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Supplement Article

Clinical Pharmacology of Electronic Nicotine Delivery Systems (ENDS): Implications for Benefits and Risks in the Promotion of the Combusted Tobacco Endgame

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Abstract

Electronic nicotine delivery systems (ENDS) such as e-cigarettes and heated tobacco products are novel battery-operated devices that deliver nicotine without combustion of tobacco. Because cigarette smoking is sustained by nicotine addiction and the toxic combustion products are mainly responsible for the harmful effects of smoking, ENDS could be used to promote smoking cessation while exposing users to lower levels of toxicants compared with conventional cigarettes. The currently available evidence from clinical and observational studies indicates a potential role of e-cigarettes as smoking cessation aids, although many continue to use e-cigarettes long after quitting smoking. Nicotine and toxicant delivery vary considerably by device and depend on the characteristics of the e-liquid formulation. Because smokers tend to titrate their nicotine intake to maintain their desired pharmacologic effects, device and liquid characteristics need to be considered when using ENDS as an aid to quit smoking. Factors potentially limiting their use are the currently still unknown long-term safety of these products and concerns regarding widespread use among youth. Implications of clinical pharmacology data on ENDS for the cigarette endgame and regulation by the U.S. Food and Drug administration are discussed.

Keywords

e-cigarettes, electronic nicotine delivery, heat-not-burn, nicotine, tobacco

Cigarette smoking remains a major cause of premature death and morbidity worldwide. The pharmacologic effects of nicotine initiate and sustain tobacco addiction. Nicotine per se is not harmless, but is much less harmful than combusted tobacco use. The idea that devices that can deliver nicotine like a cigarette but without toxic products of combustion might replace cigarettes and thereby reduce smoking-induced harm has been considered by tobacco control researchers for many years.[1] However, making such devices that deliver nicotine to the lung for rapid absorption had been technically challenging.

History of Electronic Nicotine Delivery Systems

The earliest iteration of today's marketed e-cigarettes appeared in a U.S. patent application by Herbert A. Gilbert in 1963 for a "smokeless nontobacco cigarette" that contained a battery-powered heating element that would heat flavor-containing components without combustion (US Patent No. 3,200,819).[2] Beginning in 1990, Philip Morris, a tobacco company, developed a puff-activated electric smoking device comprising a permanent heater, a liquid applicator, a liquid aerosol-generating medium, a battery-powered circuit, and a disposable delivery module and in 1994 developed a capillary aerosol generator that produced aerosol by pumping liquid into a heated tube.[3] Although Philip Morris temporarily halted development of the nicotine aerosol device in 1998 and instead applied the aerosol technology to a handheld inhaler designed to deliver drugs into the body, Philip Morris resumed its work on a nicotine aerosol device in 2001 and in 2013, released MarkTen e-cigarette through NuMark.

Hon Lik, a Chinese pharmacist, produced an e-cigarette in 2003 that was introduced on the Chinese market under the brand name Ruyan.[4] This product, along with another brand, Janty, entered the US market

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by the mid-2000s.[5] Since then, numerous technological advances have occurred, with the emergence of several generations of e-cigarettes, as well as heated tobacco ("heat-not-burn") products, all of which can be described as electronic nicotine delivery systems (ENDS). In our review, we will discuss the nature of ENDS, the clinical pharmacology of nicotine delivered by ENDS, epidemiology of use, potential benefits for smoking cessation, concerns regarding risks to health, and potential contributions of ENDS to the cigarette endgame. For background, we begin with a brief discussion of nicotine pharmacology. For a comprehensive discussion of nicotine addiction and its treatment, readers are referred to a recent review.[6]

Nicotine Pharmacology and Addiction

Nicotine Addiction

Nicotine is structurally similar to the endogenous neurotransmitter acetylcholine and acts by activating nicotine cholinergic receptors (nAChRs).[7] When nicotine binds to the nAChR, the ion channel opens, allowing entry of calcium or sodium ions, which then activate the receptor. Nicotine acts predominantly presynaptically to release other neurotransmitters, including dopamine, norepinephrine, acetylcholine, serotonin, beta-endorphin, and gamma-aminobutyric acid.[8] The pharmacological effects of these neurotransmitters include signaling of pleasure, arousal and stimulation, and reduction of anxiety and mood stabilization. Other nicotinic effects include an increase in metabolic rate and suppression of appetite.

With prolonged exposure to nicotine, as occurs with regular tobacco use, brain neuroadaptation occurs, which is associated with development of tolerance to many of the pharmacologic effects of nicotine as well as an increase in $\alpha 4\beta 2$ receptors and generation of new synaptic connections. When regular use of nicotine stops, a withdrawal syndrome ensues with effects consistent with reduced levels of those neurotransmitters. Withdrawal symptoms include irritability, restlessness, anxiety, difficulty concentrating, increased hunger and eating, and craving for tobacco. A major withdrawal symptom, believed to be related to deficient dopamine release, is hedonic dysregulation, a state of malaise and inability to experience pleasure. A single cigarette or other sources of nicotine can immediately reverse these symptoms, resulting in high rates of relapse when a person tries to stop smoking. The neuroplasticity changes in the brain appear to be long-lasting and to pose a risk of relapse for months or even years after quitting nicotine use.

In addition to the direct effects of nicotine on the brain, nicotine actions contribute to conditioned responses that sustain tobacco use. Such cues may include feeling tired or lethargic, difficulty concentrating, anxiety, or depression, all of which the person had experienced during brief intervals of nicotine withdrawal and which were rapidly reversed by tobacco use. Thus, compulsive nicotine use can be seen as a combination of seeking the positive rewarding effects of nicotine (positive reinforcement) and avoiding the aversive effects of nicotine withdrawal (negative reinforcement). A regular nicotine user titrates nicotine intake on a daily basis to optimize pleasure, arousal, and mood and tends to take in the same amount of nicotine from day to day. When a smoker switches cigarette products, such as from a high- to a low-yield commercial cigarette, they alter their smoking behavior to take in the same amount of nicotine as before switching (termed compensation).[9] This is relevant to switching from cigarettes to ENDS or to comparing the potential toxicity of different ENDS, as will be discussed later. Of note is that some people use tobacco products intermittently, and their nicotine craving is primarily seeking positive reinforcement rather than avoiding withdrawal.

Nicotine Chemistry, Pharmacokinetics, and Metabolism

Nicotine is a weak base that is highly water soluble and can also readily cross lipid membranes to penetrate tissues.[10,11] Nicotine has a pKa of 8.0, at which pH, 50% is in freebase form and 50% is ionized. The freebase form of nicotine penetrates mucous membranes and body tissues quickly, which is why products like oral and transdermal products are buffered to high pHs. The freebase form of nicotine in high concentrations can be irritating to inhale. Large cigars contain nicotine at a high pH, facilitating buccal absorption of nicotine, but making the smoke too harsh to inhale. Nicotine is present predominantly in the ionized form at an acidic pH. Cigarette smoke has a pH of around 5.5, resulting in less harshness and greater ease of inhalation. As will be discussed later, nicotine in ENDS can be predominantly present either in the freebase or ionized form, depending on the liquid formulation, which affects the tolerability of inhaled high concentrations of nicotine, with implications for both addictiveness and safety.

When a cigarette or an ENDS is inhaled, aerosols containing nicotine are generated and taken into the lung. Nicotine moves quickly from the lung to pulmonary circulation then out to systemic circulation and the brain. Rapid delivery of nicotine to the brain (within 15 to 30 seconds) is an important aspect of its abuse liability for several reasons. Inhalation generates high concentrations in arterial blood, resulting in greater pharmacologic effects. Rapid onset of effect from the time of dosing allows puff-to-puff titration of dose to achieve rewarding effects without toxicity. And rapid reinforcement after drug self-administration is associated with a higher probability of repeated use.

Figure 1. Typical electronic nicotine delivery system (ENDS) devices showing different generations of electronic cigarettes and IQOS, a heated tobacco product.

Nicotine is metabolized rapidly by the liver enzyme CYP2A6, such that the rate of metabolism is liver blood flow dependent. Minor pathways of metabolism include glucuronidation and N-oxidation. A generally small fraction of nicotine is excreted in the urine, although this fraction can be larger with acidified urine and in people who are genetically slow metabolizers of nicotine. The half-life of nicotine averages around 2 hours. As such, with regular smoking throughout the day, blood nicotine rises over the first 6 to 9 hours, plateaus until the time of the last cigarette, then declines with a half-life of 2 hours, but persisting in significant amounts in the body even after overnight nicotine abstinence. Cotinine, the major metabolite of nicotine, has a half-life averaging 16 hours, which makes it a more stable measure of daily nicotine intake.

Nature and Evolution of E-Cigarettes and Heat-Not-Burn Devices

Electronic Cigarettes

Electronic cigarettes (also called "e-cigarettes" or "vaporizers") are battery-operated devices that deliver nicotine without combustion of tobacco.[12–15] These devices heat a liquid ("e-liquid") containing propylene glycol and/or vegetable glycerin, flavorings, and commonly also nicotine, to produce an aerosol that is inhaled similarly to the smoke of conventional cigarettes.[12–16] The humectants propylene glycol and vegetable glycerin serve as the vehicle solution to produce the aerosol,[13,15] whereas thousands of different flavorings have been identified, ranging from "traditional" ones such as tobacco, mint/menthol, and fruit to more "unconventional" ones such as flavors of candies, snacks, and alcohol.[17] An e-cigarette typically consists of a battery, a cartridge containing the e-liquid, and a vaporizing chamber with a metal or ceramic heating element, typically with a silica or cotton wick.[15,18,19]

Since their first appearance in the early 2000s, e-cigarettes have been constantly and rapidly evolving with the disposable "first-generation" e-cigarettes devices, designed to resemble conventional cigarettes ("cig-a-likes"), varying considerably in features and design compared with e-cigarettes of later generations, which are larger, refillable, and rechargeable (Figure 1, Table 1).[20]

The different design features can affect not only nicotine delivery (users of "third-generation" devices can achieve higher nicotine concentrations while vaping lower concentration e-liquids than second-generation users)[21] but also toxicity because greater formation of harmful toxicants such as formaldehyde and acrolein has been reported with high voltage.[22,23] Alternative ways of use such as "dripping" (ie, dripping drops of the e-liquid directly onto the heating element and then inhaling the produced vapor) can lead to high liquid heating temperatures and generation of harmful thermodegradation chemicals.[24,25]

Table 1. Characteristics of the Various E-Cigarette Generations

Generation/Device Type	Features/Characteristics
First generation	Disposable, designed to resemble conventional cigarettes ("cig-a-likes"). Prefilled cartridges of nicotine. Generally low power (< 10 watts).
Second generation	Larger than first-generation "pen"- or "tank"-style ("tank systems"), refillable, and rechargeable, with transparent cartridges. Fixed power, usually higher than first generation (around 10 watts).
Third generation	Also referred to as "mods" or "advanced personalized vaporizers." Allow the user to adjust the power of the device and select coils to adjust the heating temperature of the device and the amount of aerosol generated. Typically operated at higher power than other devices.
"Pod Mod" devices	Introduced in recent years, use replaceable cartridges ("pods") containing the e-liquid (often nicotine salt-based and in high concentrations), some closely resemble a USB stick in appearance. Typically, low battery voltage and some with temperature control circuitry to reduce thermal degradation of liquid constituents. The most popular in the United States has been JUUL.

Data from Barrington-Trimis and Levental,[26] Barua et al,[12] Bhatnagar et al,[20] Grana et al,[16] and National Academies.[102]

In addition to the more modern design and discrete appearance, a novel feature of the pod system devices is that, in contrast to prior e-cigarettes that commonly use freebase nicotine e-liquids, many use nicotine salt-based e-liquid. Nicotine salt solutions with lower pH result in greater percentages of protonated nicotine and less irritation when inhaled, thus increasing tolerability and the capacity to deliver high concentrations of nicotine.[12,26] Typical concentrations of freebase nicotine e -liquids are 3 to 24 mg/mL, whereas nicotine salt e-liquids are available in concentrations of up to 100 mg/mL nicotine.[20,26–28] A typical nicotine salt concentration such as in JUUL is 59 ng/ml. Although e-liquids with high nicotine concentrations are freely available in some parts of the world such as the United States, in Europe e-liquids cannot be marketed in concentrations of more than 20 mg/mL nicotine.[29]

Heat-Not-Burn Devices

Heat-not-burn devices (also called "heated tobacco" products) represent another type of ENDS (Figure 1). These battery-powered devices also consist of a heating element but instead of an e-liquid, they typically use a disposable tobacco stick, which is inserted into a holder and then heated to about 350°C (rather than combusted at around 800°C of a conventional cigarette).[30–33] Examples of currently available products based on this technology are Philip Morris International's IQOS ("I Quit Ordinary Smoking") and British American Tobacco's glo. IQOS was first launched in countries such as Japan, Italy, and Switzerland in 2014[34] and was approved for marketing in the United States in 2019.[35] Other products such as Japan Tobacco International's Ploom TECH direct an aerosol from heated e-liquid through a capsule of tobacco from which nicotine and flavor are absorbed.

Heat-not-burn products are likely less harmful than conventional cigarettes because they expose users to considerably lower levels of combustion-generated toxicants than cigarettes.[36] These products are still relatively new, and more studies are needed to better identify potential risks and benefits of this technology compared with conventional cigarettes and other ENDS, as well as how various findings of laboratory studies translate into human exposure. Most of the currently available research on heat-not-burn products was manufacturer funded[34]; findings from independent studies show that although exposure to many harmful constituents can be substantially lower, heat-not-burn emissions contain other potentially toxic substances at higher levels than conventional cigarettes.[33] For example, an analysis of Philip Morris International's modified-risk tobacco product (MRTP) application to the Food and Drug Administration (FDA) for IQOS found that levels of 56 constituents were higher in IQOS emissions; 22 were >200% higher, and 7 were >1000% higher than in 3R4F reference cigarette smoke.[33] It is not clear to what extent these chemicals contribute to the toxicity of IQOS or whether the nature of effects would be qualitatively different from those associated with tobacco smoking. Similar to the e-cigarettes, there are geographical differences regarding their availability and popularity, with specific heat-not-burn products having been popular for several years in Japan,[37] while only recently getting approved in other countries, such as the United States.[35] In 2020 the US FDA authorized marketing of IQOS as a MRTP with "reduced-exposure" information. In recent years, various heat-not-burn devices have also been available in numerous European countries and other world regions.[34,37]

Pharmacokinetics and Pharmacodynamics of ENDS as Nicotine Delivery Device

Pharmacokinetics

Although ENDS are intended to mimic nicotine delivery from a cigarette, because the devices can vary so much in design, there is potentially much more variability in nicotine delivery from ENDS than from

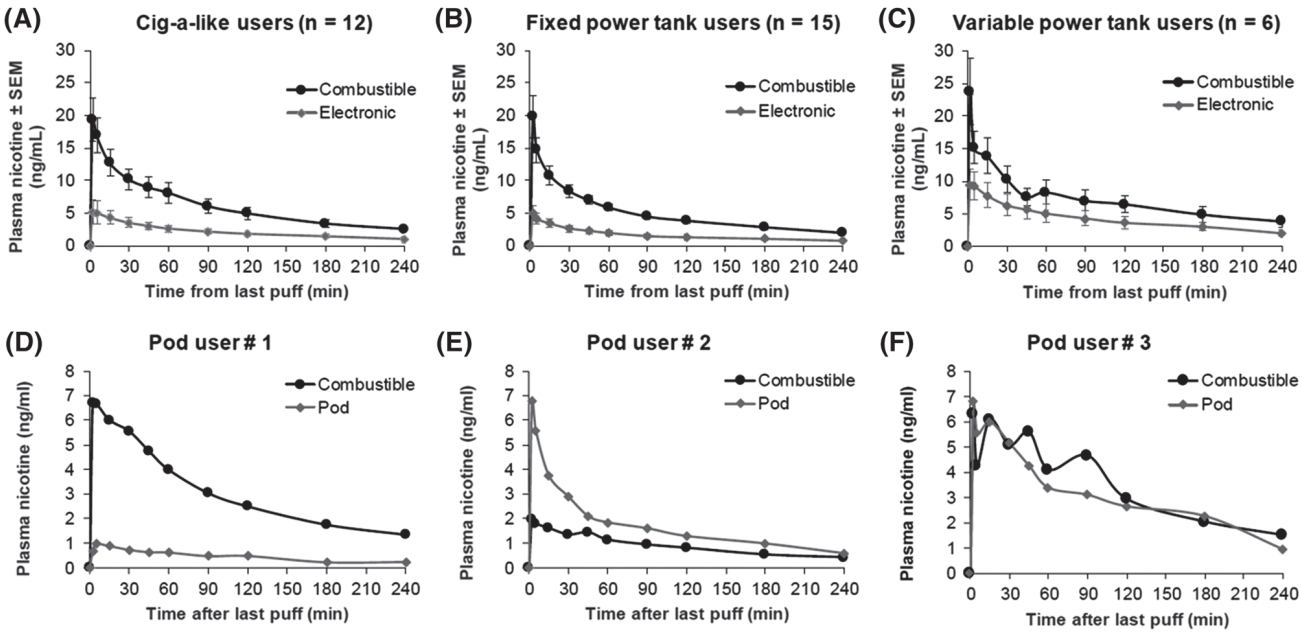

Figure 2. Average plasma nicotine concentrations with standardized use of different types of e-cigarette devices (A-C) and with 3 individuals using the same JUUL brand pod device (D-F), illustrating interindividual variability. All participants were regular dual users who inhaled their usual brand of tobacco or electronic cigarette (from St.Helen et al[50]).

cigarettes. Cigarettes generally contain 10 to 15 mg nicotine per rod, and although puffing patterns may differ among smokers, on average each cigarette delivers 1.0 to 1.5 mg nicotine into the bloodstream of the smoker.[10] Most of the nicotine from cigarette tobacco is delivered into the air as secondhand smoke. That the cigarette burns down in 8 to 12 minutes places bounds on the per-cigarette nicotine delivery.

Nicotine delivery from e-cigarettes, on the other hand, depends on nicotine concentration and propylene glycol/vegetable glycerin levels in the liquid, the heating temperature of the coil, and puff duration.[38,39] All these factors influence the amount of aerosol generated and the nicotine delivery. When large amounts of aerosol are generated, such as with tanks and modular (mod) devices, much aerosol including nicotine may be exhaled. But many vapers, especially those using high-nicotine/low-power devices, exhale very little aerosol. The amount of secondhand e-cigarette nicotine inhaled by a nonuser depends on factors such as how much is exhaled, proximity of the nonuser to the vaper, and extent of room ventilation. Of the nicotine that is inhaled from an e-cigarette, more than 90% is retained by the smoker.[40]

The pharmacokinetics of nicotine delivery by ENDS has been studied in 2 ways.[40–44] Most studies have used standardized puffing protocols or brief periods of ad libitum use, with time of use similar to that of smoking a cigarette (typically 5 to 10 minutes). This approach aims at comparing nicotine delivery across devices in a standard way and comparing e-cigarettes with tobacco cigarettes. The limitation of this study paradigm is that vapers do not inhale e-cigarettes as they do tobacco cigarettes, but rather tend to space the e-cigarettes puffs over time, with smaller puff clusters.[44] A second approach is to sample blood nicotine for periods throughout the day with ad libitum use, which provides a more realistic estimate of nicotine intake. This has been done with brief (90-minute) or longer (24-hour) sessions.[44,45] Another way to assess daily intake of nicotine is to measure cotinine in blood, saliva, or urine or the sum of nicotine and its metabolites in urine at steady state.[21,46,47]

In general, nicotine delivery is lowest with the early-generation cig-a-like devices and higher with tanks, mods, and pods.[42,48,49] Figure 2 shows an example of plasma nicotine concentrations over time in users of different types of e-cigarettes compared with cigarette smoking with a standardized puffing session.[50] The rate of rise of nicotine is similar for cigarettes and e-cigarettes, but in general peak levels of nicotine are lower with e-cigarettes. Also noted in Figure 2 are data from 3 pod users (JUUL) showing that the nicotine pharmacokinetic profile can be quite different across individuals, even with a standardized puffing protocol, demonstrating that the user has considerable control over nicotine exposure even for a given device.[50] Other pharmacokinetic studies show that experienced e-cigarette users take in more nicotine than naive users and that vapers can take in much more nicotine with 5 minutes of ad libitum use compared with 5 minutes with a standardized puffing protocol.[41,49] In a crossover

study of vaping different flavored liquids, it was also shown that flavor influences nicotine intake, even with a standardized puffing protocol.[50]

Systemic intake of nicotine from standardized vaping and smoking sessions after overnight abstinence from nicotine has been estimated from area under the nicotine plasma concentration-time curve (AUC).[50] Average nicotine intake from e-cigarettes was 0.9 mg compared with 2.2 mg from a cigarette. Nicotine intake was higher, averaging 1.8 mg, from variable power e-cigarettes. It is difficult to extrapolate from nicotine in the liquid to systemic dose. For example, assuming 1 to 1.5 mg nicotine per cigarette, a 5% nicotine JUUL pod containing 0.7 mL of liquid with 59 mg/mL nicotine or 41 mg nicotine, would equate to 27 to 41 cigarette-equivalents. However, using both emission data in laboratory testing and human exposure studies, one 5% JUUL pod seems to be equivalent in systemic nicotine delivery to smoking around 18 cigarettes per day.[51]

Studies of nicotine intake with ad libitum use demonstrate a similar time course of plasma nicotine with e-cigarettes compared with tobacco cigarettes, although on average levels are a bit lower with e-cigarette use. In 1 study of 36 dual users using only e-cigarettes or cigarettes ad libitum, plasma nicotine AUC was on average 30% lower while vaping, but 25% of individuals took in as much or more from vaping compared with smoking (Figure 3).[45] Circadian plasma nicotine level differed by type of device (Figure 4). Of interest, the circadian pattern of nicotine intake differed from participant to participant, but was similar while vaping versus smoking, as seen in data from 3 of the same pod-type device users (Figure 5).

Heat-not-burn devices with single-use sessions deliver nicotine at similar levels or slightly lower than with conventional cigarettes.[52–54]

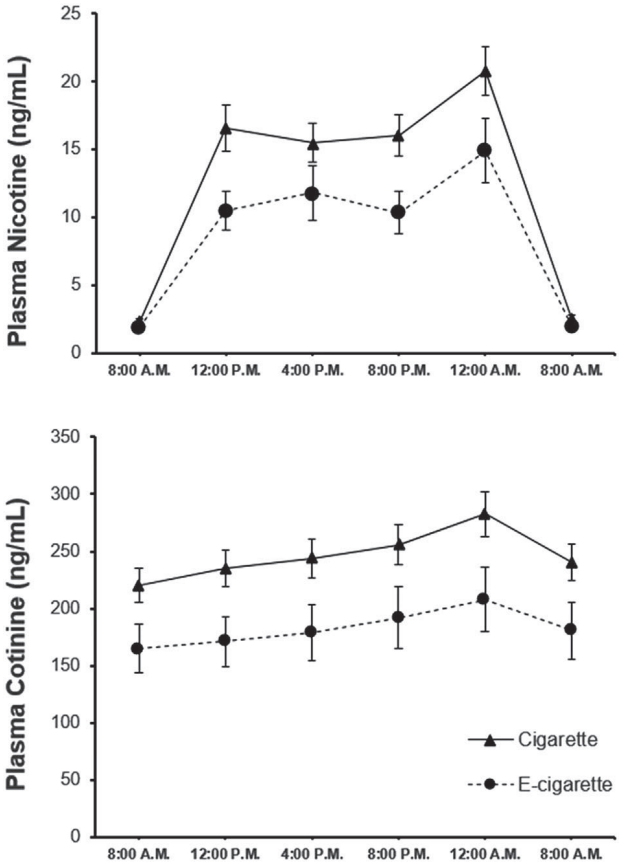

Figure 3. Twenty-four-hour average plasma nicotine and cotinine concentrations with ad libitum use of tobacco or electronic cigarettes (n = 36). All participants were regular dual users who inhaled their usual brand of tobacco or electronic cigarette (from Harvanko et al[45]).

Nature of E-Liquids and Nicotine Delivery

Although human pharmacokinetic data are lacking, laboratory data suggest that the nature of the e-liquid can affect absorption profiles. Propylene glycol is more volatile than vegetable glycerin, and high propylene glycol/vegetable glycerin liquids generate smaller particles and are perceived as having more a "throat hit" (referring to the intensity of sensory impact) and to be harsher.[38,55] Throat hit may be desirable for a regular smoker, as it simulates the effects of smoking a cigarette, but may be undesirable for a nonsmoker. Liquids with high ratios of propylene glycol/vegetable glycerin also deliver more nicotine than lower ratio solutions with the same nicotine concentration.

The pH of nicotine in e-liquids could impact the deposition and pharmacodynamics of inhaled nicotine. For liquids that contain nicotine in the freebase form, the higher the nicotine concentration, the higher was the pH.[56] At higher pH, a large fraction of nicotine is in the freebase form. Freebase nicotine is volatile, leaves particles readily, and can deposit in the mouth and upper airway, activating sensory nerves in these sites. Nicotine salt liquids typically have a pH in the 5-6 range, such that nicotine is primarily in the ionized form, remaining in liquid particles until reaching the lower airway. Although an impact of liquid pH on the pattern of nicotine distribution in the lung seems likely, we are aware of no data to assess this possibility to date. The proportion of nicotine in salt versus the freebase form does not influence the delivery of nicotine into the aerosol.[57]

Titration of Nicotine Intake

As described previously, dependent smokers tend to take in the same amount of nicotine from day to day (titration), presumably to optimize pharmacologic effects of nicotine. Titration of nicotine intake has also been observed with e-cigarette use. Comparison of cotinine levels in plasma or saliva has found that, on average, regular exclusive vapers and exclusive smokers and

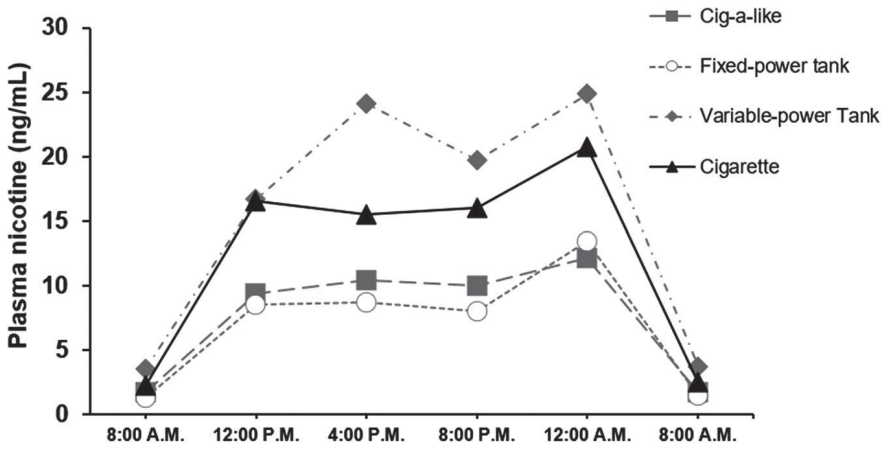

Figure 4. Twenty-four-hour average plasma nicotine concentrations with ad libitum use of tobacco or various types of electronic cigarette devices: variable power (n = 6), fixed power (n = 15), and cig-a-likes (n = 12). All participants were regular dual users who inhaled their usual brand of tobacco or electronic cigarette (from Harvanko et al[45]).

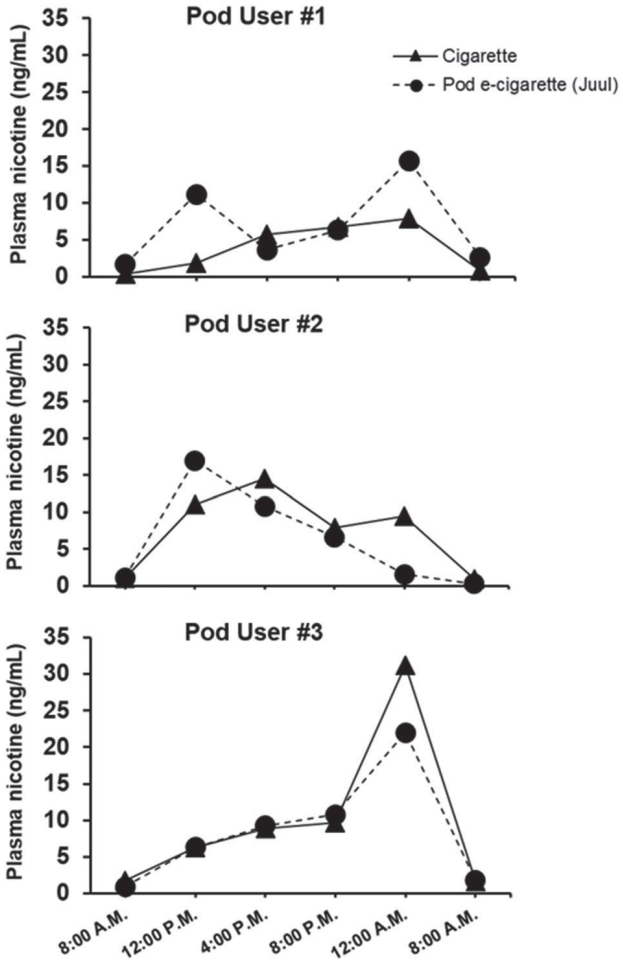

Figure 5. Twenty-four-hour plasma nicotine concentrations with ad libitum use of tobacco or pod type electronic cigarettes in 3 individuals using the same JUUL pod device, showing similar circadian patterns (from Harvanko et al[45]).

dual users have similar levels, indicating similar daily intake of nicotine.[46,47,58] Remarkably, similar daily intake of nicotine is seen in cross-sectional studies comparing vapers who use quite low-nicotine (3-6 mg/mL) compared with high-nicotine (59 mg/mL) liquids.[21,59] This can be achieved because liquids with low nicotine concentration are typically used with high-power devices (tanks or mods) that generate large-volume aerosol at high temperature, whereas high-nicotine liquids are used with low-power devices that generate relatively small-volume aerosol. Compensatory behavior has also been observed in the laboratory, associated with more intensive patterns of puffing with low- versus high-nicotine liquids.[60] The titration phenomenon has potential safety implications. Exposure to large-volume aerosol generated at high temperature that also generates high levels of oxidizing chemicals and toxic thermal degradation products is likely to present a greater health risk compared with smaller volumes of aerosol generated at lower temperatures.[61] Importantly, some vapers transition from lower-to higher-power devices while at the same time using liquids with lower nicotine concentrations, believing that they are reducing their nicotine dependence, whereas, in fact, their nicotine intake has not changed.[60]

Pharmacodynamics

Many studies have examined the subjective effects of vaping in relation to enjoyment, satisfaction, and modulation of nicotine withdrawal symptoms and craving.[43,45,49,50,62] In general, e-cigarettes are not perceived to be as enjoyable as tobacco cigarettes, but e-cigarettes do effectively reduce nicotine withdrawal symptoms and craving. Some studies have shown that higher nicotine delivery from e-cigarettes is associated with greater satisfaction, but when higher nicotine is associated with high vegetable glycerin/propylene glycol

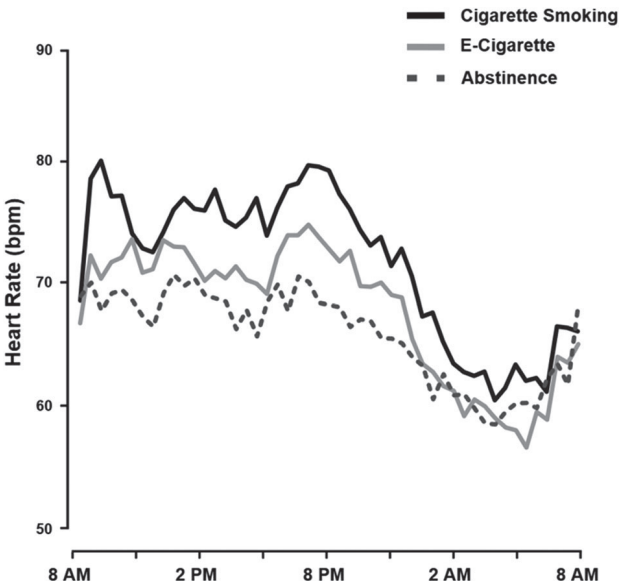

Figure 6. Twenty-four-hour average ambulatory heart rate with ad libitum use of tobacco or electronic cigarettes compared with no nicotine product use (n = 36). Daily and daytime average heart rate was significantly higher with cigarette smoking versus e-cigarette use and with e-cigarette use versus abstinence. All participants were regular dual users who inhaled their usual brand of tobacco or electronic cigarette (from Benowitz et al[63]).

solutions, satisfaction is lower, possibly reflecting less of the sensory reward from the cloud sensation.[38] Nicotine is a sympathomimetic drug that increases heart rate and transiently increases blood pressure. Both standardized and ad libitum e-cigarette use produces heart rate acceleration similar to cigarette smoking, both in the short term and over 24 hours (Figure 6).[43,62,63]

Prevalence of ENDS Use

From 2014 to 2016, the prevalence of ever use of e-cigarettes among US adults increased from 12.6% to 15.3%, whereas current use (used in past 30 days) decreased from 3.7% to 3.2%.[64] In 2018, current use was 3.2% (2018 National Health Interview Survey)[65] and 2.3% in 2018-2019 (2018-2019 Tobacco Use Supplement to the Current Population Survey).[66] The prevalence of current e-cigarette use among US adult workers during 2017-2018 was 2.3%, of which 43.1% was among daily users.[67]

Dual use of e-cigarettes and combustible cigarettes remains the dominant use pattern among adults who use e-cigarettes. Between 2013 and 2015, 44.3% of adult e-cigarette users maintained dual use, whereas 48.8% stopped using e-cigarettes and 12.1% quit smoking.[68] In 2018 to 2019, 8.1% of current cigarette smokers were also current e-cigarette users; current e-cigarette use prevalence was 4.8% among former smokers and 0.8% among never smokers.[66] During 2017 to 2018, 49.5% of adult workers who were current e-cigarette users also smoked cigarettes.[67]

In 2020, 19.6% of high school students and 4.7% of middle school students in the United States reported current use of e-cigarette (2020 National Youth Tobacco Survey [NYTS]).[69] In comparison, 27.5% of high school students and 10.5% of middle school students reported current use of e-cigarettes in the 2019 NYTS.[70] Using pooled data from 2017 to 2020 Monitoring the Future, the prevalence of current e-cigarette use among 10th- to 12th-grade US students was 22%.[71] Among current e-cigarette users in the 2020 NYTS, 38.9% of high school students and 20.0% of middle school students used e-cigarettes on at least 20 of the past 30 days, and 22.5% of high school students and 9.4% of middle school students reported daily use of e-cigarettes in 2020.[69] More frequent use is indicative of greater e-cigarette dependence.[72] Most teen e-cigarette users used flavored e-cigarettes (82.9%), and prefilled pods or cartridges were the most widely used (48.5%).[69] Prevalence of JUUL, a pod-based device that has been widely used among teens, decreased from 58.7% in 2019 to 41.1% in 2020, whereas use of other brands, such as Vuse and the disposal Puff Bar, increased.[71]

Current use of e-cigarettes among 16- to 19-year-old adolescents in 2019 was 17.8% in Canada, 12.6% in England, and 18.5% in the United States (Nielsen Consumer Insights Global Panel).[73] Prevalence of e-cigarette use on at least 20 of the past 30 days was 5.7% in Canada, 2.7% in England, and 6.7% in the United States. In 2017, 2.0% of Korean adolescents reported current use of e-cigarettes.[74]

Potential to Aid Smoking Cessation/Support Harm Reduction

Because e-cigarettes emit fewer and have lower toxicants than combustible cigarettes,[75] e-cigarettes might have the potential for harm reduction or to aid smoking cessation if used as a substitute for tobacco cigarettes. Compared with nicotine replacement products, e-cigarettes are used in a manner that mimics the experience of cigarette use, including tactile and other sensory aspects such as "throat hit," thus contributing not only to the physical but also the behavioral aspects of addiction.[76] However, e-cigarettes are currently not part of the evidence-based smoking cessation guidelines in most countries, including the United States, mainly because of lack of sufficient data regarding their efficacy and long-term safety profile. In the United Kingdom, current recommendations suggest that although the evidence is still developing, e-cigarettes are not expected to be risk free but to be less harmful than smoking, and thus smokers willing to completely

switch from tobacco cigarettes to e-cigarettes should be informed accordingly.[77]

In contrast to the currently approved smoking cessation pharmacotherapies (ie, nicotine replacement therapy, varenicline, and bupropion) for which there is clear evidence of efficacy,[78,79] data from smoking cessation randomized clinical trials with e-cigarettes are relatively few. Based on the latest Cochrane systematic review on e-cigarettes for smoking cessation (now a living systematic review to rapidly incorporate new data), there was moderate-certainty evidence for higher quit rates with nicotine-containing e-cigarettes compared with nicotine replacement therapy (risk ratio, 1.69; 95% confidence interval, 1.25-2.27), but with evidence limited by imprecision.[80] Limitations of the analysis include the limited number of available randomized clinical trials, particularly regarding comparisons between e-cigarettes and smoking cessation aids other than nicotine replacement therapy. In general, studies of high quality (eg, Walker et al,[81] Hajek et al,[82] Bullen et al,[83] Eisenberg et al[84]) are still sparse, and although the currently available data are mostly supportive, there are also reports of low cessation and high relapse rates or dual use as outcome, and long-term data are missing.

Because many smokers who quit smoking continue to use e-cigarettes, uncertainty remains about long-term benefits. The long-term health risks of e-cigarette use as well as the risk of relapsing from e-cigarettes to cigarettes are as yet unknown. The limitation of using relatively short-term outcomes for assessing smoking cessation is common to all currently available licensed smoking cessation products because only 15% to 35% of smokers remain abstinent for longer than a year, which further highlights the importance of more research on treatment of nicotine addiction.[85] Other limitations include the different nicotine concentrations and devices used and differences in the duration of supply and the intensity of additional behavioral support provided in the various studies.[80] Furthermore, even in the case of well-conducted double-blind, randomized clinical trials, a potential Hawthorne effect, that is, a change in behavior merely from being under observation and not because of the study intervention, cannot be excluded.[86,87]

All large randomized, controlled trials of e-cigarettes for smoking cessation to date have been performed outside the United States, often in countries with historically greater regulatory oversight on nicotine content and other constituents of such products. For example, the sale of nicotine-containing e-cigarettes is allowed only with medical prescription in Australia,[88] and the idea of licensing e-cigarettes as medicines is also being pursued in other countries such as the United Kingdom.[89] In the United States, the general direction is currently also toward more federal regulation, but this may not be something that can be achieved easily.

Importantly, many of the early trials used first-generation cig-a-likes that deliver relatively low doses of nicotine, possibly influencing quit rates. Supporting the idea that nicotine dose is an important determinant of success in smoking cessation, quitting rates in the population as a whole are higher when later-generation e-cigarettes with higher power such as tank-style devices are used compared with first-generation devices[90] and when e-cigarettes are used more frequently.[90,91] The only trial to date using modern pod devices was a harm reduction study using 59 mg/mL nicotine pods.[92] This study found a reduction in a primary pulmonary carcinogen exposure overall, a reduction of tobacco cigarette consumption in those who used both e-cigarettes and continued to smoke, with approximately one-fourth of the participants switching exclusively to e-cigarettes.[92] Another recent study reported higher quit rates with a combination of nicotine patches and nicotine-containing e-cigarettes compared with the patches and nicotine-free e-cigarettes,[81] which supports the importance of adequate nicotine substitution as well as the potential of e-cigarettes to be used as an aid in addition to the currently licensed pharmacotherapies. Similar strategies with combination of e-cigarettes with other nicotine replacement products could be further investigated in future studies to optimize nicotine delivery during smoking abstinence and thus improve the currently still low cessation rates. Furthermore, not all participants in the included studies in the recent Cochrane review had to be motivated to quit,[80] whereas higher quit rates are to be expected among highly motivated populations of smokers. Thus, to optimize quitting rates, smokers need to be both motivated to quit and to use e-cigarette devices able to deliver adequate nicotine doses to replace the nicotine from tobacco cigarettes.

Further factors to be considered include that, in contrast to first-line pharmacotherapies, which have a usual duration of treatment of approximately 3 months, based on the findings of recent studies, many participants who achieve smoking abstinence with e-cigarettes remain e-cigarette users for long periods. In the Hajek study, 18% of smokers quit using e-cigarettes, but 80% of those who quit smoking continued to use e-cigarettes at 1 year.[82] Although total abstinence from both tobacco cigarettes and e-cigarettes would be optimal to reduce adverse health consequences of use of nicotine products, switching to less harmful e-cigarettes long-term would likely reduce smoking-related disease risk and would be an acceptable alternative compared with regular use of tobacco cigarettes. Some smokers reduce the number of tobacco cigarettes smoked per day with the help of e-cigarettes, but the degree to

which harm is reduced is unclear. Although a reduction by 50% among participants who smoked ≥15 tobacco cigarettes per day has been found to significantly reduce lung cancer risk,[93] even a very low smoking rate of 1 to 4 cigarettes per day is associated with substantial cardiovascular disease risk,[94] and because of the limited duration of the available studies, it is unclear if these smokers continue to smoke tobacco cigarettes at lower rates or return to prior patterns of use after some time.

Population studies can also provide information regarding the potential role of e-cigarettes for quitting smoking. In the general population, smokers choose to use e-cigarettes on their own, without medical intervention or advice. In cross-sectional data from the United Kingdom, smokers trying to quit without professional support were more likely to report abstinence when using e-cigarettes than with nicotine replacement therapy or no cessation aid.[95] An increase in the prevalence of e-cigarette use was associated with an increase in the success rate of quit attempts and overall quit rates in a time series analysis of population trends.[96] Another cross-sectional survey found increased chances of self-reported abstinence with e-cigarettes or varenicline compared with participants not using these aids.[97] Data from US surveys have found an association between the increase in e-cigarette use and smoking cessation rates[98] and higher prevalence of a recent successful quit attempt among exclusive e-cigarette users compared with users of other or no noncigarette tobacco products use.[99] A recent meta-analysis of population-based studies confirmed increased quitting with daily but decreased quitting with nondaily e-cigarette use.[91] These findings should be interpreted in the light of the previous mentioned limitations in relation to the large heterogeneity of the available e-cigarette devices and nicotine concentrations, as well as limitations associated with the study design (eg, cross-sectional design not allowing assessment of causality).

For heat-not-burn products, the available data regarding their potential role in aiding smoking cessation is even more limited than for e-cigarettes. However, there are reports of an accelerated decline in cigarette sales in Japan corresponding to the introduction of heat-not-burn products into the market,[100] which might represent their potential in supporting population quitting smoking.

Safety Concerns With ENDS

General Safety Considerations

Safety concerns with the use of ENDS can be viewed both in comparison with cigarette smoking and as absolute safety. ENDS are likely to be far less harmful than smoking, but not harmless.[101,102] Safety concerns include direct long-term adverse health effects as well as adverse impacts on public health. The latter include dual use of ENDS and cigarettes, resulting in less smoking cessation, normalization of nicotine and tobacco product use, and gateway effects to youth smoking among youth. In this review, we focus on potential adverse effects of health, including concerns about ENDS use by youth.

Toxicant Exposure

In considering the risk of ENDS relative to cigarette smoking, one must start with cigarette smoke. Cigarette smoke is a complex mixture of >7000 chemicals, including oxidizing chemicals, volatile organic compounds, carbon monoxide, carbonaceous particulates, trace metals, and nicotine. Compared with cigarette smoke, ENDS aerosols contain many fewer chemicals, including propylene glycol, vegetable glycerin, much lower oxidants and volatile organic compounds, minimal or no carbon monoxide, liquid particles of unknown toxicity, some metals, nicotine, and flavor chemicals.[103] Importantly, the nature of the aerosol is highly influenced by the temperature of heating of the liquids.[23,61] At higher temperatures there is thermal degradation of propylene glycol and vegetable glycerin into toxic volatile organic compounds, such as acrolein, formaldehyde, and acetaldehyde. Some flavor chemicals such as diacetyl and cinnamaldehyde and potentially acetals of vanillin and other flavors raise toxicity concerns.[104] Based on the far lower number and levels of potential toxins in ENDS aerosol, it is predicted that toxicity will be much lower than that of smoking, but toxicity will likely differ by device. Trace metals, including chromium, nickel, copper, lead, and tin may be present in ENDS liquids, with wide variation in levels of various metals in different devices and liquids.[105,106] Metals have been implicated in causing oxidative stress, inflammation, and DNA damage and in carcinogenesis.[107] The sources of trace metals are corrosion of metallic components, including heating coils and electrical connectors between the battery and the coil. Metal transfer from ENDS liquid to the aerosol is generally low, averaging 1% to 4.7%, but the levels of some metals such as chromium and nickel can be as high as in mainstream cigarette smoke.[105] Whether the doses of metals derived from ENDS use are adequate to produce disease is still unclear.

Several studies have examined human exposure to volatile organic compounds and other toxicants in users of ENDS compared with smoking, both in cross-sectional and crossover studies. All show that urine metabolites of volatile organic compounds and carcinogenic tobacco-specific nitrosamines in ENDS users are much lower than those of smokers and similar to or slightly above those of nonsmokers.[47,103,108,109]

Caveats in Interpreting Studies of Adverse Health Effects of ENDS

As mentioned above, ENDS are highly variable with regard to the nature and amount of aerosol released. Thus, it is hard to extrapolate from studies of 1 device to harms of other devices. Preclinical studies often expose cell cultures or animals to high levels of ENDS aerosol with exposure schedules that are quite different from human exposures. Acute studies of effects of ENDS in humans may not reflect long-term effects. Epidemiology studies are hard to interpret because most adult ENDS users are either current or former smokers. Many are cross-sectional studies with self-reports of disease and limited data on temporal relationships between ENDS use and disease diagnosis. The numbers of ENDS-only users in the age range of typical incidence of smoking-related diseases are low. Finally, some illnesses related to vaping, such as the recent "E-cigarette or vaping use–associated lung injury" (EVALI) outbreak, were, to a large extent, among those vaping cannabis liquids that were contaminated with vitamin E acetate.[110] However, the customizability of open-system ENDS, which allows users to add a variety of additives to e-liquids and the wide range of power settings of some ENDS, suggests that an EVALI-like outbreak among ENDS users is possible in the future if e-liquids are adulterated with a pulmonary toxicant.

Common to cigarettes and ENDS are chronic exposure to nicotine. Although nicotine is not the major cause of smoking-related health problems, nicotine may be associated with some health risks. These include addiction, cardiovascular disease, reproductive disorders, infectious disease risk, and acute poisoning.[111,112] Because of space limitations, several of these are not discussed here.

We do briefly review ENDS-related health concerns for cardiovascular disease, pulmonary disease, and use by youth.

Cardiovascular Disease

Cigarette smoking causes coronary heart disease, stroke, aortic aneurysm, and peripheral arterial disease.[113] Smoke constituents such as nicotine, carbon monoxide, oxidizing gases, other oxidizing chemicals, heavy metals, and particulate matter are significant contributors to smoking-related cardiovascular disease risk. The sympathomimetic action of nicotine causes neuronal and adrenal gland release of catecholamines, which stimulates increased heart rate, blood pressure, and myocardial contractility, increasing myocardial demand for oxygen and nutrients, and potentially contributing to arrythmogenesis .[111] Oxidant chemicals and heavy metals promote cardiovascular disease through pathways such as inflammation, endothelial dysfunction, endothelial cytotoxicity, vascular injury, and thrombotic activation.[114,115] E-cigarette aerosols contain oxidizing chemicals, although in much lower levels than in cigarette smoke, as well as varying levels of volatile organic compounds such as acrolein, formaldehyde, cytotoxic flavorants, and heavy metals.[102]

Cell culture, animal, and human studies have shown increased oxidative stress, inflammation, platelet activity, and altered vascular function after exposure to e-cigarette aerosol. Various cell cultures exposed to e-cigarette aerosols, e-liquids, or serum obtained from e-cigarette users had increased generation of reactive oxygen species, DNA damage, cell proliferation inhibition, morphological changes, cell death, and induced proinflammatory state.[116–118] In mice, exposure to e-cigarette aerosol caused platelet hyperactivity[119] and increased aortic stiffness and impaired vascular reactivity responses.[120] Blood level of endothelial progenitor cells sampled from e-cigarette users increased after a 10-puff bout, suggesting endothelial activation or stress.[121] In people, endothelial dysfunction evidenced by impaired flow-mediated dilation occurs acutely after e-cigarette use[122] but not with chronic use after switching from cigarettes.[123] Another study found increased systemic oxidative stress and a shift toward sympathetic predominance in e-cigarette users compared with nonusers.[124]

Few epidemiologic studies have investigated the long-term cardiovascular effects of e-cigarettes because of the recency of e-cigarette entry in the marketplace. Findings, primarily from cross-sectional studies, have serious methodologic problems and have been conflicting with respect to cardiovascular risk.[125–128] Although preclinical studies show that cardiovascular harm from e-cigarettes is biologically plausible, at present the risk in the human population is uncertain.

On the other hand, a few studies have provided evidence of potential cardiovascular benefits from switching to e-cigarettes among adult smokers. In a randomized, controlled trial of healthy smokers who switched to e-cigarettes, participants who had elevated blood pressure at baseline had a significant reduction in systolic blood pressure at 52 weeks compared with baseline.[129] Similarly, significant reductions in blood pressure were observed in hypertensive smokers who quit or substantially reduced their combustible cigarette consumption by switching to e-cigarettes.[130]

Respiratory Disease

Repeated inhalation of any foreign chemicals raises concerns about respiratory disease. Respiratory concerns of e-cigarette use have included acute lung injury, asthma, and chronic obstructive pulmonary disease (COPD; emphysema and bronchitis) through mechanisms such as endothelial barrier breaching; increased

airflow resistance; bronchial hyperreactivity, and bronchoconstriction; adverse airway remodeling; and excessive mucus production. In cell culture studies, exposure to e-liquids or aerosol extracts led to altered permeability of human bronchial epithelial cells,[131] decreased cell proliferation and diminished lung endothelial barrier function,[132] release of proinflammatory cytokines,[133] and increased oxidative stress and reduced cell viability of human bronchial epithelial cells.[134] Animal studies have described e-cigarette-induced oxidative stress in animal lungs, inflammatory cytokine release,[132,135] impaired antimicrobial defenses,[136] increased airway hyperreactivity, protease release, and airspace enlargement,[137] reduction in mucus clearance,[138] and emphysema.[137] Donor lungs exposed to e-cigarette aerosol induced interleukin-6 production and increased levels of intracellular mucin 5AC (MUC5AC) protein, which is associated with hypersecretion of mucous in the respiratory tract and COPD.[139] Studies of e-cigarette users have also reported increased levels of proteins associated with COPD, increased expression of neutrophil-related proteins, consistent with the inflammatory response, and an elevated concentration of MUC5AC.[140] Further, emerging evidence from animal[141] and human[142] studies suggest that exposure to e-cigarette aerosols increases the risk of viral infections such as influenza by suppressing host-defense functions against these viral infections.

Cross-sectional studies have reported a positive relationship between e-cigarette use and COPD, particularly among dual users,[143–146] but these studies have relied on self-reported COPD diagnoses and e-cigarette use. Studies also suggest that e-cigarette use among youth may be associated with greater prevalence and exacerbation of asthma.[147–150] On the other hand, respiratory benefits have been reported for smokers who switched to e-cigarettes. This includes reduced incidence of self-reported respiratory infections[151] and reduction in annual COPD exacerbation 1, 2, and 3 years after switching to e-cigarettes.[152,153]

Youth Vaping

As described in the prevalence of use section, there has been considerable uptake of vaping by youth in the United States as well as in some (but not all) other countries. Concerns about youth vaping include nicotine addiction in youth who would never have used other tobacco products, serving as a gateway to smoking and causing harm to the adolescent brain and other adverse health effects.

Addiction to e-cigarettes can be assessed in part by frequency of use. Daily use of a nicotine product with use for pharmacologic effect (such as stimulation, relaxation, stress reduction, etc.) is a criterion that has been used to determine cigarette addiction in youth. The majority of youth use e-cigarettes fewer than 20 days per month, and most who do are current or former smokers.[154] Whether youth who are using e-cigarettes now will continue as adults is unknown. Youth who are nonsmokers but who vape are more likely to try cigarettes, but thus far there is no evidence that they become regular smokers.[155] Furthermore, although vaping prevalence among youth in the United States has risen, smoking prevalence has decreased, suggesting no overall gateway effect.[156] However, because the use of e-cigarettes by youth is a relatively recent phenomenon, we cannot dismiss the possibility that if youth prevalence of e-cigarette use increases and is sustained over time, the result might be an increase in the prevalence of combustible tobacco use.

Concern about damage to the adolescent brain derives from studies in rodents, in which nicotine exposure in adolescent rats slows maturation of parts of the brain, including the prefrontal cortex, which is responsible for executive function, decision-making, and impulse control.[157] It is difficult to assess whether brain changes seen in rodents occur in young people because of confounding effects of sociocultural and genetic factors. The main direct health effects of vaping among youth appear to be respiratory, with the greater risk of asthma and cough [147–150,158] Although there is debate about the magnitude of risk of vaping among youth, all public health authorities agree that youth vaping should be avoided if possible.

Implications for Public Health

A summary of the major conclusions with respect to the clinical pharmacology of ENDS is provided in Table 2. We offer comments here on the application of ENDS science to the promotion of public health.

ENDS and the Cigarette Endgame

The immediate priority for protection of public health against tobacco-caused disease is the end of the use of combusted tobacco products, primarily cigarettes. Although ENDS are not harmless, they are most likely much less harmful than cigarette smoking. If smokers used ENDS to quit smoking, even if they continued to use ENDS, we expect that there would be an enormous benefit to public health. As discussed previously, given a choice, most smokers would rather continue smoking cigarettes rather than use e-cigarettes. However, with appropriate encouragement, including supportive public health messaging, e-cigarettes might be able to outcompete with cigarettes.

There is debate in the public health community about how best to position ENDS to promote smoking cessation. Some think ENDS are best used as medicine-like cessation agents, with use guided by health

Table 2. Summary of Clinical Pharmacology-Informed Observations Relating to Electronic Nicotine Delivery Systems (ENDS)

1.	ENDS aerosolize nicotine that can be inhaled and rapidly absorbed, moving to the brain quickly and in high concentrations, similar to that seen after cigarette smoking. This provides desired psychological reward and nicotine substitution without exposure to harmful tobacco combustion products.
2.	ENDS products reduce craving and withdrawal symptoms during cigarette abstinence, but most smokers find them less satisfying than cigarette smoking. The satisfaction from ENDS is related to level of nicotine delivery.
3.	Nicotine delivery varies considerably by electronic cigarette device, depending on the nicotine concentration and propylene glycol/vegetable glycerin ratio of the liquid, battery voltage, coil heating temperature, and user puffing behavior.
4.	Nicotine in electronic cigarettes can be predominantly in the free or ionized form, depending on the pH of the liquid. Freebase nicotine predominates at higher pH, produces greater throat and upper airway irritation, and is harder to inhale. Ionized nicotine predominates in nicotine salt liquids with more acidic pH and is easier to inhale, with implications for both addiction and safety.
5.	Regular users of nicotine products tend to titrate intake of nicotine to maintain desired levels and effects of nicotine. Daily nicotine intake is on average similar in exclusive smokers and vapers and among vapers using different ENDS devices.
6.	ENDS using low nicotine concentration liquids require the user to inhale large amount of aerosol generated at higher temperatures to obtain desired levels of nicotine. Aerosol is generated at higher temperatures from such devices, resulting in greater exposure to oxidant chemicals and various toxic thermal degradation products.
7.	ENDS using high nicotine concentrations (such as nicotine salt-containing liquids) allow the user to inhale small amounts of aerosol generated at lower temperatures to obtain desired levels of nicotine, resulting in lesser exposure to oxidant chemicals and thermal degradation products.
8.	ENDS can promote smoking cessation both during formal smoking cessation interventions and in the general population. Successful cessation is associated with use of ENDS that deliver higher levels of nicotine and regular daily use.
9.	Owing to lack of combustion, ENDS products expose users to much lower levels of toxicants compared with cigarette smoking. Of greatest concern for direct toxicity is exposure to oxidant chemicals, thermal degradation products and some flavoring chemicals. The potential toxicity of ENDS varies considerably based on the nature of the device.
10.	The long-term safety of ENDS use is unknown because the products have not been used for long-enough periods.
11.	Nicotine addiction among youth is of concern, particularly with the availability of nicotine salt liquids that are easy to inhale. Concerns include nicotine-induced impaired maturation of the adolescent brain and development of long-lasting nicotine addiction.

ENDS, electronic nicotine delivery systems.

professionals. Others argue that most smokers would like to quit smoking on their own and would like to have free access to safer nicotine products that give cigarette-like reward that they can use without prescription. Possibly ENDS could be available in both these scenarios.

In 1994 Benowitz and Henningfield proposed the idea of federal regulation to establish a nicotine threshold for addiction.[159] The idea was to reduce the nicotine content of tobacco in cigarettes to minimally addictive levels so that children who experimented with cigarettes would not become addicted and that it would become easier for addicted smokers to quit. The 2009 Family Smoking Prevention and Tobacco Control Act passed by the US Congress granted the FDA the authority to promulgate tobacco product standards as appropriate for the protection of public health.[160] Included was the authority to reduce nicotine yields of products as long as it does not require total nicotine to be reduced to "0." Since 2009 a number of clinical trials have demonstrated that nicotine reduction could reduce nicotine dependence and enhance quitting, without harmful effects related to compensation.[161–163] In 2018 the FDA issued an advance notice of proposed rule-making for a tobacco product standard for nicotine level of combusted cigarettes.[164] A population-based simulation model from 2016 to 2100 predicted that nicotine reduction would result in 5 million smokers quitting within 1 year of implementation, 13 million within 5 years, and would prevent 33 million youth and adults from becoming smokers by 2100.[165]

A concern with reduction of nicotine levels in cigarettes is that many smokers would experience severe withdrawal symptoms, and many would resort to black market cigarettes and/or product tampering to obtain the nicotine that they need. The availability of ENDS would provide an attractive alternative to conventional cigarettes and would likely enhance public acceptance of a nicotine reduction policy that could represent the cigarette endgame.[166]

FDA Regulation

In 2016 a deeming rule was issued that granted the FDA regulatory authority over ENDS.[167] Under this authority, tobacco products marketed after 2017 need to submit a premarket tobacco application to remain on the market. Approval as a modified-risk tobacco product is necessary to allow claims of reduced risk or reduced exposure. The regulatory authority of the FDA over ENDS provides an opportunity to favorably influence the benefits versus risks of ENDS for public health. Devices and liquids can be regulated to reduce exposure to toxic thermal degradation products and dangerous flavor chemicals. FDA regulations could regulate marketing of and access to ENDS for children to deal with concerns relating to youth use of ENDS. And the FDA could provide public education in support of its own "nicotine-focused framework for public health," which was announced in 2016.[168]

A particular challenge for FDA and other countries of the world relates to limits on nicotine concentrations and availability of flavors in e-cigarette liquids. In the

European Union, for example, e-liquids can contain a maximum of 20 mg/mL of nicotine,[29] whereas at present there are no limits in the United States. Liquids containing higher concentrations of nicotine in salt form potentially result in less direct harm because nicotine is inhaled in high concentrations with relatively small volumes of aerosol generated at relatively low temperatures. Such products would be ideal to support the transition from cigarettes smoking to ENDS. However, these products are easier for youth to inhale, exposing them to higher levels of nicotine, and are likely more addictive compared with the use of freebase nicotine liquids at lower concentrations. Conversely, low nicotine concentration limits are likely to result in nicotine-addicted smokers inhaling larger volumes of aerosol generated at higher temperature with greater thermally generated toxicants. Such nicotine limits are predicted to be more harmful for smokers who switch, but less likely to addict youth. Similarly, flavor restrictions pose different benefits and risks for adult smokers versus youth. Flavors attract youth, but also attract many adult smokers and support their switch from cigarettes to ENDS. How the FDA and the European Union determine the optimal regulatory strategy for nicotine limits and flavors will be of great interest and consequence for public health.

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Conflicts of Interest

Dr. Benowitz serves as a consultant to Pfizer and Achieve Life Sciences, companies that market or are developing smoking cessation medications, and has been an expert witness in litigation against tobacco companies. Dr. Liakoni reports smoking cessation counselling as part of clinical work and academic institution research support for investigation of the pharmacology and toxicology of e-cigarettes and travel support for speaking at research meetings. The authors declare no other potential conflicts of interest.

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Data Sharing

No novel data sets were generated for this review. All included information was obtained from previously published reports.

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