSI is associated with smoking-induced deprivation, measured as prioritization of cigarettes over household essentials such as food (*52*). Both items are used for dosing nicotine replacement medications, discussed in the "Tobacco Control Population-Based and Policy Approaches" section, with higher doses for heavier smokers and those who smoke within 30 min of waking. HSI scores predict difficulty with quitting smoking (*53*) and the likelihood of developing tobacco-related diseases, such as heart disease, COPD, and lung cancer (*54*, *55*). Smoking affects gene expression, and the two HSI items correlate with candidate genes previously associated with cocaine, alcohol, and heroin addiction (*56*). The rate of nicotine metabolism also correlates significantly with the HSI (*57*). The HSI items have demonstrated very good test-retest reliability among adolescents and adults (*58*, *59*). The HSI items come from the longer Fagerström Test for Cigarette Dependence (*60*). A similar instrument has been developed to assess severity of dependence on e-cigarettes (*61*) with demonstrated validity, including among adolescents (*28*).

While nicotine is necessary for tobacco dependence, conditioned behavior is also an important factor and has strong implications for behavioral treatment. When a person quits smoking, cravings for cigarettes persist long after nicotine withdrawal symptoms have resolved (*62*). A smoker typically associates smoking with particular situations, moods, or environmental factors that become cues to smoke. Thus, smokers often smoke after a meal, with coffee or alcohol, while driving, and/or with friends who smoke. Smoking a cigarette reverses the negative mood, anxiety, and irritability of nicotine withdrawal (*62*). This repeated experience can generalize to a condition in which anxiety or depression from any cause becomes a cue to smoke. The act of smoking, with the handling, hit to the throat, and taste and smell of cigarettes, which are often associated with the neurochemical effects of smoking, signals reward and becomes a cue to smoke. Exposure to tobacco advertising, particularly prevalent at point-of-sale retail and in popular media (e.g., movies, TV, and music), and exposure to others smoking can also elicit craving and smoking behavior (*63*–*65*).

Vulnerability to nicotine addiction

Not all smokers become regular, daily, or addicted users. The younger a person starts smoking cigarettes, the greater the risk of stronger physiological addiction to nicotine. Smoking co-occurs with mental illness and other addictive disorders, suggesting greater vulnerability, and research suggests the potential for a gateway effect. Genetic factors also influence the risk of nicotine dependence.

Adolescents and the developing brain. Nearly all (9 in 10) individuals who smoke started by the age of 18. Adolescence is a critical window for brain development, with the brain not reaching full maturity until the mid-20s. Adolescence is a period of enhanced neuroplasticity during which the underdeveloped neural networks necessary for adult-level judgment (the prefrontal cortical regions) cannot yet properly regulate impulses and emotion (*66*). As a consequence, adolescents are highly vulnerable to drug experimentation and addiction (*67*).

Nicotine exposure during adolescence may have lasting adverse consequences for brain development. In animals, nicotine exposure during adolescence produces permanent changes in brain structure and function, including enhanced self-administration of nicotine and other drugs as adults (*68*). In humans, adolescents experience symptoms of dependence at lower levels of nicotine exposure than adults (*69*, *70*). Earlier onset of daily smoking is associated with higher nicotine dependence scores (*71*) and heavier and longer smoking careers compared to late-onset smokers (*72*, *73*). Individuals who begin smoking as teens are more likely to become lifelong smokers than those who start smoking in their 20s or later (*74*–*76*). In a study of 1200 individuals, those who initiated smoking before age 13 had the lowest likelihood of quitting, followed by those who initiated between ages 14 and 17, while adult initiators (18+) had the highest likelihood of quitting (*77*). A number of studies have yielded similar results (*78*). The findings have implications for policy interventions aimed at preventing initiation in youth.

Smoking among people with mental illness. Mental illness commonly co-occurs with tobacco addiction (*79*, *80*), including major depression, bipolar disorder, posttraumatic stress disorder (PTSD), and schizophrenia. Evidence that nicotine may improve cognitive function and sensory gating and reduce psychotic symptoms has led to the self-medication hypothesis, which posits that people with psychiatric disorders smoke to lessen their symptoms (*81*). The tobacco industry funded research in support of the self-medication hypothesis (*82*). Bidirectional models maintain that smoking and psychiatric symptoms influence each other (*83*), and studies indicate that early-onset smoking may predispose to depression, anxiety disorders, and schizophrenia (*80*). There is also evidence of modest shared genetic susceptibility to tobacco dependence and mental illness.

Cigarette smoking induces the metabolism of some psychiatric medications leading to lower blood levels, with reduced sedation, and may explain, in part, the improvements observed in cognitive function (*84*). Studies in youth and adults, cross-sectional and prospective, have found that current smoking is predictive of future suicidal behavior—independent of depressive symptoms, previous suicidal acts, and other substance use—and that longer lifetime smoking (>40 years versus ≤10 years) is associated with a twofold higher odds of suicide (*80*). Notably, quitting smoking appears to mitigate the risk (*85*).

The self-medication hypothesis—that people smoke to manage their mental health symptoms—drove concerns that treating smoking would worsen mental health. This belief and the perceptions that smoking is a chronic, rather than acute, concern have been substantial barriers to addressing tobacco use in psychiatric settings (*86*). Newer research, however, indicates that quitting smoking is associated with improvements in mental health, including reductions in depression, anxiety, psychotic symptoms, emotional lability, and PTSD symptoms (*87*–*89*). In a randomized trial with smokers recruited from inpatient psychiatry, the tobacco cessation intervention was associated with a significantly lower likelihood of rehospitalization out to 18-month follow-up (*90*). A meta-analysis of 26 longitudinal studies assessing mental health before smoking cessation and at least 6 weeks after abstinence found reduced depression, anxiety, and stress and greater overall well-being compared with continuing to smoke (*49*). The effects were comparable for those with and without psychiatric disorders. If people self-medicate nicotine for acute relief, it does not appear to produce sustained benefits and is a form of self-medication that should be discouraged.

Smoking among people with other addictions. Three in four adults with alcohol use disorder and 9 in 10 adults with drug use disorders smoke tobacco (*91*). Early-onset smoking is a significant predictor of lifetime drinking, more excessive alcohol consumption, and the subsequent development of lifetime alcohol abuse and dependence (*72*). Nicotine addiction, in the form of cigarette smoking, causes greater morbidity and mortality than any other single drug addiction and the combination of all other risks (*92*). Among individuals treated for alcohol dependence, tobacco-related diseases were responsible for half of all deaths, greater than alcohol-related causes (*93*).

While the causal progression remains under debate, tobacco use has been implicated as a "gateway" to other drugs of abuse (*94*). Possible mechanisms include nicotine enhancing the rewarding effects of other drugs, nicotine reducing the negative effects of another drug (for example, less sedation with alcohol use), and shared genetic susceptibility. Mice given nicotine in their drinking water for a week had an increased response to cocaine; nicotine caused epigenetic changes in DNA, in particular, affecting expression of the *FosB* gene found related to addiction (*95*). In human adults, cocaine users who smoked cigarettes before starting cocaine had a two- to threefold greater likelihood of cocaine dependence compared to those who tried cocaine before smoking cigarettes and compared to those who never became regular smokers (*95*). The inference was that brain changes due to early exposure to nicotine made it more likely that the individuals would become addicted to cocaine.

While concomitant smoking and drug use are common, treating smoking may improve sobriety outcomes in the long term. A meta-analysis of randomized controlled tobacco cessation trials with smokers in treatment for substance use disorders found that tobacco cessation interventions were associated with a 25% increased likelihood of sobriety from alcohol and drugs relative to usual care (*96*).

Genetic factors. Genetic factors also influence the risk of nicotine dependence. The strongest genetic factor associated with nicotine dependence involves the *CHRNA5* gene, which encodes the α5 nAChR subunit (*43*, *56*). The rs16969968 single-nucleotide polymorphism on chromosome 15 is associated with greater risk of becoming dependent, a lower likelihood of smoking cessation, and increased risk of lung cancer and COPD. The nAChR with a reduced function α5 subunit is thought to result in less aversiveness to nicotine and greater nicotine intake and, therefore, greater dependence. The other major genetic risk factor for nicotine dependence is the *CYP2A6* gene, which is associated with the rate of nicotine metabolism and greater nicotine dependence including smoking more cigarettes per day, more rapid onset of withdrawal symptoms during abstinence, and lower quit rates (*35*, *97*).

TREATING NICOTINE ADDICTION IN ADULTS, WITH A FOCUS ON CONVENTIONAL CIGARETTES

As discussed, tobacco dependence is characterized as a physiological dependence (addiction to nicotine) and behavioral (or conditioned) habit of using tobacco. Hence, for maximal effectiveness, as recommended by U.S. Clinical Practice Guidelines, tobacco dependence treatment engages a multipronged approach (*98*). Addiction can be treated with FDA-approved medications for smoking cessation; the behavioral habit can be treated through counseling and behavior change programs, and policy interventions can promote smoke-free environments, discussed in the "Tobacco Control Population-Based and Policy Approaches" section.

Counseling and psychosocial treatments

Brief cessation advice

With 7 in 10 tobacco users seeing a healthcare provider in a given year, opportunities exist for brief cessation clinical advice. Treating smoking is relevant to all areas of medicine, and the evidence in support of brief clinical cessation advice is strong (*99*). The U.S. Preventive Services Task Force gives a "grade A" recommendation for clinician-delivered brief tobacco cessation interventions (*100*). Counseling by nonphysician health providers, including nurses (*101*), oral health professionals (*102*), and pharmacists (*103*), also increases quit rates.

The gold standard for brief cessation advice is the National Cancer Institute's (NCI) 5A's to (i) ask all patients about use of all forms of tobacco; (ii) advise tobacco users to quit; (iii) assess patient readiness to quit; (iv) assist in the quit attempt with counseling, medications, and referrals; and (v) arrange follow-up. The 5 A's increase patient treatment engagement, quit attempts, and tobacco abstinence (*104*).

Recognizing time constraints in the clinical setting, an alternate approach with evidence is Ask-Advise-Refer (AAR), whereby clinicians ask about tobacco use, advise tobacco users to quit, and then refer patients to an outside entity for assistance and follow-up, such as a tobacco quitline (1-800-QUIT-NOW) (*105*, *106*). Further adaptation is Ask-Advise-Connect (AAC), the distinction being that the referral is provided in the form of a direct connection, such as a fax or other electronic referral (*107*). Comparison of AAR to the 5 A's delivered in 68 dental clinics found comparable quit rates, and both approaches were better than usual care (*106*). Sustained quit rates at long-term follow-up, however, were under 4% in all three study arms. A recognized standard of care, brief provider advice is effective for engaging patients in treatment and supporting quitting (*98*); however, to further improve sustained abstinence rates, more intensive interventions are needed.

Intensive counseling

Clinical practice guidelines recommend intensive cessation counseling offered in person, individually or in groups, in clinical, behavioral, or community settings for treating smoking (*98*). The counseling framework tends to be cognitive behavioral and motivational, although, increasingly, other clinical approaches (e.g., mindfulness, acceptance, and commitment therapy) are being incorporated. A systematic review of 49 randomized trials with some 19,000 participants concluded that intensive counseling only (without medications) delivered by a cessation counselor on a one-to-one basis was more effective than minimal contact (i.e., brief advice and self-help materials) and had greater effects when combined with cessation medications (*108*). Intensive individual and group counseling treatments also have demonstrated effectiveness in workplace settings (*109*). Access to intensive counseling may be limited because of travel, time, cost, or privacy concerns. To overcome these barriers, tobacco quitlines were developed to improve accessibility and reach of tobacco cessation counseling treatment.

Tobacco quitlines

Tobacco quitlines are staffed by trained counselors or coaches who provide information, individual counseling, local referrals, self-help materials, and, in some cases, limited supplies of free cessation medications. The effectiveness of tobacco quitlines is well demonstrated

(*110*). Quitline services are available at no cost to U.S. residents and accessed via a toll-free national portal (1-800-QUIT-NOW or 1-855-DÉJELO-YA), which links callers to their state quitline based on their area code. While specific services vary by state, by county, and over time, most state quitlines provide at least one counseling session to any adult tobacco user who calls, and many states provide a multi-call program that includes reactive and proactive calls. The reactive approach relies upon smokers to initiate the calls, whereas the proactive approach makes outbound calls to engage tobacco users. In meta-analyses, better outcomes are seen with multi-call versus single-call protocols (*110*) and with proactive versus reactive quitline services (*111*).

Although free, convenient, and confidential, quitlines in most states reach an average of only 1% of smokers annually (*112*). Even among smokers aware of quitlines and making a quit attempt, reach is only about 8% (*113*). The Centers for Disease Control and Prevention's (CDC) Tips From Former Smokers (Tips) tobacco education campaign, developed to encourage quitting and raise awareness of state quitline services and conducted annually since 2012, has generated hundreds of thousands of additional calls to state quitlines (*114*). The Tips campaign and its impact on quitting are discussed under media campaigns in the "Tobacco Control Population-Based and Policy Approaches" section. To further expand reach, some state quitlines have incorporated mobile health technologies.

Mobile technologies: Internet, text, and social

Mobile technologies, such as internet interventions, email, chat, and texting, are being leveraged for health promotion at a low cost, with broad reach potential and with evidence of efficacy.

Internet. Internet-delivered tobacco cessation interventions have existed for more than 25 years and have continued to develop in sophistication, level of interaction, and complexity of functionality, as well as treatment efficacy. In 2011, the Community Preventive Services Task Force deemed the evidence insufficient to recommend internet-based interventions for tobacco cessation (*115*). Two years later, a 2013 review concluded that internet-based interventions can assist in achieving long-term smoking cessation, particularly interactive programs tailored to the individual (*116*). A 2016 review noted significant improvements in internet-based smoking cessation interventions with evidence of superior efficacy relative to print materials and equivalent efficacy to telephone and in-person counseling (*117*). Relative to quitlines, internet-delivered interventions have 27 times greater national reach [annually, 11 million for internet versus 400,000 for quitlines (*112*)] and at a lower cost per quit [e.g., $291 for internet versus $900 for quitlines (*118*)].

A model example of an internet-delivered tobacco cessation program is NCI's Smokefree.gov, which combines evidence-based guidelines for quitting smoking, tailored to readiness to quit, with availability of professional assistance via instant messaging and telephone (1-877-44U-QUIT). The site has also tailored offerings for veterans, women, adolescents, Spanish-speaking smokers, and older adults. SmokefreeTXT is an additional mobile service that provides encouragement, advice, and tips for young adults to quit smoking. Smokefree smartphone apps are offered to provide motivational reminders and help with tracking progress with quitting smoking. The Smokefree.gov site had 3.6 million visitors in 2016 (*118*) and received high user satisfaction ratings (*119*). Randomized trial evidence supports Smokefree.gov as a population-based intervention for smoking cessation (*118*, *120*).

Mobile technologies. Mobile phone–based tobacco cessation interventions that send automated low-cost messages (i.e., texts) were deemed to have sufficient evidence of efficacy to be recommended by the Community Preventive Services Task Force (*121*). Trials in New Zealand and the United Kingdom evaluated text messages sent daily up to the quit day that tapered to a maintenance phase; texts included general information, motivational messages, quitting advice, and distraction strategies, and effects on quit rates were significant relative to no-text controls (*122*, *123*). A 2016 review found significant short-term effects of text-based smoking cessation interventions, although they were not sustained at long-term (>6 months) follow-up (*124*). Given the chronic, relapsing nature of nicotine addiction, more intensive extended interventions may be needed.

With the potential for more dynamic interactions, smoking cessation apps (applications) are available for download from digital marketplaces (e.g., iTunes and Google Play) for use on smartphones, tablets, and other handheld devices. A 2014 search identified 546 smoking cessation apps in the Apple Store and on Google Play that were downloaded some 3.2 million times in the United States and 20 million times worldwide (*125*). Broad reach and high scalability make apps particularly well suited for serving remote and resource-poor settings. Advantages include low or no cost to the user, self-tracking and tailored feedback functionalities, and use of images and video for enhanced health literacy. However, a 2015 review of 225 Android apps for quitting smoking found that most provide simplistic tools (e.g., calculators and trackers); use of tailoring was limited, although positively related to app popularity and user ratings of quality (*126*). Evaluation of intervention effects on quitting smoking is sorely needed. Notably, one randomized trial found that a simpler, direct texting program outperformed a smoking cessation app (*127*).

Social media. Social media, such as Twitter and Facebook, are being explored for delivering cessation treatment. In the United States, 74% of online adults use social media, 80% of whom are seeking health information, and a majority access the sites daily (*128*). A promising technology, efforts to sustain engagement are key and can be challenging; like predecessor technologies such as bulletin boards and listservs, initial interest may be high but then tends to wane (*129*, *130*). There is preliminary evidence, however, of good acceptability and efficacy. Using Twitter, small, private groups of 20 smokers, who interact for 100 days, have been studied. The intervention (Tweet2Quit) seeds the groups with twice-daily automessages to encourage group sharing and support. In a randomized trial, the Tweet2Quit Twitter groups added to Smokefree.gov and the nicotine patch fostered peer-to-peer support for quitting and significantly doubled the likelihood of reported sustained abstinence relative to the website and patch alone (*131*). Similar efforts are being developed on Facebook, with a focus on engaging young adults into cessation treatment. In a randomized trial, a novel Facebook smoking cessation intervention increased abstinence at the end of treatment, although effects were not sustained out to 1-year follow-up (*132*).

Social media can provide varying degrees of anonymity, which may be attractive. Having tried and failed to quit smoking in the past, smokers may not initially publicize their quit attempts within their main social circle (*133*). With social media sites that are largely uncurated or expert moderated, however, users should be forewarned that inaccurate information may be posted. For example, online communities may encourage use of non–evidence-based treatments (e.g., laser, herbs, acupuncture, or hypnosis for quitting smoking)

(*129*). A heterogeneous group of emerging applications and knowledge gaps remain concerning best strategies for maximizing the reach and efficacy of mobile technologies for treating nicotine addiction as well as the comparative effectiveness relative to in-person approaches.

Monetary incentives

Monetary incentives that reward outcome (i.e., quitting smoking) or engagement (e.g., treatment participation) have been evaluated in 33 trials, with a meta-analysis finding evidence of increased abstinence that persisted after the incentives ceased (*134*). The level of the incentives ranged from zero (self-deposits) to between $45 and $1185, with no clear direction of effect by level of incentive. Conditional payments (i.e., payment for abstinence) outperformed nonconditional payments. Findings from a subgroup analysis of eight trials conducted with smokers with substance use problems were consistent with the overall analysis. A summary of nine trials with pregnant smokers reported more than twofold greater odds of abstinence at longest follow-up assessment (up to 24 weeks postpartum). The findings are particularly important given the substantial health harms of smoking to mother and baby and that, currently, there is no other effective cessation intervention for pregnant smokers.

Pharmacotherapies to aid smoking cessation

While counseling and psychosocial treatments help promote cessation, medications that address the neuropharmacological effects of nicotine and nicotine withdrawal further enhance the likelihood of quitting. E-cigarettes, which allow continued self-administration of nicotine without combustion, can also promote quitting smoking.

Smoking cessation guidelines, such as those from the U.S. Public Health Service and National Cancer Center Network, recommend smoking cessation medications for all daily smokers where feasible and safe (*98*, *135*). Pharmacotherapy can be considered for nondaily smokers as well, although there are few clinical trials to guide treatment in this group. The mechanism of benefit in nondaily smokers would be reduction of nicotine reward from cigarettes by nicotinic receptor desensitization or antagonism, as discussed below. Table 2 presents the FDA-approved smoking cessation medications, including dosing guidelines, advantages, disadvantages, adverse effects, and precautions. FDA-approved medications are NRT in the form of gum, patches, lozenge, nasal spray and inhaler, varenicline, and bupropion. Nicotine gums, lozenges, and patches are available over the counter in the United States, while the nicotine nasal spray, nicotine inhaler, varenicline, and bupropion are by prescription only. Nicotine mouth spray is available outside of the United States and has evidence of acceptability, efficacy, and safety, including with minimal behavioral support (*136*).

In general, medications serve to make smokers more comfortable while they learn to live and cope with daily cues/triggers and life stressors without smoking cigarettes. There are three main mechanisms by which medications can facilitate smoking cessation: (i) reduction of nicotine withdrawal symptoms, (ii) reduction of the rewarding effects of nicotine from smoking by blocking or desensitizing nicotine receptors, and (iii) providing an alternative source of nicotine with the desired pharmacologic effect previously provided by nicotine from cigarettes. NRT medications are not as satisfying as cigarette smoking because of slower absorption of nicotine; nicotine delivery from e-cigarettes can resemble that of a cigarette, and these devices tend to be much more satisfying. Most smoking cessation medications are recommended for 8 to 12 weeks, although use for 6 months or longer may be necessary to achieve optimal quit rates. It makes sense to use medications to support smoking cessation for as long as the individual feels at risk for relapse. For those switching to e-cigarettes as a less harmful substitute for cigarette smoking, use sometimes continues for many months or years.

Nicotine replacement therapy

Nicotine medications consist of purified nicotine that is administered to ameliorate symptoms of physical dependence on nicotine. The particular actions of different products vary according to route of administration and rate of nicotine absorption into the bloodstream. For example, nicotine patches deliver nicotine slowly, relieving nicotine withdrawal symptoms and reducing positive effects of cigarette smoking, without providing much, if any, direct positive effects of nicotine. Nicotine gums, lozenges, sprays, and inhalers deliver nicotine more rapidly, providing some acute nicotine effects that may serve as a substitute for smoking a cigarette. Combining a short-acting (gum, lozenge, spray, or inhaler) with a long-acting (nicotine patch) NRT results in superior quit rates compared to any NRT product alone and is recommended as a first-line treatment (*137*).

NRT products are marketed in different strengths, with higher doses recommended for more dependent smokers based on the number of cigarettes smoked per day or time to first cigarette upon wakening. A 2019 Cochrane review concluded that 4-mg gum is more effective than 2-mg gum in more highly dependent smokers and that 21-mg patch is more effective than 14-mg patch in general (*137*). While clinical trials do not demonstrate superiority of 42- to 21-mg dose nicotine patch, some clinicians do use high-dose patch for smokers with particularly severe withdrawal symptoms. Tapering of nicotine doses over time is an option for nicotine patches but does not appear to affect outcome in clinical trials.

All forms of NRT have shown similar efficacy in clinical trials (*137*), increasing quit rates by 50 to 100% compared to behavioral treatment alone. For the NRTs, compliance is greatest with nicotine patches, lower with gum and lozenge, and lowest with the nasal spray and inhaler. Nicotine patches are usually placed on the skin in the morning and deliver nicotine over 16 to 24 hours. Some smokers experience nicotine patch–related insomnia and/or abnormal dreams and do better removing the patch at bedtime. Use of patches for 16 or 24 hours is equally effective in promoting quitting smoking. The pharmacokinetics of nicotine gum, lozenge, and inhaler are similar, with gradual absorption of relatively low doses of nicotine over 15 to 30 min. Use every 1 to 2 hours provides the best pharmacologic response. The nicotine inhaler is a plastic device inhaled like a cigarette but delivers nicotine to the oropharyngeal area rather than to the lungs, which explains its slow absorption. The main advantage of the inhaler is providing a hand-to-mouth experience similar to smoking. All oral nicotine products have an alkaline pH, which results in a high proportion of nicotine in the free base form, which is rapidly absorbed across mucous membranes. Acidic beverages (e.g., coffee, citrus juice, sodas, and many alcohol beverages) reduce the pH and reduce nicotine absorption and should be avoided for >10 min before using oral NRT products. The nicotine nasal spray is absorbed much faster than the other rapid-release products, most closely resembling a cigarette. More dependent smokers may find nicotine nasal spray to be more effective than other NRT products for smoking cessation. The spray is associated with more local toxicity, including a burning sensation, watery eyes, and sneezing; however, tolerance develops to these effects with regular use of the spray over 1 to 2 days.

Table 2. FDA-approved medications for smoking cessation.

	Nicotine Replacement Therapy (NRT) Formulations					Bupropion SR	Varenicline
	Gum	Lozenge	Transdermal Patch	Nasal Spray	Oral Inhaler		
Product	**Nicorette**[1]**, Generic** OTC 2 mg, 4 mg original, cinnamon, fruit, mint	**Nicorette**[1]**, Generic Nicorette**[1] **Mini** OTC 2 mg, 4 mg; cherry, mint	**NicoDerm CQ**[1]**, Generic** OTC (NicoDerm CQ, generic) 7 mg, 14 mg, 21 mg (24-hr release)	**Nicotrol NS**[2] Rx Metered spray 10 mg/mL nicotine solution	**Nicotrol Inhaler**[2] Rx 10 mg cartridge delivers 4 mg inhaled vapor	**Zyban**[1]**, Generic** Rx 150 mg sustained-release tablet	**Chantix**[2] Rx 0.5 mg, 1 mg tablet
Precautions	•Recent (≤ 2 weeks) myocardial infarction •Serious underlying arrhythmias •Serious or worsening angina pectoris •Temporomandibular joint disease •Pregnancy[3] and breastfeeding •Adolescents (<18 years)	•Recent (≤ 2 weeks) myocardial infarction •Serious underlying arrhythmias •Serious or worsening angina pectoris •Pregnancy[3] and breastfeeding •Adolescents (<18 years)	•Recent (≤ 2 weeks) myocardial infarction •Serious underlying arrhythmias •Serious or worsening angina pectoris •Pregnancy[3] and breastfeeding •Adolescents (<18 years)	•Recent (≤ 2 weeks) myocardial infarction •Serious underlying arrhythmias •Serious or worsening angina pectoris •Underlying chronic nasal disorders (rhinitis, nasal polyps, sinusitis) •Severe reactive airway disease •Pregnancy[3] and breastfeeding •Adolescents (<18 years)	•Recent (≤ 2 weeks) myocardial infarction •Serious underlying arrhythmias •Serious or worsening angina pectoris •Bronchospastic disease •Pregnancy[3] and breastfeeding •Adolescents (<18 years)	•Concomitant therapy with medications/conditions known to lower the seizure threshold •Hepatic impairment •Pregnancy[3] and breastfeeding •Adolescents (<18 years) •Treatment-emergent neuropsychiatric symptoms[4] BOXED WARNING REMOVED 12/2016 **Contraindications:** •Seizure disorder •Concomitant bupropion (e.g., Wellbutrin) therapy •Current or prior diagnosis of bulimia or anorexia nervosa •Simultaneous abrupt discontinuation of alcohol or sedatives/benzodiazepines •MAO inhibitors in preceding 14 days; concurrent use of reversible MAO inhibitors	•Severe renal impairment (dosage adjustment is necessary) •Pregnancy[3] and breastfeeding •Adolescents (<18 years) •Treatment-emergent neuropsychiatric symptoms[4] BOXED WARNING REMOVED 12/2016
Dosing	*1st cigarette ≤30 minutes after waking:* 4 mg *1st cigarette >30 minutes after waking:* 2 mg Weeks 1–6: 1 piece q 1–2 hours Weeks 7–9: 1 piece q 2–4 hours Weeks 10–12: 1 piece q 4–8 hours •Maximum, 24 pieces/day •Chew each piece slowly •Park between cheek and gum when peppery or tingling sensation appears (~15–30 chews) •Resume chewing when tingle fades •Repeat chew/park steps until most of the nicotine is gone (tingle does not return; generally 30 min) •Park in different areas of mouth •No food or beverages 15 minutes before or during use •Duration: up to 12 weeks	*1st cigarette ≤30 minutes after waking:* 4 mg *1st cigarette >30 minutes after waking:* 2 mg Weeks 1–6: 1 lozenge q 1–2 hours Weeks 7–9: 1 lozenge q 2–4 hours Weeks 10–12: 1 lozenge q 4–8 hours •Maximum, 20 lozenges/day •Allow to dissolve slowly (20–30 minutes) •Nicotine release may cause a warm, tingling sensation •Do not chew or swallow •Occasionally rotate to different areas of the mouth •No food or beverages 15 minutes before or during use •Duration: up to 12 weeks	*>10 cigarettes/day:* 21 mg/day x 4–6 weeks 14 mg/day x 2 weeks 7 mg/day x 2 weeks *≤10 cigarettes/day:* 14 mg/day x 6 weeks 7 mg/day x 2 weeks •Rotate patch application site daily; do not apply a new patch to the same skin site for at least one week •May wear patch for 16 hours if patient experiences sleep disturbances (remove at bedtime) •Duration: 8–10 weeks	1–2 doses/hour (8–40 doses/day) One dose = 2 sprays (one in **each** nostril); each spray delivers 0.5 mg of nicotine to the nasal mucosa •Maximum −5 doses/hour or −40 doses/day •For best results, initially use at least 8 doses/day •Do not sniff, swallow, or inhale through the nose as the spray is being administered •Duration: 3 months	6–16 cartridges/day Individualize dosing; initially use 1 cartridge q 1–2 hours •Best effects with continuous puffing for 20 minutes •Initially use at least 6 cartridges/day •Nicotine in cartridge is depleted after 20 minutes of active puffing •Inhale into back of throat or puff in short breaths •Do NOT inhale into the lungs (like a cigarette) but "puff" as if lighting a pipe •Open cartridge retains potency for 24 hours •No food or beverages 15 minutes before or during use •Duration: 3–6 months	150 mg po q AM x 3 days, then 150 mg po bid •Do not exceed 300 mg/day •Begin therapy 1–2 weeks **prior** to quit date •Allow at least 8 hours between doses •Avoid bedtime dosing to minimize insomnia •Dose tapering is not necessary •Duration: 7–12 weeks, with maintenance up to 6 months in selected patients	Days 1–3: 0.5 mg po q AM Days 4–7: 0.5 mg po bid Weeks 2–12: 1 mg po bid •Begin therapy 1 week **prior** to quit date •Take dose after eating and with a full glass of water •Dose tapering is not necessary •Dosing adjustment is necessary for patients with severe renal impairment •Duration: 12 weeks; an additional 12-week course may be used in selected patients •May initiate up to 35 days before target quit date OR may reduce smoking over a 12-week period of treatment prior to quitting and continue treatment for an additional 12 weeks

continued on next page

	Nicotine Replacement Therapy (NRT) Formulations					Bupropion SR	Varenicline
	Gum	Lozenge	Transdermal Patch	Nasal Spray	Oral Inhaler		
Adverse Effects	•Mouth and throat irritation •Jaw muscle soreness •Hiccups •GI complaints (dyspepsia, nausea) •May stick to dental work •Adverse effects more commonly experienced when chewing the lozenge or using incorrect gum chewing technique (due to rapid nicotine release): –Lightheadedness/dizziness –Nausea/vomiting –Hiccups –Mouth and throat irritation	•Mouth and throat irritation •Hiccups •GI complaints (dyspepsia, nausea)	•Local skin reactions (erythema, pruritus, burning) •Sleep disturbances (abnormal or vivid dreams, insomnia); associated with nocturnal nicotine absorption	•Nasal and/or throat irritation (hot, peppery, or burning sensation) •Ocular irritation/tearing •Sneezing •Cough	•Mouth and/or throat irritation •Cough •Hiccups •GI complaints (dyspepsia, nausea)	•Insomnia •Dry mouth •Nausea •Anxiety/difficulty concentrating •Constipation •Tremor •Rash •Seizures (risk is 0.1%) •Neuropsychiatric symptoms (rare; see Precautions)	•Nausea •Sleep disturbances (insomnia, abnormal/vivid dreams) •Headache •Flatulence •Constipation •Taste alteration •Neuropsychiatric symptoms (rare; see Precautions)
Advantages	•Might serve as an oral substitute for tobacco •Might delay weight gain •Can be titrated to manage withdrawal symptoms •Can be used in combination with other agents to manage situational urges •Relatively inexpensive	•Might serve as an oral substitute for tobacco •Might delay weight gain •Can be titrated to manage withdrawal symptoms •Can be used in combination with other agents to manage situational urges •Relatively inexpensive	•Once-daily dosing associated with fewer adherence problems •Of all NRT products, its use is least obvious to others •Can be used in combination with other agents; delivers consistent nicotine levels over 24 hours •Relatively inexpensive	•Can be titrated to rapidly manage withdrawal symptoms •Can be used in combination with other agents to manage situational urges	•Might serve as an oral substitute for tobacco •Can be titrated to manage withdrawal symptoms •Mimics hand-to-mouth ritual of smoking •Can be used in combination with other agents to manage situational urges	•Twice-daily oral dosing is simple and associated with fewer adherence problems •Might delay weight gain •Might be beneficial in patients with depression •Can be used in combination with NRT agents •Relatively inexpensive (generic formulations)	•Twice-daily oral dosing is simple and associated with fewer adherence problems •Offers a different mechanism of action for patients who have failed other agents •Most effective cessation agent when used as monotherapy
Disadvantages	•Need for frequent dosing can compromise adherence •Might be problematic for patients with significant dental work •Proper chewing technique is necessary for effectiveness and to minimize adverse effects •Gum chewing might not be acceptable or desirable for some patients	•Need for frequent dosing can compromise adherence •Gastrointestinal side effects (nausea, hiccups, heartburn) might be bothersome	•When used as monotherapy, cannot be titrated to acutely manage withdrawal symptoms •Not recommended for use by patients with dermatologic conditions (e.g., psoriasis, eczema, atopic dermatitis)	•Need for frequent dosing can compromise adherence •Nasal administration might not be acceptable or desirable for some patients; nasal irritation often problematic •Not recommended for use by patients with chronic nasal disorders or severe reactive airway disease •Cost of treatment	•Need for frequent dosing can compromise adherence •Cartridges might be less effective in cold environments (≤60°F) •Cost of treatment	•Seizure risk is increased •Several contraindications and precautions preclude use in some patients (see Precautions) •Patients should be monitored for potential neuropsychiatric symptoms[4] (see Precautions)	•Patients should be monitored for potential neuropsychiatric symptoms[4] (see Precautions) •Cost of treatment
Cost/day[5]	2 mg or 4 mg: $1.90–$3.60 (9 pieces)	2 mg or 4 mg: $3.33–$3.60 (9 pieces)	$1.52–$2.90 (1 patch)	$8.72 (8 doses)	$14.88 (6 cartridges)	$2.58–$8.25 (2 tablets)	$15.14 (2 tablets)

Abbreviations: MAO, monoamine oxidase; NRT, nicotine replacement therapy; OTC, over-the-counter (nonprescription product); Rx, prescription product.
For complete prescribing information and a comprehensive listing of warnings and precautions, please refer to the manufacturers' package inserts.

[1]Marketed by GlaxoSmithKline. [2]Marketed by Pfizer. [3]The U.S. Clinical Practice Guideline states that pregnant smokers should be encouraged to quit without medication based on insufficient evidence of effectiveness and theoretical concerns with safety. Pregnant smokers should be offered behavioral counseling interventions that exceed minimal advice to quit. [4]In July 2009, the FDA mandated that the prescribing information for all bupropion- and varenicline-containing products include a black-boxed warning highlighting the risk of serious neuropsychiatric symptoms, including changes in behavior, hostility, agitation, depressed mood, suicidal thoughts and behavior, and attempted suicide. Clinicians should advise patients to stop taking varenicline or bupropion SR and contact a health care provider immediately if they experience agitation, depressed mood, or any changes in behavior that are not typical of nicotine withdrawal, or if they experience suicidal thoughts or behavior. If treatment is stopped due to neuropsychiatric symptoms, patients should be monitored until the symptoms resolve. Based on results of a mandated clinical trial, the FDA removed this boxed warning in December 2016. [5]Approximate cost based on the recommended initial dosing for each agent and the wholesale acquisition cost from Red Book Online. Thomson Reuters, December 2018.

Overall, NRT products are well tolerated and present few safety concerns. Safety concerns with NRT are primarily skin irritation with patches, gastrointestinal symptoms with oral products, and nasal/throat burning and irritation with nasal spray. Nicotine's cardiovascular effects raised concern about NRT cardiovascular safety. Nicotine enhances sympathetic neural activity, resulting in increased heart rate, constriction of blood vessels, induction of proatherogenic lipid profiles (lower high-density lipoprotein cholesterol), development of insulin resistance, and possible promotion of arrhythmias (*138*). Cigarette smoke delivers not only nicotine but also many oxidants, prothrombotic and other toxic chemicals, making smoking much more toxic than nicotine alone. Clinical trials and other studies of NRT in patients with cardiovascular disease find no increase in adverse cardiovascular events due to NRT (*139*, *140*).

Varenicline

Varenicline is a partial agonist at the nicotinic α4β2 receptor, the major receptor mediating nicotine addiction. Varenicline both activates (about 50% of the maximal effect of nicotine) and blocks the effects of nicotine on the α4β2 receptor (*141*). The agonist effect serves to reduce withdrawal symptoms, while the antagonist effects reduce the rewarding effects of nicotine from cigarette smoke. Varenicline treatment before smoking cessation is often associated with reduced smoking, presumably because smoking is less satisfying, an effect that can promote subsequent cessation.

In clinical trials, varenicline is more effective than bupropion or nicotine patch in promoting smoking cessation and is comparably effective to combined NRT (*142*). The EAGLES trial, the largest smoking cessation trial conducted with 8000 smokers, directly compared varenicline, bupropion, nicotine patch, and placebo. Varenicline outperformed all conditions; bupropion and nicotine patch were comparable to each other and were significantly better than placebo (*143*). EAGLES included smokers without and with psychiatric diagnoses. Quit rates were higher in those without psychiatric diagnoses, but the relative efficacy of the various treatments was similar. Extended treatment with varenicline for 6 months is superior to the standard 12-week treatment and is recommended for smokers who feel at risk of relapse (*144*).

The most common adverse effect of varenicline is nausea, which is dose related and to which tolerance develops over time. Concern about nausea is the rationale for starting at lower doses (0.5 mg once to twice daily) for a week before starting the full dose (1.0 mg twice daily). Some smokers cannot tolerate the normal dose but do well on continued use of the lower dose. Anecdotal reports of neuropsychiatric adverse effects of varenicline used for smoking cessation have been reported, prompting a black box warning in the label after the drug was marketed (for both varenicline and bupropion). The putative neuropsychiatric side effects included depression, psychosis, and suicide, with potentially higher risk in smokers with psychiatric disease. However, the EAGLES trial found no evidence of increased neuropsychiatric adverse events for varenicline or bupropion relative to nicotine patch or placebo, in smokers with or without psychiatric illness, and in 2016, the black box warnings were removed for both varenicline and bupropion (*143*). Varenicline has been shown to enhance smoking cessation in patients with cardiovascular disease, including stable coronary heart disease and acute coronary syndrome (*145*, *146*). Concern was raised about possible cardiovascular toxicity due to the nicotine-like effects of varenicline and anecdotal reports of adverse cardiovascular events, but several meta-analyses, a large retrospective cohort study, and clinical trials in smokers with cardiovascular disease, as well as the EAGLES trial, showed no increase in cardiovascular risk (*147*, *148*). Varenicline has also been found efficacious for cessation of smokeless tobacco use (*149*).

Bupropion

Bupropion is a stimulant drug originally marketed as an antidepressant. Bupropion blocks neuronal uptake of dopamine and norepinephrine and has antagonist activity on the α4β2 nicotinic receptor. By blocking reuptake, bupropion increases brain levels of dopamine and norepinephrine, simulating effects of nicotine. Bupropion is marketed for smoking cessation as a sustained-release preparation. The drug works in both depressed and non-depressed smokers. The usual duration of bupropion treatment is 12 weeks, but extended bupropion therapy for a year reduces relapse and enhances long-term quit rates (*150*). With lower quit rates, bupropion is considered to be second-line, after combination NRT and varenicline.

The main adverse effects of bupropion relate to its nervous system stimulant actions. Some smokers are intolerant to bupropion because of anxiety, agitation, and insomnia. Bupropion reduces the seizure threshold and should not be used in smokers who are at risk for seizures. In overdose, bupropion causes tachycardia and hypertension, but there is no evidence of increased cardiovascular events in smokers with preexisting stable cardiovascular disease (*151*, *152*).

Combination pharmacotherapy

Combined NRT with patch and a more immediate acting product results in higher quit rates than single NRT [Cochrane meta-analysis: risk ratio (RR), 1.34; 95% confidence interval (CI), 1.18 to 1.48] (*137*). The combination of varenicline and nicotine patch has been evaluated with mixed results (*153*). The mechanism for why NRT should augment effects of varenicline is unclear, but the combination appears to be safe. The combination can be considered in a smoker who does not quit with dual NRT or varenicline. Bupropion in combination with nicotine patch or dual NRT increases quit rates compared to these drugs given alone (*154*). One trial reported promising results with the combination of varenicline and bupropion, although neuropsychiatric adverse effects were greater in the first 2 weeks compared to varenicline alone (*155*).

Preloading pharmacotherapy

Many smokers would like to quit but are not prepared to commit to a quit date when seen by a healthcare provider. Starting pharmacotherapy while the smoker is still smoking with the expectation that quitting will be easier at a later date has been studied with the use of nicotine patches and varenicline. The pharmacological basis for this approach is that NRT, by desensitizing nicotinic receptors and reducing withdrawal symptoms between cigarettes, and varenicline, by antagonizing effects of nicotine from cigarettes and also providing relief of withdrawal symptoms, will reduce satisfaction from smoking and decrease the number of cigarettes smoked per day. Preloading trials with nicotine patches have shown mixed benefit on quitting with a weak overall effect, although some trials showed large beneficial effects (*156*, *157*). Varenicline trials have shown benefit with a flexible quit date, and this approach is approved by the FDA (*158*). The attraction of precessation pharmacotherapy is that the clinician can now approach every patient who smokes, regardless of whether they are prepared to quit at the time of the visit, with a pharmacological intervention along with communication that this will help with quitting smoking in time, just as the clinician would advise every patient with hypertension to take medication to prevent future disease. In this regard, a small trial involving heavy smokers with COPD, who were initially unprepared to quit, prescribed varenicline for as long as they wanted, without a fixed quit date, and by 18 months, most had quit (*159*).

Gradual reduction

Meta-analysis finds similar quit rates for gradual reduction in cigarettes smoked per day before quitting as compared to abrupt quitting (*160*). Even in trials that found that abrupt quitting resulted in higher quit rates, many in the gradual reduction group successfully quit. Precessation varenicline with instructions to reduce cigarettes per day by 50% at 4 weeks, 75% at 8 weeks, and completely quit at 12 weeks showed substantial benefit compared to placebo (*161*).

Targeted pharmacotherapy

Personalized medicine aims to use individual patient characteristics to select the most effective and/or safest medications for their medical

problem. With long-term quit rates of 30% or less in most smoking cessation trials, there is interest in individualizing treatment to enhance efficacy. A promising approach involves phenotyping based on an individual rate of nicotine metabolism. Rapid metabolizers of nicotine, on average, smoke more cigarettes and take in more nicotine per day compared to slower metabolizers, presumably to maintain desired levels of nicotine in the body (*35*). Rapid metabolizers also have more severe withdrawal symptoms when not smoking (*97*). The nicotine metabolite ratio is a phenotypic marker of the rate of nicotine metabolism, which can be measured in blood, saliva, or urine (*162*, *163*). In a prospective clinical trial, smokers were stratified as slow or normal metabolizers and treated with nicotine patch, varenicline, or placebo. In slow metabolizers, varenicline and nicotine patch were equally effective [odds ratio (OR), 1.13; $P = 0.56$], but in rapid metabolizers, varenicline was more effective (OR, 2.17; $P < 0.001$) (*164*). Side effects were greater for varenicline in slow metabolizers. The results indicate that slow metabolizers can be successfully treated with nicotine patch, at lower cost and with fewer side effects, but normal metabolizers are better treated with varenicline. More research is needed for confirmation.

Cytisine

Cytisine is an alkaloid extracted from the seeds of *Cytisus laburnum*, commonly known as golden chain or golden rain, a common garden plant in central and southern Europe. Cytisine has been used for smoking cessation in eastern and central European countries for more than 50 years. Cytisine, like varenicline, is a partial agonist at the α4β2 nAChR. Thus, it has nicotine-like effects, while at the same time it desensitizes and/or blocks the effects of nicotine from tobacco on the α4β2 nAChR. The recommended treatment regimen involves tapering doses over 25 days, a treatment course that is shorter than the 12 weeks recommended for most other smoking cessation medications, with significant effects relative to placebo (meta-analysis; RR, 1.74; 95% CI, 1.38 to 2.19) (*165*). The cost of cytisine in Europe is several-fold less than that of other smoking cessation medications. The drug is well tolerated, with the most common side effects being nausea, vomiting, dyspepsia, and dry mouth. Clinical trials of cytisine for FDA-approved use in the United States are underway.

Second-line smoking cessation medications

While not approved by the FDA, nortriptyline and clonidine have demonstrated efficacy in clinical trials for smoking cessation (*166*, *167*). These drugs are used primarily by smoking cessation specialists for patients who have not responded to other treatment. Nortriptyline is a tricyclic antidepressant that blocks neuronal reuptake of norepinephrine, thereby increasing levels of the neurotransmitter in the brain. These actions simulate some of the actions of nicotine on brain neurotransmitters. Clonidine is a central α2 adrenergic receptor agonist that reduces sympathetic activity, resulting in sedation and anxiolysis. The benefit of clonidine is thought to be mediated by its anxiolytic and calming effects and appears to be most useful in smokers with anxiety as a major withdrawal symptom.

Smoking cessation pharmacotherapies in development or that have failed

A number of medications have been considered as possible candidates for smoking cessation (*168*). While animal and/or small studies in people show effects on nicotine reward or smoking behavior, none of these medications alone has been shown in adequately sized clinical trials to be effective in promoting cessation, including (i) serotonin agonists (lorcaserin), (ii) acetylcholinesterase inhibitors (galantamine and rivastigmine), (iii) drugs affecting GABA receptors (baclofen, topiramate, and gabapentin), and (iv) *N*-methyl-D-aspartate (NMDA) receptor modulators (cycloserine, memantine, and *N*-acetylcysteine).

A promising new medication is lorcaserin, a selective 5-hydroxytryptamine 2c receptor agonist. The drug induces food satiety by increasing pro-opiomelanocortin production in the hypothalamus and is FDA approved for weight loss in overweight individuals. Lorcaserin has also been reported to reduce nicotine self-administration in rodents. Because weight gain after stopping smoking is common and sometimes triggers relapse, lorcaserin alone or in combination with other smoking cessation medications has been of interest. In a placebo-controlled trial combining lorcaserin (10 mg twice daily) with varenicline, the combination significantly increased 3-month continuous abstinence (OR, 3.0; 95% CI, 1.5 to 6.2) versus placebo (*169*), and weight gain was significantly less.

Medications evaluated in clinical trials and judged ineffective for quitting smoking include mecamylamine, serotonin-specific uptake inhibitors, anxiolytics (benzodiazepines and buspirone), MAO inhibitors (moclobemide and selegiline), modafenil, naltrexone, rimonabant, silver acetate, ondansetron, lobeline, nicotine vaccines, and Nicobrevin (quinine, methyl valerate, camphor, and eucalyptus oil).

E-cigarettes

A general discussion of e-cigarettes and other tobacco products for harm reduction, including consideration of benefits versus risks, is presented in the "Discussion: What Evidence Is Needed" section. Here, we specifically discuss evidence regarding e-cigarettes for smoking cessation. To date, no e-cigarette company has undergone FDA review and approval for use of e-cigarettes as a therapeutic aid for quitting smoking. Less than a handful of randomized controlled trials of e-cigarettes for smoking cessation have been published, and none has been conducted in the United States; hence, most of the evidence to date is observational.

E-cigarettes produce an aerosol from a liquid that typically contains nicotine. The e-cigarette concept is to deliver nicotine by an inhaled route without generating products of tobacco combustion. NRT medications can aid cessation as discussed previously, but most smokers do not find NRT very satisfying, and quit rates are modest. The performance of e-cigarettes as nicotine delivery devices has evolved over time. The earliest devices looked like cigarettes but delivered very low levels of nicotine. The two clinical trials performed with these devices were encouraging, but the quality of evidence was low (*170*). Recently, a randomized clinical trial with 886 smokers treated in the United Kingdom's National Health Service evaluated a second-generation e-cigarette refillable tank–type device to patients' choice of NRT provided free of cost for up to 3 months (*171*). All received standard behavioral support. At 1 year, the sustained abstinence rate in the e-cigarette group was twofold greater than the NRT group (RR, 1.83; CI, 1.30 to 2.58). Among participants randomized to the e-cigarette arm who quit smoking, 80% were still using e-cigarettes at 1 year; in comparison, among those randomized to the NRT arm, continued use of NRT was 9% for those who quit smoking. While e-cigarettes were found to significantly increase smoking cessation, some have expressed concern about the unknown health risks of long-term e-cigarette use. Adverse effects reported during the trial included greater throat or mouth irritation in the e-cigarette group and more nausea in the NRT group. Overall, adverse effects were minor in severity.

Population-based observational studies report different results depending on the intention of the smokers to quit, how e-cigarettes are used, and where the study was conducted. A four-country comparison found the likelihood of quitting with e-cigarettes to differ by the regulatory environment (*172*). In Canada and Australia, which have more restrictive e-cigarette regulations, e-cigarette use was associated with a significantly lower likelihood of quitting smoking relative to unassisted quitting (i.e., no medication or e-cigarette use), whereas in the United States and United Kingdom, which have less restrictive e-cigarette regulatory environments, e-cigarette use was associated with increased quitting, consistent with other reports (*173*, *174*). The United Kingdom estimates that, annually, 22,000 to 57,000 long-term cigarette quitters are associated with e-cigarette use, more than quits attributed to NRT or other forms of pharmacotherapy (*175*). In the United States and United Kingdom, daily use of e-cigarettes is associated with a greater likelihood of quitting smoking than nondaily use (*176*, *177*). In a study from France, e-cigarette use was associated with not only higher smoking cessation rates but also greater relapse to smoking (*178*).

In conclusion, with respect to e-cigarettes, there is evidence that e-cigarettes can aid smoking cessation. This can occur both in the general population, where e-cigarette use is adopted as an acceptable and safer alternative to cigarette smoking, and in the context of a health service. The risks of long-term e-cigarette use are still unknown, and some medical professionals oppose the use of e-cigarettes for that reason. As discussed in the "Discussion: What Evidence Is Needed" section, there are also concerns about the use of e-cigarettes by children possibly creating a new epidemic of primary nicotine addiction, leading some U.S. public health professionals to conclude that the potential benefits of e-cigarettes for smoking cessation in adults are outweighed by the risks to youth.

TOBACCO CONTROL POPULATION-BASED AND POLICY APPROACHES

U.S. population-based and policy approaches successful for tobacco control include mass media tobacco education campaigns, expanded healthcare coverage for tobacco cessation treatment, excise taxation on tobacco products, clean air laws, and Tobacco 21 policies, which raise the minimum legal age to purchase tobacco products to age 21 (*92*). Other population-based interventions to reduce tobacco use have faced challenges in the United States at the federal level (e.g., pictorial warnings on products, regulation of advertising, and promotion at point of sale), and even state tobacco taxes and clean air laws have slowed (*179*, *180*). In contrast, interventions in the tobacco retail environment are increasing rapidly at the local level (*181*). Also gaining traction at the FDA, and discussed in the "Discussion: What Evidence Is Needed" section, is an effort to reduce the amount of nicotine in combusted tobacco products to reduce its addictive effects.

Mass media tobacco education campaigns

An important component of comprehensive tobacco control programs, mass media tobacco education campaigns are composed of paid and earned media on TV, radio, community placements (e.g., billboards and bus shelters), magazines, newspapers, and digital/social media platforms. Well-designed mass media campaigns implemented with sufficient reach, intensity, and duration can help counter pro-tobacco marketing, build support for tobacco control policies, increase awareness of tobacco's harmful effects, promote quitting, and reduce smoking prevalence (*182*). Here, we describe the success of two ongoing U.S. campaigns.

Tips from former smokers

The CDC's Tips national mass media tobacco education campaign has been implemented annually since 2012. Tips profiles real people living with serious long-term health consequences from smoking and secondhand smoke exposure based on evidence that messages graphically depicting the physical consequences of smoking-related diseases can encourage quit attempts (*182*, *183*). While Tips primarily targets adult smokers, secondary audiences include family members, healthcare providers, and faith communities able to reach people who smoke. Campaign goals include building public awareness of tobacco's harms to self and others, encouraging smokers to quit, and making free help available (e.g., national quitline). Tips has been effective at increasing population-level quit intentions, quit attempts, and sustained quits, with effectiveness persisting over time (*184*). In 2016, Tips ads featured Rebecca, a former smoker with depression. In a national evaluation, greater exposure to the Rebecca ads was associated with a greater likelihood of intending to quit and with making a quit attempt specifically among smokers with mental health conditions (*185*). National media campaigns are an important population-level strategy for reaching specific population groups, such as people living with mental health conditions, who are experiencing tobacco-related disparities.

Real cost

The FDA's Real Cost campaign is a national tobacco education campaign aimed at preventing tobacco initiation and established tobacco use in youth ages 12 to 17. The campaign is disseminated on national TV and radio, via the internet/social media, in magazines and movie theaters, and on posters distributed to schools. The Real Cost's central theme in 2014–2016 was "Every cigarette costs you something," with attention to teen-relevant concerns (e.g., cosmetic effects, loss of control, and toxic chemicals). Between 2014 and 2016, the Real Cost campaign estimated that 350,000 fewer adolescents initiated cigarette smoking (*186*). This time period was also when e-cigarettes surpassed combustible cigarettes in popularity among U.S. youth. In 2018, the Real Cost campaign shifted to a focus on e-cigarette prevention in youth.

Tobacco taxes

In the United States, tobacco tax increases have produced the desired effects of both dissuading young people from starting to smoke and encouraging smokers of all ages to quit, with the Community Preventive Services Task Force deeming the evidence strong (*187*). Given limited resources, at some point, the health, financial, and social costs of smoking outweigh the perceived benefits or drive of the addiction. Increasing tobacco taxes is suggested as a population-level strategy for reducing smoking among individuals with alcohol, drug, and mental health disorders (*188*). With tobacco tax increases should be the availability and promotion of cessation treatments via insurance coverage and resources such as the state quitlines.

Healthcare coverage for tobacco cessation treatments

Healthcare reform legislation can increase receipt of tobacco cessation treatment for smokers from disparity groups. The U.S. Affordable Care Act (ACA) mandated comprehensive coverage for tobacco

treatment for most private health plans and newly eligible Medicaid beneficiaries in states that expanded Medicaid, including at least two tobacco cessation attempts per year and four tobacco cessation counseling sessions (each 10+ min long) and prohibited cost-sharing and previous authorization restrictions for FDA-approved tobacco cessation medication. The ACA also removed coverage limits and preexisting condition exclusions. Concerning, however, was the ACA's allowance for states to decide whether employers could charge smokers up to 50% more in premiums. Several states rejected the surcharge outright, while other states capped the maximum penalty at a lower level. National data from 2011 to 2014 indicate that in the first year of implementation, penalized smokers were less likely to be insured and the penalty did not encourage cessation (*189*). Charging smokers higher insurance premiums could discourage getting health insurance or lead to concealment of one's smoking status; either would reduce opportunities for treatment. Tobacco cessation treatments are cost effective. In Massachusetts, for every $1 spent on cessation services for state Medicaid program beneficiaries, more than $3 was saved (*190*).

Smoke-free air

The Community Preventive Services Task Force deemed smoke-free air policies to have strong evidence for reducing youth initiation of tobacco use, increasing quitting among smokers, reducing exposure to secondhand smoke, reducing tobacco-related morbidity and mortality, and reducing healthcare costs (*191*). Furthermore, smoke-free policies do not adversely affect businesses. Smoke-free air policies in the home similarly reduce harmful secondhand smoke exposure, increase quit attempts and abstinence, and decrease cigarette consumption in adult smokers (*192*). A U.S. study found that statewide smoking bans in restaurants and bars were associated with reduced smoking among those with psychiatric conditions (*193*). Psychiatric facilities are increasingly adopting smoking bans, although still not mandated nationally.

Tobacco 21 legislation

Given that few people start smoking after age 20 and that brain development continues through the mid-20s, with early drug exposure predictive of greater likelihood of chronic, addictive use, legislation has sought to raise the minimum tobacco sales age to 21 (i.e., Tobacco 21). The Institute of Medicine concluded, based on simulation models, that Tobacco 21 laws would reduce smoking and related mortality (*194*). Lacking a federal Tobacco 21 law, states and local jurisdictions have passed legislation, with regional differences in coverage. As of January 2019, most U.S. residents aged 18 to 20 were not covered by a Tobacco 21 policy, with the largest gaps in coverage in the South (*195*). As of 1 June 2019, 14 states and >400 local jurisdictions have passed Tobacco 21 legislation; 16 of the non-adopting states preempt lower levels of government from implementing these regulations. Analyzing national data, a recent study found that Tobacco 21 policies were associated with a significant absolute 3% reduction in the prevalence of smoking among 18 to 20 year olds (*196*). Surveys indicate that two-thirds to three-quarters of U.S. adults are in favor of raising the minimum age of tobacco sales to 21 (*197*, *198*).

Tobacco retailer restrictions

Tobacco products are readily accessible for open sale in retail outlets throughout the United States and globally. In the United States, there are an estimated 375,000 tobacco retailers (*199*); this equates to 27 tobacco retail locations for every McDonald's restaurant. The tobacco retail environment contributes to tobacco-related disparities. Tobacco retailers concentrate disproportionately in disadvantaged areas (*200*). Even after adjusting for the density of retailers, cigarettes and little cigars/cigarillos cost less in these areas. The same is true for areas with a higher proportion of African American residents (*201*).

In its blueprint to end the U.S. tobacco epidemic, the Institute of Medicine recommended that governments develop, implement, and evaluate legal mechanisms for restructuring retail tobacco sales and restricting the number of tobacco outlets (*202*). In response, there has been a rapid rise in planning and implementation of retail interventions by states and communities (*181*). For example, at least two states and >200 localities restrict the sale of flavored tobacco (45 communities restrict the sale of menthol cigarettes); dozens have set a minimum price and pack size for little cigars/cigarillos, and at least three prohibit price discounts and coupon redemption (*203*). By restricting the sales and distribution of tobacco, the long-term goal of these interventions is to reduce tobacco use and inequities in the retail environment. With a focus on youth, a global study of bans on tobacco point-of-sale ads in retail environments reported lower odds of ever smoking, lower smoking prevalence, and less daily smoking (*204*). A growing evidence base is informing best practices for state and local programs aimed at countering tobacco industry influence at the point of sale.

DISCUSSION: WHAT EVIDENCE IS NEEDED

Tobacco use remains the leading preventable cause of death in the United States and worldwide. While important public health gains have been achieved in reducing the prevalence of cigarette smoking, because of population growth and diversification of product, the absolute number of tobacco users in the United States has stayed relatively constant over the last 50 years, at about 40 million. Furthermore, dual use of tobacco products is on the rise (*21*, *22*), and declines in smoking have not been equitable for all groups. Disproportionately affected by tobacco-related morbidity and mortality are people of certain racial/ethnic groups (e.g., African Americans and American Indian/Alaska Native people), individuals of lower income and lower education, and people with mental illness and substance use disorders.

Among adolescents, cigarette smoking has declined to under 10%; however, the use of e-cigarettes has increased markedly, with 27.5% of high school students reporting past 30-day use. Today, more young people in the United States are exposing their brains to nicotine than in recent years. Although free of the toxins from combustion, e-cigarettes typically still contain nicotine, the main psychoactive and addictive component in tobacco.

Our review covered evidence-based methods to treat smoking in adults and policy approaches to prevent nicotine product use in youth. The smoking cessation treatments with evidence in adults include seven FDA-approved cessation medications (Table 2), individual and group counseling, quitlines and other mobile technologies, and monetary incentives. At the population level, mass media education campaigns, product regulations, health insurance coverage of cessation treatments, and enactment of tobacco control policies (e.g., clean air, Tobacco 21, flavor bans, and retailer density restrictions) are promising interventions. Most efficacious are combinations

of medication and behavioral treatments leveraged in an environment with strong tobacco control policies. Notably absent are evidence-based treatments for stopping e-cigarette use, particularly in adolescents, an area of public health interest.

The changing marketplace and the challenges of treating addiction necessitate the sustained efforts of clinical providers, policymakers, and researchers. Investment in comprehensive tobacco cessation treatment at the state and federal levels and continued research in the development of novel behavioral and medication treatments, diagnostics for personalized medicine, technological innovations for broader reach, and evidence-based policies are warranted. Here, we briefly highlight some areas for further investigation.

Candidate new mechanisms of action for cessation pharmacotherapy

As reviewed above, existing medications aid in smoking cessation, but none has high success rates during a single course of treatment. As we learn more about the effects of nicotine on the brain and the mechanisms of addiction, we may gain insight into new molecular targets for nicotine addiction. In addition, combinations of treatments with different actions, as exemplified by varenicline plus lorcaserin to both promote quitting and prevent associated weight gain, need to be explored.

Long-term effects of alternative/harm reduction products

The potential harms to health from various harm reduction products could not be extensively discussed here, but assessment of harm is a critical component of a reasoned benefit versus risk analysis. On the basis of current evidence, it is believed that e-cigarettes and heated tobacco will be very much less harmful than cigarette smoking, but how much less harmful is unknown. Heated tobacco products have been successfully marketed in Japan where 4.7% of the population used the products in 2017, although 72% of heated tobacco users also continued to smoke cigarettes (*205*). The prevalence of cigarette smoking has declined substantially in recent years in Japan, and although speculated that heated tobacco use is responsible for that decline, this is unproven. Heated tobacco products are marketed in many other countries and are approved for use in the United States, but so far, uptake has been limited. As yet, there are no data on abuse liability and no trials of heated tobacco for combustible cigarette cessation, and we are unaware of any data on youth uptake of IQOS.

Considerable national and international debate has also occurred regarding the use of smokeless tobacco for harm reduction (*206*, *207*). While the use of some forms of smokeless tobacco is associated with oral, esophageal, and pancreatic cancer and other adverse health effects, low nitrosamine smokeless tobacco is associated with much lower risk (*208*, *209*). In Sweden, snus (ground tobacco in a teabag-like pouch placed between lip and gum) is manufactured and marketed under strict quality standards, resulting in low levels of nitrosamines (potential carcinogens) (*210*). In Sweden, 20% of men and 8% of women use snus, while the smoking prevalence is lower than in other countries. The incidence and mortality from smoking-related diseases is significantly lower in Sweden than in other European countries (*211*). Epidemiologic studies indicate that the health risks of Swedish snus use are low, including a small, if any, increase in cancer and cardiovascular disease risk and no increased risk of lung disease. On the basis of these observations, some public health experts advocate that smokeless tobacco be encouraged as an alternative to cigarette smoking. The potential harm reduction benefit of smokeless tobacco most likely varies by country and cultural norms. In Sweden, there is a long tradition of smokeless tobacco use, and most men use snus without a transition to cigarette smoking. However, in the United States, where smokeless tobacco use is much less widely accepted, there is concern that smokeless tobacco use is a gateway to smoking among youth (*212*). There is also concern that smokeless tobacco could reduce smoking cessation in dual users, because smokeless tobacco could be used in circumstances where smoking is prohibited. Controlled clinical trials of smokeless tobacco as an approach to aid smoking cessation or in switching from cigarettes to smokeless tobacco have shown modest benefits, similar to NRT (*213*, *214*).

Further mechanistic and epidemiologic studies are needed to help inform harm reduction public policy. In addition, likely an area of research development and interest in the very near future are study of cessation treatments for those users who want to quit their e-cigarette, heated tobacco, or snus use. Given the mechanism of nicotine addiction, it would seem reasonable that medications helpful in quitting smoking would prove efficacious; however, no randomized controlled trial to address these questions has been conducted to date.

Understanding and treating dual tobacco use

As mentioned at the start, dual use of tobacco products is on the rise (*21*, *22*), and rates of dual use are threefold greater for high school students (11%) (*13*) than adults (3.7%) (*11*), with smoking cigarettes and vaping e-cigarettes the most common combination. Analysis of survey data from the United States, United Kingdom, Canada, and Australia concluded that adults who smoke cigarettes and e-cigarettes concurrently should be considered a distinct group given higher levels of nicotine dependence and generally more pro-attitudes toward both smoking and vaping (*215*). Dual use may represent greater dependence and compulsion to dose nicotine in settings where smoking is prohibited or may reflect motivation to quit combustible cigarettes (*23*). In a nationally representative study, interest in quitting and attempts to quit were comparable among dual tobacco–using adults and cigarette-only users (*216*). The research on dual tobacco use is still nascent. Greater and more detailed study is needed to understand use patterns of two or more tobacco products; the implication of different types of combinations; and the relationship of dual use to addiction, biomarkers of harm, and success with quitting.

Tobacco-drug co-use and translational potential

Treatment studies of cannabis use disorder in adults suggest that about half of participants also currently smoke tobacco. Among adolescents (*217*, *218*) and adults (*219*), persistent tobacco use is associated with poorer treatment outcomes for cannabis use disorders, and individuals who use both cannabis and tobacco in combination have higher rates of psychiatric and psychosocial problems as compared to individuals who smoke cannabis only (*219*). Blunt smoking (i.e., cannabis smoked in a cigar shell) is associated with greater difficulty controlling cannabis use (*220*) and high levels of toxicant exposures (e.g., carbon monoxide and carcinogens) (*221*), as compared to joint smoking. Despite decades of research on cannabis and tobacco use separately, there is little treatment research addressing the co-use of cannabis and tobacco. In addition, although currently the co-use of cannabis and nicotine by vaping is

relatively rare and primarily occurs among established tobacco or cannabis users, given the growth in popularity of both cannabis and nicotine vaping, it is likely to increase and expand to tobacco/cannabis naïve individuals. Study of the behavioral co-use patterns and pharmacologic effects, with an understanding of addiction potential and quantified toxicant exposures, and the potential for pulmonary injury is needed.

There is a high concordance of tobacco use with virtually all other drugs of abuse, including cannabis, alcohol, opiates, and stimulants. Neurobiology research has found interacting neural circuits between nicotine and other abused substances. Such research may lead to discovery of medications that simultaneously treat multiple drugs of abuse. Likewise, studies of the genetics of addiction to nicotine and other substances of abuse, as well as genetic signals of concordance of nicotine addiction with other addictions and mental illnesses, may lead to the discovery of similar therapeutic targets.

Vulnerable populations

Smoking cessation treatment has been particularly challenging in some populations, including among people with mental illness, those with other substance use disorders, adolescents, pregnant smokers, and light and nondaily smokers. In addition, cessation success varies by race and ethnicity, as seen with lower quit rates in African American and American Indian/Alaska Native smokers. State data from Alaska indicate that the proportion of people who have quit smoking among those who have ever smoked (i.e., the quit ratio) is 41% for Alaska Native adults compared to 62% for Alaskan adults of other races/ethnicities (*222*). This means that for the Alaska Native community, there are more current than former smokers. Behavioral interventions that are culturally relevant for specific populations and individualized pharmacotherapy approaches are needed. As an example, with funding from the National Heart, Lung, and Blood Institute (NHLBI), our research is testing the efficacy of internet-assisted tobacco cessation counseling in the remote region of Norton Sound with Alaska Native men and women (*223*). The treatment includes combination NRT, and we are evaluating the nicotine metabolism ratio in predicting treatment outcome. To promote cessation in groups particularly vulnerable to tobacco use, emerging research has supported the value of targeted communication (*185*) and regulatory policies such as reducing nicotine levels in cigarettes (*224*), discussed next.

Regulation of cigarette addictiveness: Very low nicotine content cigarettes

In 1994, Benowitz and Henningfield proposed the idea of federal regulation of the nicotine content of cigarettes to reduce levels over time, resulting in lower intake of nicotine and a lower level of nicotine dependence (*225*). When nicotine levels get very low, cigarettes would be much less addictive. Now, 25 years later, the concept of regulating combustible tobacco to very low levels of nicotine content is being seriously considered.

Very low nicotine content cigarettes (VLNCs) are engineered to have reduced yields of nicotine in the tobacco contained in the cigarette rod. These cigarettes deliver much lower levels of nicotine than earlier cigarettes that were marketed as "light" or "ultralight" but which in practice allowed smokers to obtain levels of nicotine similar to regular "full-flavor" cigarettes through compensation behaviors, such as blocking ventilation holes or inhaling more deeply (*225*). Reducing the nicotine content of cigarettes to approximately 0.5 mg per cigarette is believed to render cigarettes minimally addictive and lead to lower levels of consumption, making it easier for smokers to quit (*225*). Randomized trials examining the effects of VLNCs have shown reductions in smoking and dependence and increases in quit attempts for VLNCs in comparison with standard nicotine cigarettes. A 6-week trial found decreases in nicotine exposure and dependence on nicotine for VLNCs, decreases in craving during abstinence from smoking, and decreases in the number of cigarettes smoked without significantly increasing levels of expired carbon monoxide or total puff volume, which suggests minimal compensation behavior (*226*). In a randomized, parallel-arm, semiblinded study of adult cigarette smokers, participants receiving 0.05 mg/g cigarettes showed greater relief of withdrawal from usual-brand cigarettes than the nicotine lozenge, significantly higher abstinence at the 6-week follow-up than the 0.3 mg/g cigarette, and a similar rate of cessation as the nicotine lozenge (*227*). At 12-month follow-up, however, findings were not sustained (*228*).

In clinical trials, VLNCs generally have lower acceptability than commercially available cigarettes, and these trials have encountered problems with nonadherence (with upward of 70% of participants substituting traditional cigarette brands for VLNCs) and study dropout rates of 25 to 45% (*229*, *230*). Combining VLNCs with nicotine patches may aid with the transition to VLNCs and increase compliance, but doing so was not found to improve long-term quit rates. If the nicotine content in all cigarettes was reduced to make them less addictive, either through federal regulation or by the tobacco industry's own initiative, then problems with adherence and attrition could be less of an issue and long-term cessation rates could be higher.

A series of laboratory and experimental studies have tested VLNCs with smokers, with mental illness (depression and schizophrenia) and substance use (opioid use) disorders finding VLNCs less satisfying than usual brand cigarettes and leading to reduced smoking while decreasing craving, withdrawal, and depressive symptoms and without leading to compensatory smoking (*224*). In one study that found negative cognitive performance associated with VLNCs, use of the nicotine patch reversed the decrements (*231*). The findings support FDA-mandated reduction in the nicotine content of cigarettes to a minimally addictive level to reduce cigarette use among smokers with mental illness.

The Family Smoking Prevention and Tobacco Control Act bars the FDA from completely removing nicotine from cigarettes. The FDA, however, is allowed to reduce the amount of nicotine in cigarettes to very low levels. In July 2017, the FDA indicated that it would issue an Advance Notice of Proposed Rulemaking to seek input on the potential public health benefits and any possible adverse effects from lowering the nicotine content of cigarettes (*232*). The process of review continues. The WHO emphasizes that a nicotine reduction strategy ought to cover all combustible tobacco products, not just cigarettes; include provision of tobacco cessation treatment; and consider toxicant exposures from switching to noncombustible forms of tobacco to sustain nicotine intake and for what duration (*233*).

The future of e-cigarettes and public health impact

The overall impact of e-cigarettes on public health remains a question of debate. While e-cigarettes may have adverse effects on respiratory health and possibly other diseases, the harm is generally

accepted to be much less than that of cigarette smoking (*24*). Thus, if smokers were to switch completely to e-cigarettes, then smoking-related disease is predicted to decrease substantially. Population-based models of the impact of e-cigarette use predict an overall health benefit, because many smokers will quit, while those who continue vaping or take up e-cigarettes anew experience much less harm (*234*). On the other hand, many parents, pediatricians, public health officials, and others are extremely concerned about youth uptake of e-cigarettes and are encouraging local communities to ban e-cigarette sales. E-cigarette use in youth shows exposure to toxins with concern about the long-term health effects from sustained use (*235*). The overall benefit versus risk for a community is likely to depend on the prevalence of cigarette smoking in the community. Where smoking prevalence is high, the potential benefits of e-cigarettes in reducing smoking are high. Where smoking prevalence is low, the benefit is low and the potential risk of e-cigarettes to youth becomes the major community concern.

Another consideration regarding e-cigarettes is a role that it may play in a broader public health regulatory intervention. Reducing the nicotine content of combustible tobacco would make the products less satisfying to smokers. The availability of less harmful noncombusted sources of nicotine, such as e-cigarettes, could help a smoker transfer their nicotine addiction from combustibles to e-cigarettes. Presumably, many, if not most, people would stop smoking, and the result would be prevention of most tobacco-related disease. In time, a former smoker who switched to e-cigarettes could quit nicotine use or remain a long-term e-cigarette user but with much less harm than from smoking cigarettes.

In closing, with the evolving nicotine product market, critically important is the need for evidence to inform innovations in tobacco control policies and tobacco treatment approaches (behavioral, pharmacologic, and technology based), with consideration of the risks and benefits for all populations affected.

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