Electronic Cigarettes and Vape Devices

A Comprehensive Guide for Clinicians and Health Professionals

Susan Chu Walley
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Editors

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ISBN 978-3-030-78671-7 ISBN 978-3-030-78672-4 (eBook)
https://doi.org/10.1007/978-3-030-78672-4

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

We dedicate this book to the memory of Regina Whitmore, MPH, director of the Division of Tobacco Control at the American Academy of Pediatrics (AAP) and center administrator of the AAP Julius B. Richmond Center of Excellence from 2010 to 2015. Regina was a staunch supporter of the crusade against tobacco and tobacco-related diseases and a tireless advocate for children. Regina's hope was that someday, all children might live in a world free of tobacco and secondhand smoke. We hope to carry that vision forward through this work.

Introduction

In the 1960s, 43% of adults in the United States smoked cigarettes, and it was routine to see smoking on planes, restaurants, and even in hospitals. While today's rate of adult smokers is still unacceptably high, in 2020 it had dropped to 13%. At the same time, youth tobacco use has skyrocketed, largely due to the use of a new type of tobacco product, e-cigarettes and vape devices. Data from the National Youth Tobacco Survey 2020 (data collection prior to the pandemic) reports that 19.6% of high school students had used e-cigarettes in the past 30 days.

In order to understand the impact of e-cigarette use on individual and population health, it is crucial to understand more about these products and the factors that have resulted in the rapid increase in awareness and use. *The Health Impacts of Electronic Cigarettes and Vape Devices* addresses these questions with some of the foremost experts in the field of tobacco control using a scientific approach to the available literature. Thus, the book begins with a history of tobacco and efforts of the tobacco industry to market and advertise to youth.

There is no question that e-cigarettes have negative health impacts for youth users and non-users of tobacco and nicotine. There is overwhelming evidence detailed that e-cigarettes have harmful health effects in the short term, while the impact of long-term health effects, particularly on the developing body and mind, may not be fully understood for decades. This book reviews not only the health effects for the user, but the potential health impact of secondhand aerosol exposure. It was not until 1986 that the Surgeon General reported in *The Health Consequences of Involuntary Smoking* on the harmful health effects of secondhand smoke exposure; we now know tobacco smoke exposure causes a myriad of diseases, while worsening and contributing to many more.

The impact of e-cigarettes on population health has been more challenging to answer. The literature on e-cigarettes as a smoking cessation device has not favored the use of e-cigarettes over FDA-approved tobacco cessation pharmacotherapy. One of the most revealing facts is that at the time of this publication, no e-cigarette company has filed an application to the FDA as a smoking cessation device. Meanwhile, millions of youth are frequent users of e-cigarettes, and there is limited research and resources to address adolescent nicotine addiction. Chapter 6 of this book addresses

treatment for youth e-cigarette use and presents recommendations to address nicotine addiction while recognizing that there is a fervent need for more research on treating adolescent nicotine action.

In considering the final question of the factors that have contributed to the rapid rise of youth e-cigarette use, it is relevant to consider the framework proposed by Dr. Julius Richmond, 12th Surgeon General of the United States, for advancing public health policy. He described a three-pronged strategy which includes strengthening the knowledge base, social strategies, and political will. While many of the chapters of this book summarize the knowledge base on e-cigarettes, the social strategies and political will necessary to reverse the trend of youth e-cigarette use is equally as important for readers to consider. Chapters 8 and 9 of this book address the role of marketing and advertising in changing social norms around tobacco use as well as the federal, state, and local policies and advocacy opportunities.

There has never been a more important time to focus on prevention and treatment of tobacco use, particularly as we consider the known and potential health harms of e-cigarette use to our youth. Tobacco use is a social determinant of health, contributing to the significant and unacceptable health disparities present in the population. We must learn from the lessons of the past and hope this book provides a useful summary of the current literature and opportunities for research, advocacy, and education.

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Chapter 1
A Brief History of Tobacco and Implications for New Tobacco Products

Jonathan D. Klein and Elissa A. Resnick

Before the late 1800s, combustible tobacco use (smoking) in America was largely limited to Native American ceremonial usage. Despite popular imagery to the contrary, this ceremonial usage was infrequent, and burning the leaves of the plant was either sacred or medicinal in intent, rather than casual, commercial, or addicted use [1]. Habitual tobacco use through most of the nineteenth century was limited to chewing tobacco. Cigarettes became more readily available in 1881 with the advent of the automatic cigarette rolling machine. At the turn of the twentieth century, combustible tobacco also came to be preferred, as public health efforts discouraged spittoon use to try to curb the spread of both influenza and tuberculosis [2].

Early advocacy against tobacco was led by religious health advocates, including the YMCA, Salvation Army, and Woman's Christian Temperance Union. These groups were largely concerned that cigarette smoking would lead to the use of alcohol and narcotics. The Anti-Cigarette League of America, founded in 1899 by Woman's Christian Temperance Union member Lucy Page Gaston, had more than 300,000 members by 1901. Their advocacy led to cigarette sale bans in 15 states by 1921 [3].

World War I brought an end to the early anticigarette movement in the US. Servicemen smoking helped elevate the image of cigarettes as a symbol of masculinity and strength, rather than as a gateway drug for those who were "weak." Previous supporters of the anticigarette movement began distributing cigarettes to the troops in an effort to be seen as patriotic [3]. Cigarettes were considered necessary for troop morale and Congress ordered their inclusion in daily rations for those overseas. The tobacco industry seized this opportunity and developed patriotic-themed advertisements [4]. At the same time, smoking among women also increased, due to targeted advertising and changing social roles during the war [5]. The tobacco industry successfully lobbied to repeal anticigarette laws, often employing

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S. C. Walley, K. Wilson (eds.), *Electronic Cigarettes and Vape Devices*,
https://doi.org/10.1007/978-3-030-78672-4_1

members of the American Legion and Veterans of Foreign Wars to argue that these laws were unpatriotic. The antitobacco movement was also undermined by governments' need for funds during prohibition, when alcohol tax revenues were not available.

Postwar public health research started to show the connection between smoking and cancer, and shorter life expectancy [6, 7]. Despite these findings, cigarette consumption continued to increase rapidly during this time period, and smoking began to be considered a normative behavior, fueled by advertising and the media. (See Fig. 1.1 for a historical view of smoking over the course of the twentieth century).

To combat growing public health concerns about cigarettes, tobacco companies used physicians' endorsements in advertisements [8, 9]. American Tobacco's Lucky Strike cigarettes was the first to mention physicians. The company promoted "toasted" tobacco, a product created by heat-curing rather than drying tobacco leaves, claiming they decreased throat irritation – and included an image of a white-coated doctor on their advertisements. Importantly, neither the doctor nor the health claim was real. RJ Reynolds also employed medical advice with Camel's slogan "More doctors smoke Camels than any other cigarette" (Fig. 1.2). The claim was

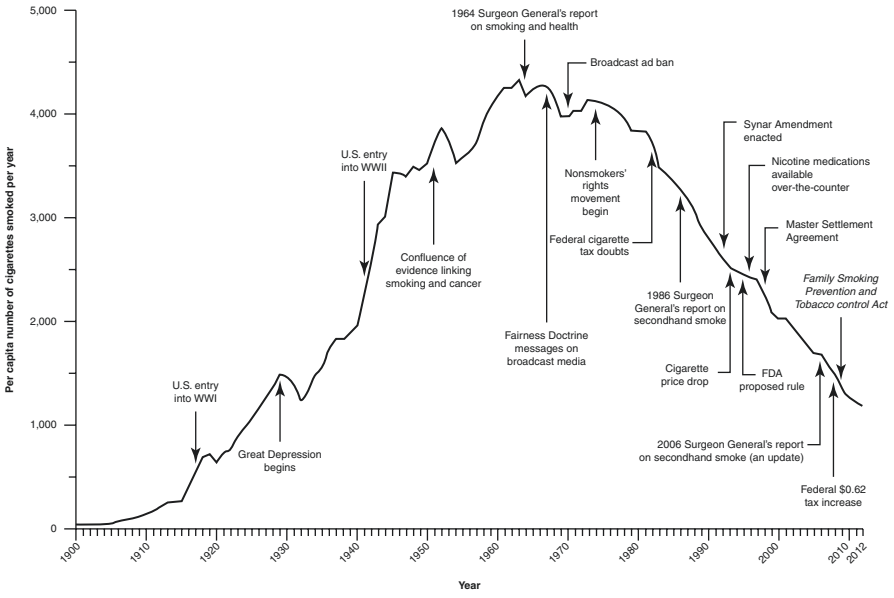

Fig. 1.1 From the 2014 Surgeon General's Report. Adult (≥18 years) per capita cigarette consumption and major smoking and health events, United States, 1900–2012 (*Source:* From the National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General. Atlanta (GA): Centers for Disease Control and Prevention (US); 2014. 2, Fifty Years of Change 1964–2014. https://www.ncbi.nlm.nih.gov/books/NBK294310/as adapted from Warner 1985; U.S.DHHS 1989; Creek et al. 1994; U.S. Department of Agriculture 2000; U.S. Census Bureau 2013; and US Dept of the Treasury 2013)

Fig. 1.2 Camel Doctor Advertisement. R.J. Reynolds's campaign to reassure the public about the safety of their products used an image of a doctor with the statement "More Doctors smoke Camels." R.J. Reynolds was able to make this claim through surveys conducted immediately after Camel cigarette samples were gifted to doctors at medical conventions (From the collection of Stanford Research Into the Impact of Tobacco Advertising (tobacco.stanford.edu))

based on a survey the company conducted immediately after providing free cartons of Camels to physicians at an AMA meeting [10].

During the so-called Golden Age of Hollywood, tobacco companies partnered with movie studios to portray smoking as glamorous [11]. Cross promotion of movies and tobacco benefited both industries, but damaged public health. From 1937 to 1938, American Tobacco paid the over $218,000 (the equivalent of $3.7 M today) to 42 Hollywood stars. These actors and actresses smoked on screen and appeared in ads, in exchange for which American Tobacco paid for the film studio's advertising campaigns. As the US entered World War II, the daily rations of cigarettes for soldiers was increased above what had been provided during World War I. Tobacco companies created advertisements with soldiers, further cementing smoking as a symbol of strength and patriotism [4, 12] (Fig. 1.3). Even cartoon strip soldiers were depicted as smokers [13].

In the early 1950s, more evidence linking smoking to lung cancer became public, resulting in a slight dip in cigarette sales. The tobacco industry responded by forming the Tobacco Industry Research Committee in 1953, an organization dedicated to attacking scientific studies [14]. That same year, companies created filtered cigarettes and promoted the new product as a healthy alternative. Despite the illusion that these new products were safer, smokers of filtered cigarettes often inhaled as much or more tar, nicotine, and other toxins as those who smoked unfiltered cigarettes. Although the tobacco companies knew and recognized (in internal documents) that filters did not make their products safer, they continued to advertise them as such [15]. Tobacco company product placement also continued in the 1950s, expanding to television as this media became more popular. Cigarette brands sponsored shows and invested in product placement; and even Fred Flintstone smoked Winston cigarettes [16]. (This video and other images from tobacco's marketing efforts are available at http://tobacco.stanford.edu/tobacco_main/videolist_tvshows.php from the Stanford Research into the Impact of Tobacco Advertising website.)

In 1958, the tobacco industry centralized their efforts to undermine public health by forming the Tobacco Institute, which supported the Tobacco Industry Research Committee's attempts to discredit public health science. The Tobacco Institute claimed that antitobacco advocates and scientists had distorted evidence and overinterpreted findings. They argued that there was insufficient or inconclusive evidence to support tobacco legislation or regulation. In addition to casting doubts on science, the Tobacco Institute described smoking as a personal choice rather than an addiction and argued that health problems afflicting smokers were due to heredity and lifestyle choices other than smoking [17].

Cigarette consumption continued to escalate, peaking in early 1960s. After this, rates began to decline as a result of public health efforts, starting with the 1964 report "Smoking and Health: Report of the Advisory Committee of the Surgeon

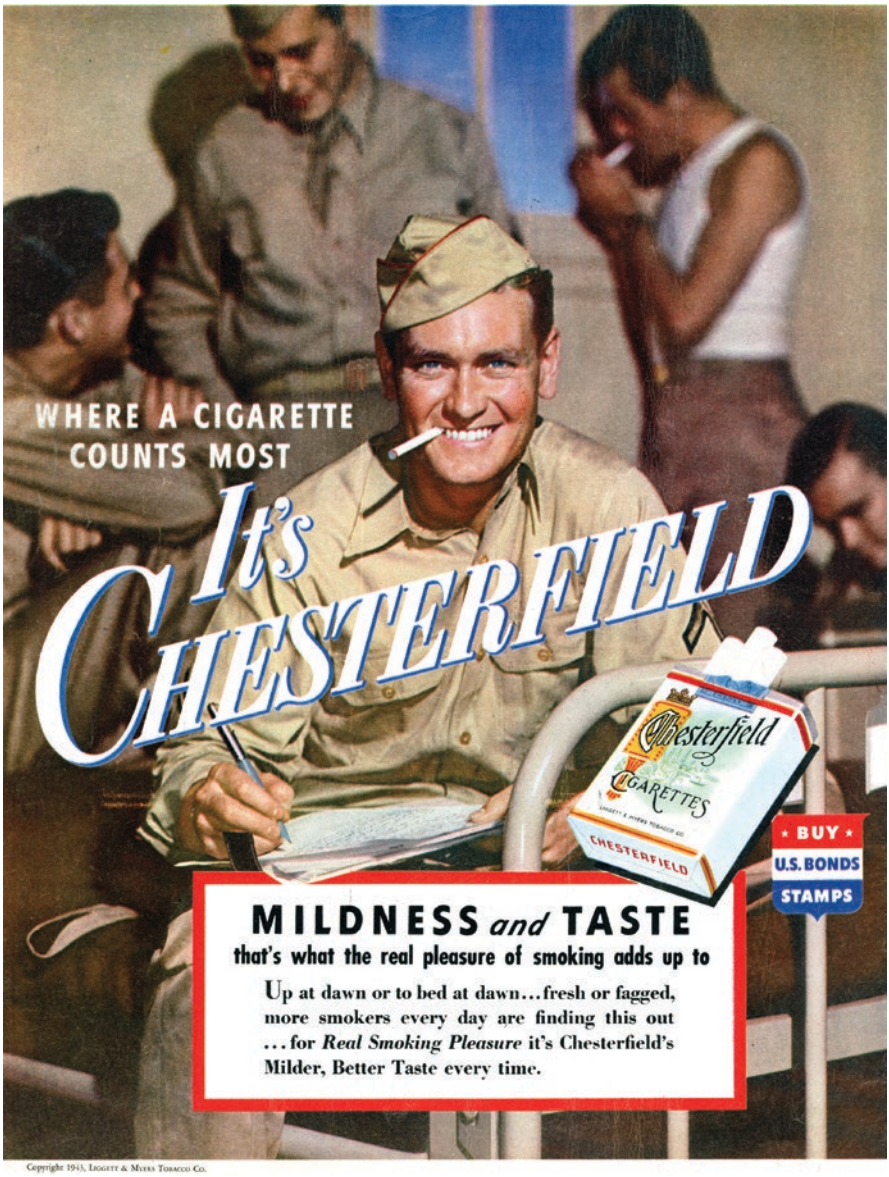

Fig. 1.3 Chesterfield Soldier Advertisement. Cigarette advertisements during WWII portrayed smoking as patriotic, strong, and good for relieving the stress of battle (From the collection of Stanford Research Into the Impact of Tobacco Advertising (tobacco.stanford.edu))

General of the Public Health Service" [18]. This report publicized the public health community's conclusion that smoking causes cancer and other serious diseases. As a result, the 1965 Federal Cigarette Labeling and Adverting Act passed, mandating that cigarette packages carry warning labels. Starting in 1967, television stations were required to air antismoking public service announcements for each cigarette advertisement aired, under the Federal Communication Commission's 1949 Fairness Doctrine, which required broadcast license holders to present equitable and balanced views of controversial issues. Soon after, in 1969, the Public Health Cigarette Smoking Act required that warning labels appear in print advertisements, too.

Antitobacco televised messages were highly effective; thus, the tobacco industry agreed to a voluntary advertising ban, taking cigarette advertisements off television in 1971 [19]. However, despite the television ban, the tobacco industry's ties to Hollywood remained strong. Product placement, and other forms of nonadvertising brand promotion, developed and remains a strong way for cigarette brands to stay in the public's view. Film producers would offer tobacco executives opportunities to market by choosing which cigarettes various characters would smoke. One producer pitched "film is far better than any commercial run on television or in any magazine, because the audience is totally unaware of any sponsor involvement" [20].

The nonsmokers' rights movement also started to grow in the 1970s, as evidence of the dangers of secondhand smoke emerged. Public health activists, powered by new evidence and the 1975 Surgeon General's Report concluding that exposure to environmental, second-hand smoke was harmful to nonsmokers, successfully pushed for smoke-free places in workplaces, airlines, restaurants, and other public settings [21]. Smoke-free, clean air laws made smoking less convenient and more stigmatizing, leading to further decreases in smoking rates in the US.

Efforts to decrease tobacco use were gaining ground, and the US Armed Forces had finally removed cigarettes from troop's rations in 1975 [4]. However, when America began Operation Desert Storm in 1991, the tobacco companies again sought to target the US Armed Forces. Philip Morris sent 10,000 cartons of free Marlboro cigarettes to soldiers. When these cigarettes were met with criticism, the cigarette manufacturers pivoted to providing promotional materials: Camel and Marlboro branded playing cards and other branded items were sent to deployed troops [4]. Cigarette manufacturers also sponsored programs that helped troops communicate with family members at home, and "Welcome Home" events, complete with Camel and Marlboro branded signs to be posted on military bases [22]. These efforts were successful – while smoking decreased overall, military deployment was associated with both higher rates of smoking initiation and recidivism for those who had previously quit [23].

At the same time, public health efforts to protect youth from smoking continued to gain ground, and the 1990s saw passage of the Synar Amendment in 1992, which tied states' receipt of substance abuse block grant funds to passage and enforcement of laws to prohibit sale or acquisition of tobacco products by youth under age 18 [24].

In the late 1990s, a former executive at Brown & Williamson became a whistleblower and testified that tobacco companies had knowingly manipulated their products to increase their addictiveness and the effects of nicotine. This disclosure was a major blow to the tobacco industry, as the companies could no longer hide their manipulation of evidence or strategies to recruit youth smokers behind and within their attorney-client legal protection. This disclosure and subsequent discovery of formerly hidden correspondence precipitated two landmark cases that changed the landscape of tobacco control. First, in 1997, $300 million was awarded in the largest class action settlement to date entered by a court resulting from a suit brought on behalf of nonsmoking flight attendants exposed to secondhand smoke on planes. This settlement led to the establishment of the Flight Attendant Medical Research Institute (FAMRI), which funds secondhand smoke-related research and, since 2005, has supported the American Academy of Pediatrics Julius B. Richmond Center of Excellence, dedicated to research into prevention of exposure and protection of children and other nonsmokers from secondhand smoke and tobacco [25].

In 1998, the Tobacco Master Settlement Agreement (MSA) held that the four largest tobacco companies were responsible for paying $206 billion over 25 years to 46 participating states for tobacco-related health care costs; the industry also agreed to end some of its marketing practices specifically proven to target youth [26]. As a result of the MSA, internal industry documents were released, which showed that the industry knew that nicotine was addictive and that smokers were at increased risk for a range of illnesses – despite the fact that they vehemently denied these claims. The Tobacco Institute, which had been organized and was dedicated to refuting public health research, was formally dissolved. The MSA also required new restrictions on tobacco marketing: advertisements aimed at people under 18, tobacco billboards, and cartoons in cigarette advertising were banned. MSA funds were also used to fund public health controlled youth tobacco use prevention programing [27]. The American Legacy Foundation – later renamed as the "Truth Initiative" – and some state health departments pioneered successful antitobacco marketing campaigns focused on exposing the tobacco industry lies. These campaigns drove many young people's rejection of tobacco [28].

These video-based antitobacco counter-marketing campaigns, combined with laws promoting smoke-free air, advertising bans, and the release of industry documents, were successful in continuing to drive down youth tobacco use rates. In addition, increasing evidence showed that another effective strategy to curb youth tobacco use and sales is through tax and price increases. While tobacco addiction renders cigarette prices particularly inelastic, tax increases have been shown to decrease demand, particularly among the young [29, 30]. As states acted on these finding, the increases in both federal and state taxes have consistently reduced smoking rates among younger smokers [31]. These efforts also moved to the global level, with the World Health Organization (WHO) adopting its first treaty focused on tobacco control in 2003, The Framework Convention on Tobacco Control (FCTC) [32]. The FCTC came into force in 2005, regulating tobacco marketing and packaging, including mandated graphic warning labels. The WHO also established

a smoke-free initiative, and, with launch of the MPOWER campaign, a framework for accountability to monitor progress and effectiveness of FCTC implementation [33]. The US signed but has not ratified the FCTC. The tobacco industry also has launched several legal challenges, claiming that graphic warning labels violate their rights to free speech [34].

The tobacco industry has continued to make efforts to improve its image in recent decades. However, many of these programs have been exposed as pro-tobacco in their actual design and implementation. For example, the tobacco industry sponsored youth prevention programs and funded front groups to provide curriculum to local school districts which focused on "smoking as an 'adult' choice." However, the 2012 Surgeon General's Report concluded that these programs are not only ineffective at reducing youth smoking, but that they instead paradoxically promote smoking and increase susceptibility to addiction among youth [35, 36].

The industry's nimble and insidious attempts to circumvent protections afforded to youth by the MSA also include the widespread growth of flavored tobacco products, especially among so-called "little cigars," which are relatively indistinguishable from cigarettes. Flavorings known to be attractive to youth, including menthol, also were heavily promoted in snuff pouches, chewing tobacco, and in innovative products for nicotine delivery [37]. Using flavors is also an industry tactic to appeal to vulnerable populations: menthol-flavored branded tobacco products are heavily promoted in African-American and low-income neighborhoods, even though nonmenthol brands often use menthol for its anesthetizing mitigation of the unpleasant taste of smoke [38, 39]. However, these ongoing efforts to addict new smokers and to recruit youth to smoking pale beside the recent and rapid rise in youth initiation of nicotine addiction from e-cigarettes.

Electronic cigarettes became widely available and commercialized in the US in 2006; however, the tobacco industry has worked on development of nicotine aerosolization devices since the 1960s. E-cigarettes, or electronic nicotine delivery systems (ENDS), consist of a heating device which creates an aerosol, a battery, and a tank or reservoir with solutions that almost always contain nicotine, and which can also aerosol other substances, including marijuana. E-cigarettes are known by many other names, including e-hookahs, mods, vapes, and vape pens [40]. Some e-cigarettes are disposable; others closely resemble cigarettes; some are shaped like a pen and are refillable. The most recent generation of E-cigarette products – JUUL and similar disposable devices – became available in 2014. These allow users to inhale larger puffs and consume more e-liquid, and these flavored products have quickly come to dominate the market [41, 42].

In 2009, the Family Smoking Prevention and Tobacco Control Act was signed into law, which gave the US Food and Drug Administration (FDA) the authority to regulate the tobacco product manufacturing, distribution, and marketing. The Act further restricted marketing and sales to youth, prohibited misleading claims of "healthy" tobacco products, and banned all flavors other than menthol [43]. Though these are important steps, the tobacco industry's ability to create and market new products has generally outpaced the FDA's ability or willingness to take action, specifically as it relates to e-cigarette development and marketing to youth [44]. The

Act gave FDA immediate authority over cigarettes and also allowed FDA to extend their authority and rule-making by deeming other products within their scope. Unfortunately, this process slowed and stalled, resulting in virtually unregulated e-cigarette marketing to youth over the past decade. And it wasn't until 2016 that FDA issued a deeming rule to expand the definition of tobacco products under the Agency's jurisdiction to include previously unregulated items, including e-cigarettes [45].

The Family Smoking Prevention and Tobacco Control Act also created the Tobacco Products Scientific Advisory Committee (TPSAC), a group tasked with advising the FDA commissioner on matters related to tobacco. TPSAC includes three members from the tobacco industry: one each from manufacturers, tobacco growers, and small business tobacco manufacturers [46]. Furthermore, the FDA's Comprehensive Plan for Tobacco and Nicotine Regulation is required to seek industry input on the regulation of tobacco products [47]. Allowing members of the industry to voice input and advise on the regulation of their products is often criticized for allowing the industry to delay or avoid meaningful regulation; additionally, evidence has shown that this involvement places public health priorities in conflict with industry interests [48, 49].

In addition and in response to the FDA's limited effectiveness at the national level, many states and other jurisdictions have enacted laws to decrease youth access to tobacco products. These include flavor bans and "Tobacco 21" legislation to prohibit sales of tobacco products to youths under 21 [50]. Both of these efforts have shown some success in reducing youth smoking in states where these laws have been enacted [51, 52].

While per capita cigarette consumption continues to decrease, tobacco use is climbing among youths, driven by the popularity of e-cigarettes [53–55] (Fig. 1.4). E-cigarette manufacturers have utilized word-of-mouth and well-funded social media campaigns to market their products [56]. E-cigarette marketing utilizes images and themes that combustible cigarette advertisements had previously used (Fig. 1.5). These products are available in a range of flavors, making them appealing to a wide range of youths. As a result of predatory marketing, nearly 40% of youths believed that using e-cigarettes did not cause harm [57]. The 2009 Tobacco Control Act did not apply to these new products.

Ironically, tobacco control advocates bear some responsibility for the delays in regulating e-cigarettes. Some advocates saw e-cigarettes as part of a risk-reduction strategy that could end combustible tobacco use. Despite any evidence for safety, these novel products were perceived as less harmful and were widely promoted as tools for cessation. The unproven potential utility of e-cigarettes as a cesstion adjunct delayed any effective action to address the vigorous marketing of these products to young people; as with other efforts to regulate the tobacco industry, policies that might have limited e-cigarette availability and accessibility were delayed or weakened by promotion of "scientific controversy." As E-cigarettes became established in the US market, the tobacco companies began investing in and acquiring e-cigarette companies and leading pro-vaping advocacy campaigns [58]. Research has since emerged that shows that e-cigarettes do not help with cessation

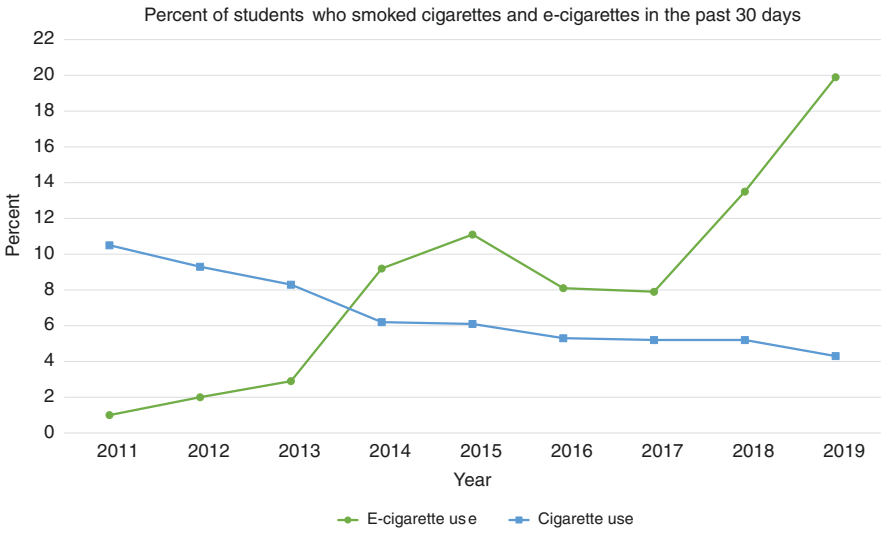

Fig. 1.4 CDC graph. Current cigarette usage has decreased among middle and high school students while e-cigarette usage has increased (Data from 2011–2019 CDC National Youth Tobacco Surveys, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion)

[59], are harmful to health, and allow tobacco companies to prey on younger consumers who believe that these are safer products [60]. But with past month use reported by more than one in four high school students [54], this data comes too late for effective primary prevention.

In 2020, the flavor bans were extended to some e-cigarette products. However, a loophole in the law limited the ban to pod-system e-cigarettes and allowed flavors to continue to be used in disposable products. As a result, almost overnight, "Puff bars" and similar, price-discounted disposable JUUL-like products flooded the market, and users simply switched to disposable e-cigarettes [61]. This most recent rapid pivot on the part of the industry only serves to emphasize the importance of having comprehensive policies regarding tobacco flavoring and other strategies to prevent youth access and addiction.

The other chapters in this book address some of the health effects of e-cigarettes or other tobacco and nicotine products on users, children, as well as nonsmokers and nonvapers exposed to the secondhand effects of these toxic products. They also address the implications of these products on clinical practice and policies and ways to advance and protect the public's health. Consistent and comprehensive action, driven by evidence and free from industry efforts to distort the truth is needed if we ever hope to achieve a truly tobacco and nicotine-free generation.

Fig. 1.5 Virginia Slims/BLU Advertisements, side-by-side. The Blu "Smoke in Style" campaign is reminiscent of the Virginia Slims "You've come a long way baby" slogan. Both advertisements feature attractive woman, have similar layouts, and appeal to the core values of style and class (From the collection of Stanford Research Into the Impact of Tobacco Advertising (tobacco.stanford.edu))

Fig. 1.5 (continued)

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Chapter 2
The E-Cigarette Phenomenon: What it is, Why it is Happening, and What You Should Know About it

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What Are E-cigarettes and What Kinds of E-cigarettes Are Available?

Electronic cigarettes (also referred to as "e-cigarettes," "e-cigs," "e-hookahs," "mods," "vape pens," "vapes," "tank systems," and "electronic nicotine delivery systems (ENDS)") came on the market in the United States (US) in 2006–2007. Since then, well over 430 brands of e-cigarettes in more than 15,500 flavors have been available [1]. E-cigarette devices typically have a battery, a heating element, and a place to hold liquid ("e-liquid" or "e-juice") that contains varying levels of nicotine and many different flavors.

E-cigarettes deliver an aerosol (often incorrectly called a "vapor") by electronically heating a solution that usually contains nicotine (a highly addictive chemical compound found in the tobacco plant [2] and made synthetically [3]), other chemicals to help make the aerosol (propylene glycol [PG] and/or vegetable glycerin [VG or glycerol]), and flavoring agents such as diacetyl, cinnamaldehyde, and vanillin [4]. E-cigarette devices can also be used to deliver cannabis and other drugs. Users inhale the aerosol into their lungs and when they exhale, bystanders can also breathe in this aerosol [5].

E-cigarette designs have evolved since they were first introduced in the US [6]. E-cigarette devices come in many sizes and shapes and include designs that are rechargeable, refillable, and/or disposable. While some e-cigarettes are made to look like conventional cigarettes, cigars, or pipes, others resemble pens, USB flash drives, highlighters, watches, hoodie sweatshirts, and backpacks. Larger devices such as tank systems or mods do not resemble other tobacco products or everyday devices [1, 5]. There are currently four "generations" of e-cigarette devices. The

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S. C. Walley, K. Wilson (eds.), *Electronic Cigarettes and Vape Devices*,
https://doi.org/10.1007/978-3-030-78672-4_2

first generation of e-cigarettes are designed to look like conventional cigarettes ("cig-a-likes," e.g., NJOY™, Vapor King™, Storm™, Totally Wicked™, Blu™, EonSmoke™, Volcano™, Lavatube™, JUUL™ and PUffbar™). These devices are composed of a battery and a cartridge containing an atomizer that heat a solution, are not rechargeable or refillable, and are intended to be discarded after the e-liquid is used up. The second generation of e-cigarettes are "pen-style" e-cigarettes (e.g., Vapor King™, Storm™, Totally Wicked™) that are somewhat larger than a cigarette, have a higher capacity battery, and contain a prefilled cartridge or a refillable cartridge. Rechargeable cigarette-shaped devices (such as Blu™, EonSmoke™) often contain an element regulating the number or duration of puffs. The third-generation e-cigarettes have refillable "tanks" or "mods" (e.g., Volcano™, Lavatube™) that are much larger than cigarettes, have higher capacity batteries, and typically contain large, refillable cartridges [4, 6]. These open systems contain separate components usually sold at vape shops or online that allow users to vary the battery power, style, and size. The vape pens allow users to reuse and refill their products with e-cigarette liquids ("e-liquids" or "e-juice") that contain varying levels of nicotine, many different flavors, and other chemicals [7]. By 2015, the e-cigarette marketplace expanded dramatically and included fourth generation "pod mods," cartridge-based e-cigarette devices that contain a prefilled or refillable pod cartridge or "pod" that come in a wide variety of flavors but are not refillable or reusable (e.g., JUUL™). These closed systems let users replace a cartridge containing a prefilled solution of nicotine and flavors. Finally, disposable e-cigarettes (such as Puff Bar™) surged in popularity between 2019 and 2020 and remain popular because they are available in flavors that were prohibited in cartridge-based e-cigarettes [6, 7].

The US e-cigarette market, including the thousands of vape shops and internet sales, was approximately $9 billion in 2019, and as of May 2020, prefilled cartridges for pods comprised 80% of sales in brick-and-mortar stores and disposable e-cigarettes were nearly 20% of the e-cigarette market, having nearly doubled their market share in one year [7]. All three major US tobacco companies have their own e-cigarette brands. Altria/Philip Morris ended sales of its own e-cigarette products, but in 2018 invested $12.8 billion in JUUL Labs giving it a 35% stake in the company [8]. Reynolds American sells its Vuse line of vapor products including pods, tanks, and disposables [9] and ITG Brands markets its blu line of pods, tanks, and disposables, with or without nicotine and in a variety of flavors [10].

Risks of E-cigarettes Versus Cigarettes

Some health care providers and policy makers have argued that e-cigarettes are a safer alternative to conventional cigarettes and are effective for quitting smoking [11, 12], and a 2018 report of the National Academies of Sciences, Engineering, and Medicine (NASEM) found substantial evidence that exposure to toxic substances from e-cigarettes is significantly lower compared to combustible cigarettes [13]. While some studies have shown that smokers who switch completely to e-cigarettes are exposed to lower levels of some carcinogens and other toxicants, which could

lower the risk of several tobacco-related diseases [14, 15], it is not clear that as actually used, cigarette smokers trying to quit do, in fact, use e-cigarettes exclusively. E-cigarettes are not currently approved by the FDA as a cessation aid [5], and there is insufficient evidence to recommend e-cigarettes for smoking cessation in adults, let alone for adolescents or young adults [16, 17].

There is mounting evidence that e-cigarette use is no better at helping cigarette smokers quit than using FDA-approved nicotine replacement therapies or using nothing at all [17, 18], and most adult e-cigarette users do not stop smoking cigarettes and instead continue to use both cigarettes and e-cigarettes (known as "dual use") [19]. Dual use of e-cigarettes with conventional cigarettes is associated with higher risks of lung and heart disease than smoking cigarettes alone [20, 21]. Rather than helping adult smokers switch from using conventional cigarettes to using purportedly less dangerous e-cigarettes or quitting altogether, e-cigarettes are not actually reducing smoking rates and are attracting adolescents to use tobacco products [22]. Any potential benefits of e-cigarettes must be balanced against the potential risks to adolescents and other nonsmokers who initiate tobacco use with e-cigarettes. The Surgeon General's 2020 report on cessation found that the evidence is suggestive but not sufficient to infer that the use of e-cigarettes is associated with increased smoking cessation, and "The potential benefit of e-cigarettes for cessation among adult smokers cannot come at the expense of escalating rates of use of these products by youth" [23].

The National Academies of Science, Engineering and Medicine report acknowledged that even if e-cigarettes are less harmful than combustible cigarettes, that does not mean they are safe or without risk [13]. While e-cigarettes deliver lower levels of some carcinogens than conventional cigarettes, they expose users to other chemicals and toxins including formaldehyde, acrolein, volatile organic compounds such as toluene, tobacco-specific nitrosamines, and metals such as nickel and lead [24–26]. Additionally, high levels of ultrafine particles may increase the risk of cardiovascular and noncancer lung diseases, and notably these kinds of diseases kill more smokers than does cancer [22]. The chemical compounds used in flavorings are also associated with negative health outcomes [27–32]. There is mounting evidence that e-cigarettes are associated with cardiovascular [20, 21, 33, 34] and respiratory harms [35–37].

There is also evidence that e-cigarette use is associated with many other mental health, social, and educational consequences. Of particular concern is the evidence, depending on the dataset, that adolescents who initiate with e-cigarettes are significantly more likely to then go on to use conventional cigarettes, thereby exposing them to the same health concerns associated with conventional cigarettes [38–40]. Young people who use e-cigarettes are at risk for becoming nicotine dependent and continuing to use tobacco products (including combustible tobacco products like cigarettes) as adults and also at risk for vaping marijuana [41]. There is also evidence that adolescent tobacco and nicotine use are associated with depression, anxiety, lower school performance, mood changes, irritability, restlessness, anxiety, problems socializing, difficulty with concentration, and insomnia [42–46].

What Are the Rates of Adolescent and Young Adult E-cigarette Use?

E-cigarette use among adolescents and young adults has increased significantly over the past 6 years. E-cigarette use among US high school students more than doubled, from 11.7% in 2017 to 27.5% in 2019 [47–49]. The most recent data released by the CDC about e-cigarette use among middle and high school students are from the 2020 National Youth Tobacco Survey (NYTS) [50], which showed that 19.6% of high school students (three million) and 4.7% of middle school students (550,000) reported using an e-cigarette in the past 30 days. This represents a modest decline from the shocking 2019 report showing that during 2017–2018, e-cigarette use increased 77.8% (from 11.7% to 20.8%) among high school students and 48.5% (from 3.3% to 4.9%) among middle school students [48]. However, the proportion of adolescent e-cigarette users who reported using e-cigarettes frequently or daily in 2020 increased compared to the previous 2 years. Among past 30-day e-cigarette users, 38.9% of high school students (up from 34.2% in 2019) and 20.0% of middle school students (up from 18% in 2018) reported using e-cigarettes frequently (defined as use on 20 or more days of the past 30 days), and 22.5% of high school users and 9.4% of middle school users reported daily use. This means that 1.3 million middle and high school students were frequent users of e-cigarettes, and more than 730,000 were daily users. Approximately one-third of high school and middle school current e-cigarette users reported dual- or poly-use, defined as using e-cigarettes along with other tobacco products, such as cigarettes, smokeless tobacco, or cigars [50, 51].

E-cigarette rates among young adults aged 18–24 are also high, and higher than among other adult age groups, with CDC data showing that 9.3% of young adults have used e-cigarettes [52]. Dual- or poly-use was common, with 18.6% of young adults reporting using two or more tobacco products (e.g., using e-cigarettes together with conventional cigarettes and/or cigars, hookah, smokeless tobacco products, or other products) [52]. More than half of these young adults (56%) reported that they never smoked conventional cigarettes [52].

Given the high rates of adolescent e-cigarette use, in 2018 the FDA Commissioner [53] and the US Surgeon General called youth e-cigarette use an “epidemic” [54]. Although the decline in adolescent e-cigarette users since 2019 is promising, adolescent use is at the same level that the Surgeon General considered an epidemic, and among e-cigarette users, more than one fifth of high school students and about one in ten middle school students are using e-cigarettes every day. This increase in use frequency may be associated with greater nicotine dependence among young users and the threat of hooking a new generation on nicotine and other tobacco products, including combustible cigarettes [47]. In contrast to the high rates of e-cigarette use among adolescents and young adults, according to the CDC’s 2020 National Health Interview Survey (NHIS), while adult smoking rates have remained constant at 14% since 2017, about 4.5% of all adults have used an e-cigarette, and almost one in four adult e-cigarette users had never smoked conventional cigarettes.

While e-cigarette use among youth has increased, rates of conventional, combustible cigarette use have declined over the past decade. According to the 2019 National Youth Tobacco Survey (NYTS), 5.8% of high school students and 2.3% of middle school students used conventional combustible cigarettes in the past 30 days [55]. It is important to note that the declines in conventional cigarette use preceded the explosion of e-cigarette use, and smoking prevalence among high school students has been dropping since 2011 [48], while high school students reporting recent e-cigarette use increased from 1.5% in 2011 to 38.9% in 2020 according to the 2020 NYTS data, and 22.5% reported daily e-cigarette use [50]. Further, the increase in adolescent e-cigarette use explains why adolescents' overall use of tobacco has increased, with 53.3% of high school students (eight million) and 24.3% of middle school students (2.9 million) reporting having ever used any tobacco product [55].

Of further concern is that numerous studies have shown that adolescents who use e-cigarettes are two to seven times more likely to then go on to use conventional cigarettes, depending on the dataset [38]. The 2018 report by the National Academies of Science, Engineering and Medicine found a causal connection between e-cigarette use and conventional cigarette smoking initiation and concluded that there is "substantial evidence that e-cigarette use increases risk of ever using combustible tobacco cigarettes among youth and young adults" [13], and the nationally representative Population Assessment of Tobacco and Health (PATH) study found that from 2013 to 2016, e-cigarette use among youth aged 12–15 was associated with more than four times the odds of trying cigarettes [38].

E-cigarettes and Smoking Cessation Treatment

As e-cigarettes are actually used (i.e., for recreational purposes, and not in controlled settings with cessation counseling to aid in cigarette smoking cessation), e-cigarette use is not associated with quitting among smokers [56–59], and adolescents are not using e-cigarettes to quit smoking conventional cigarettes. Further, the FDA has not approved any e-cigarette to be used as a smoking cessation aid for either adults or adolescents. Indeed, more research is needed to determine whether e-cigarettes are effective for quitting smoking (See Chap. 7). In any case, if adult smokers were to achieve any meaningful health benefits from e-cigarettes, they would need to switch completely to e-cigarettes and use e-cigarettes exclusively, rather than using e-cigarettes while still smoking conventional cigarettes [23].

Although e-cigarettes were originally developed as a cigarette substitute to help *adults* quit smoking [4], since 2014 they have become the most popular tobacco product for *youth* in the US, and youth are more likely than adults to use e-cigarettes [5]. Youth use e-cigarettes recreationally, and there is no evidence that youth are using e-cigarettes to help them quit smoking conventional cigarettes. However, there is substantial evidence that e-cigarette use increases the risk that youth and young adults will use combustible tobacco cigarettes [13, 17, 39].

Why Do Adolescents and Young Adults Use E-cigarettes?

The rise in e-cigarette use among youth has been attributed to many factors including attractive flavors, aggressive marketing, appealing designs, misperceptions, and highly addictive nicotine formulations [60, 61]. Each of these is described in the following sections.

Flavors in E-cigarettes Attract Youth

Flavors are the most commonly cited reason for using e-cigarettes among adolescents, and is the predominant way adolescents and young adults initiate and consume all tobacco products [61–68]. The 2020 National Youth Tobacco Survey (NYTS) found that the proportion of adolescent e-cigarette users who reported using flavored products increased from 68.8% in 2019 to 82.9% in 2020, and the most popular flavors among high school users were fruit, mint, menthol, candy, desserts, or other sweets [50]. Most youth e-cigarette users say they use e-cigarettes "because they come in flavors I like" [69].

Although cigarettes with flavors (except menthol) have been prohibited in the US since the 2009 enactment of the Family Smoking Prevention and Tobacco Control Act [70], which gave the US Food and Drug Administration (FDA) authority over tobacco products, this flavor restriction was not extended to e-cigarettes when they and all other tobacco products were brought under FDA's tobacco authority with the 2016 enactment of the Deeming Rule [71, 72]. Also, the law does not outright prohibit "flavors" per se, but instead restricts products from containing "characterizing flavors," without defining what this term means.

Tobacco companies have understood for decades that flavored tobacco products appeal to youth [73]. Companies have taken advantage of the government's failure to extend flavor restrictions to e-cigarettes and have introduced thousands of flavored e-cigarette products into the marketplace. A 2018 study found that more than 15,500 unique e-cigarette flavors were available online [1], and an earlier study found that more than 80% of the 450 e-cigarette brands offered were available in fruit, candy, and dessert flavors [74]. E-cigarettes are available in a huge variety of flavors including fruit flavors like cherry and watermelon, candy flavors like chocolate and gummy bear, and traditional mint and menthol flavors. Additionally, companies are marketing e-cigarettes and e-liquids in kid-enticing flavors such as cotton candy, strawberry shortcake, and even dozens of types of unicorn flavors [73, 74]. Vape shops that sell e-cigarettes and e-liquids offer a wide assortment of flavors and often allow customers to mix their own flavors [66, 75–78].

Flavors are appealing to youth in part because they mask the harsh taste and even smell of tobacco. Further, adolescents indicate that advertisements for flavored e-cigarettes are targeting people their age, younger or just a little older [79]. Studies also show that adolescents who use flavored e-cigarettes are more susceptible to then using conventional cigarettes [80].

In January 2020, the FDA announced that it would prioritize enforcement against unauthorized flavored cartridge-based e-cigarettes (e.g., pods such as JUUL), but exempted tobacco- and menthol-flavored products, flavored e-liquids (e.g., those sold in vape shops for tank and mod systems), and flavored disposable e-cigarettes (e.g., Puff Bar) [81]. After FDA's announcement, youth migrated to menthol products, disposable e-cigarettes, and add-on flavor enhancers (e.g., Puff Krush) in all the enticing flavors that were restricted in pods [47, 82–85]. Disposable e-cigarette use increased more than 1000% among high school e-cigarette users and more than 400% among middle school e-cigarette users [50], and menthol-flavored products accounted for more than half of all e-cigarette sales [86].

Nicotine in E-cigarettes Perpetuates Youth Use

E-cigarettes, e-liquids, and other new nicotine products (like flavored nicotine lozenges and toothpicks marketed to young people) contain different levels of nicotine and different modes of delivery. The newer formulations use nicotine salts which allow higher levels of nicotine to be inhaled more easily and with less irritation than the free-base nicotine form that had traditionally been used [54]. In addition to impacting the cardiovascular system [87], nicotine can harm adolescent brain development, pregnant women, and developing fetuses [62, 88]. In addition to these harms, nicotine can be lethal if consumed in high doses, and exposure to liquid nicotine in e-cigarettes and kid-friendly e-liquids has resulted in thousands of calls to poison control centers, including more than half that reported exposures to children under the age of six [89].

Nicotine is highly addictive, resulting in symptoms of dependence, and can harm adolescent and young adult brain development, which continues into an individual's mid-20s [90]. The Surgeon General stated, "The use of products containing nicotine in any form among youth, including in e-cigarettes, is unsafe" [62] In fact, given the many changes occurring in the brain during adolescence and young adulthood, adolescents are significantly more likely to become addicted to nicotine than are adults [80, 91]. Very few people begin using tobacco after age 25, with 90% starting tobacco use by age 18 and 99% by age 26. Very rarely does anyone over the age of 26 become addicted to nicotine [92].

Most e-cigarette products contain nicotine; however, e-cigarettes and e-liquids contain highly variable levels of nicotine and nicotine exposure from e-cigarettes, depending on product characteristics (including device and e-liquid characteristics) and how the device is operated [13]. It is difficult for consumers to know how much nicotine is contained in any particular e-cigarette product [62], and some e-cigarettes marketed as containing zero percent nicotine have been found to contain nicotine [93].

Free-base nicotine has typically been used in tobacco products, including conventional cigarettes, e-cigarettes, and e-liquids [7]. Free-base nicotine is rapidly absorbed in the lungs, but it is bitter and can be harsh. Before the introduction of

JUUL in 2015, most e-liquids used 1–2% free-base nicotine and 3% was usually the highest level [94]. However, more recent e-cigarettes (like JUUL and JUUL knock-offs and disposables like Puff Bar) and e-liquids use nicotine salts with lower pH than free-base nicotine; these salt-based nicotine products are less harsh, cause less throat irritation, and allow users to more easily inhale much higher levels of nicotine than with earlier e-cigarette devices [94, 95]. JUUL, JUUL-compatible pods, and JUUL knock-off devices offer products with 5% or more nicotine concentration, and some nicotine salt-based e-liquids offer nicotine concentrations at the 5%, 6%, and 7% level [94]. Young e-cigarette users report frequently using pods (like JUUL) with high nicotine concentrations to achieve a "head rush" [96]. High nicotine concentrations coupled with the more pleasant salt-based nicotine are major factors that contribute to their popularity and perpetuate e-cigarette use [47, 97]. The increased availability of e-cigarettes with higher concentrations of nicotine encourages more frequent use [17], and frequent use can lead to nicotine dependence and an increased likelihood for youth addiction [98].

E-cigarette Designs Appeal to Youth

The sleek and concealable design of e-cigarettes are especially attractive to youth. Many e-cigarette products resemble ordinary items including USB flash drives, pens, highlighters, remote controls, car fobs, smart phones, hoodies, and backpacks. Because these products are easily concealable (See Figs. 2.1, 2.2, and 2.3), they may not draw the attention of parents or teachers and thereby allow teens to use them discretely at home and during school [99, 100]. Young adults report that they use pod e-cigarettes because they are easy to hide, and "stealth vaping" (ability to easily conceal) is a primary reason for initiation and continued use [101]. Dubbed "the iPhone of e-cigs" [102], the design of JUUL (whose founders were graduates of

Fig. 2.1 Example of concealability of e-cigarettes: Can you find the e-cigarettes? (Picture credit: Bonnie Halpern-Felsher, 2019)

Fig. 2.2 Six e-cigarettes being concealed

Fig. 2.3 Examples of the small size and concealability of pod-based e-cigarettes. (Picture credit: Bonnie Halpern-Felsher, 2019)

Stanford University's Product Design program [103]) and other e-cigarette products is central to their youth appeal and marketing success [60, 61, 100].

Aggressive E-cigarette Marketing Targets Youth

Aggressive e-cigarette marketing that targets adolescents has been very effective [104]. E-cigarette companies use the same Big Tobacco marketing playbook that worked so well to attract kids (i.e., "replacement smokers") to cigarette smoking, including marketing directly to kids with celebrity endorsements, product placements in movies, slick TV and magazine advertisements, and sports and music sponsorships. Additionally, the wide variety of youth-appealing flavors are key to

the marketing strategy of e-cigarette companies [62, 73, 105, 106], and e-cigarettes are marketed using "influencers" and multiple social media channels [107].

A case in point is Juul's marketing campaign that led to its meteoric rise in popularity among adolescents within 3 years of its launch in 2015. JUUL directly targeted young people with the design of its device, the formulation of its flavors, and its early marketing strategies. Juul's initial advertising campaign, *Vaporized*, used young-looking models, hip themes, and flashy colors to attract youth, with huge jumbotron placements in Times Square and ads in other iconic locations. Additionally, JUUL sponsored launch parties geared to young people in major US cities and offered free product samples and the opportunity to meet celebrities. But in addition to studying and copying successful advertisements and strategies used decades ago by the leading cigarette companies, JUUL enlisted social media "influencers" (people with a huge audience of followers who feature and recommend products in their social media posts) to promote JUUL by targeting millions of followers through their social media platforms popular with youth, including Twitter, Facebook, and Instagram [107–110].

The US House Committee on Oversight and Reform began an investigation into Juul's marketing practices in June 2019 which included a review of thousands of internal company documents that revealed details of the company's marketing strategies [111]. The investigation found that JUUL deliberately targeted youth in a number of ways, including by making presentations with false claims about safety at schools, summer camps, and other youth programs; targeting vulnerable populations; and attracting and keeping users with nicotine and youth-friendly flavors. Hundreds of private and public lawsuits have been filed against JUUL alleging that Juul's deceptive marketing targeted teens and led to injuries including nicotine addiction, seizures, stroke, lung damage, and even death [108, 109].

Youth are also widely exposed to e-cigarette marketing online and at the point of sale in retail stores [112]. Companies do not effectively prevent youth access to e-cigarette websites, and studies show that significant numbers of underage youth are exposed to e-cigarette advertisements online [104, 113]. E-cigarettes are frequently displayed near candy, gum, and soda in similarly bright-colored and youth-attracting packages [55, 114]. Many retailers display e-cigarettes near cessation aids which can confuse consumers about the health risks of e-cigarettes [115].

A systematic review of the literature showed that adolescents exposed to e-cigarette advertisements reported e-cigarettes being more appealing and had higher intention to use e-cigarettes than did youth exposed to e-cigarette ads for nonflavored e-cigarettes [116]. Youth who had never used e-cigarettes or other tobacco were more likely to be susceptible to using e-cigarettes if they were able to recall e-cigarette ads, and they reported lower perceptions of risk and lower perceived addiction associated with e-cigarettes. Further, adolescent e-cigarette users recall more e-cigarette advertising and find e-cigarette ads more appealing than do non-e-cigarette users [116]. Data from the 2015 NYTS showed that adolescents exposed to tobacco advertisements including e-cigarettes were more likely to be using e-cigarettes, compared with those not exposed to ads [117]. In an experimental study with adolescents between the ages of 13–18, adolescents who used social

media more often were more likely to be willing to and intend on using e-cigarettes, had more positive attitudes about e-cigarettes, and believed that e-cigarettes were less dangerous and caused less harm, compared to adolescents with lower levels of social medial use [118]. In a study of college students in Hawaii, it was found that those young adults who were more susceptible to e-cigarette ads were more likely to believe that e-cigarettes are less harmful than cigarettes, which in turn was associated with greater e-cigarette use [119].

Adolescents and Young Adults Misperceive the Risks of E-cigarettes

Adolescents and young adults harbor many misconceptions about e-cigarettes that contribute to their increased use. Many adolescents and young adults believe incorrectly that e-cigarettes are safe to use and are just "harmless water vapor" [68, 101, 120–123]. Further, youth are more curious about flavored e-cigarette products and view them as less dangerous, less potent, and easier to use than nonflavored products, leading to increased youth appeal and use [61, 63, 64]. However, there is no evidence that flavored e-cigarettes are less dangerous, and in fact there is mounting evidence that the chemical compounds used in flavorings are themselves associated with negative health outcomes [27–32].

The vast majority of young JUUL users are unaware that their product contains nicotine [124], and most young adults are confused about how much nicotine they use and how much nicotine is in each pod [101]. Consequently, many young people have the mistaken belief that e-cigarettes are less addictive than traditional cigarettes [60]. Additionally, youth do not understand what it means to become addicted and the difficulty of quitting and often mistakenly believe that they can experiment with or use nicotine-laced tobacco products for a few years and then easily quit [125].

E-cigarettes Are Easy for Underage Youth to Access and Are Cheap

Although the federal minimum legal age to purchase all tobacco products, including e-cigarettes, was raised to 21 years in December 2019 [126], it is still easy for underage youth to buy e-cigarettes in vape shops, convenience stores, gas stations [127], and online [128]. Retail clerks frequently don't ask for identification (ID) when youth purchase e-cigarettes [129], and online age verification systems are spotty and ineffective [130–132]. For these reasons, e-cigarettes are significantly easier for underage youth to purchase than cigarettes. Also, the average price of e-cigarettes is significantly less expensive compared to the average price of a pack of conventional cigarettes, and the cost of e-liquids is even cheaper, making

e-cigarettes a more cost-effective choice than conventional cigarettes [128]. Studies show that youth are especially price sensitive [133], so selling e-cigarette products at relatively low prices is another effective way to attract and keep youth buyers [127].

Policy Implications

The decline in US cigarette smoking is not due to the increased use of e-cigarettes. Rather, much of the success is attributed to evidence-based tobacco control measures such as increased cigarette taxes, indoor smoking bans, tobacco prevention and cessation programs, and health education campaigns, [27, 134]. In order to continue making progress in reducing tobacco use, policy makers at the federal, state, and local levels must fully implement these proven strategies, along with improved health insurance coverage for smoking cessation treatments [135]. If companies wish to sell e-cigarettes as cessation aids, they must follow the same process used by makers of therapeutic nicotine replacement therapies and demonstrate to the FDA that they are safe and effective for cessation [136].

Importantly, policy makers at every level of government should enact laws and regulations that restrict all nontobacco flavors, including menthol and mint, in all tobacco products, including e-cigarettes [135, 136]. There is broad consensus that flavors are one of the most important reasons why youth use e-cigarettes [50, 61–69].

Adolescents and young adults generally do not understand the effects of nicotine dependence and addiction, and most are confused about how much nicotine they use and the nicotine content of their Juuls and other e-cigarettes [101]. They do not understand the meaning of "addiction" and that it will be difficult for them to quit using e-cigarettes and other nicotine products after experimentation or use for a few years [125]. For this reason, the current federally mandated warning label for e-cigarettes, "WARNING: This product contains nicotine. Nicotine is an addictive chemical," is not effective. This suggests that educational and clinical settings should provide comprehensive education and messaging about nicotine addiction, and federal, state, and local regulations should be enacted that require disclosure of the amount and delivery of nicotine and effective product warning labels [101, 125].

One of the most frequently cited reasons for using e-cigarettes is the ability to easily conceal and vape these products, called "stealth vaping" [101]. The FDA should use its mandate to protect youth and its authority to enforce against companies that make and sell products that are targeted to or likely to promote use by youth by cracking down on easily concealable e-cigarettes and other nicotine products. Additionally, the FDA has the authority to regulate the design of e-cigarettes so that they are less concealable [132].

Social influences, such as peer pressure and experimentation, are important factors in e-cigarette use among adolescents and young adults. Although some studies suggest that adolescents understand that JUUL and other e-cigarettes may be dangerous and may increase use of other substances, adolescents continue to use

e-cigarettes at an alarming rate. Some experts therefore suggest that campaigns and educational programs focused solely on the dangers of JUUL and other e-cigarette use may not be effective in reducing the youth epidemic, and should instead acknowledge and tackle the social realities and other underlying reasons for e-cigarette use [120]. In contrast, other studies do show that education can be effective at reducing adolescent tobacco use.

The adolescent e-cigarette epidemic has eroded successful efforts over the past few decades to reduce adolescent, young adult, and adult tobacco use. Tobacco control strategies that have proven to be effective must be implemented, including targeted education campaigns and regulations at the federal, state, and local levels. We must always be thinking several steps ahead to ensure that these efforts will apply not only to products that are currently on the market, but also to new products in the pipeline that will be enticing to adolescents and young adults to avoid a vicious cycle of recapitulation and epidemics.

Acknowledgments The research reported in this article was supported by the Taube Research Faculty Scholar Endowment to Bonnie Halpern-Felsher. Additional support was from grant U54 HL147127 from the National Heart, Lung, and Blood Institute (NHLBI) and the Food and Drug Administration Center for Tobacco Products. The content is solely the responsibility of the authors.

Conflict of Interest Dr. Bonnie Halpern-Felsher is a paid expert scientist in some e-cigarette litigation and an unpaid scientific advisor and expert regarding some tobacco-related policies. Lauren Kass Lempert has nothing to disclose.

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Chapter 3
Background and Description of E-Cigarette Products and Solutions

Rachel Boykan and Maciej L. Goniewicz

Brief History of Electronic Cigarettes and Vaping

Since 2014, electronic cigarettes (e-cigarettes) have been the most popular tobacco product among youth in the United States [1–3]. A Chinese pharmacist, Hon Lik, is credited with the invention of contemporary e-cigarettes (in 2003) and patent (in 2007), but tobacco companies had worked on designs for a nicotine aerosolizing device as early as the 1960s [4]. Project Ariel (British American Tobacco) had an outer layer which would heat up an inner cylinder containing nicotine in a solution form or coating the cylinder walls. When heated, nicotine would vaporize, or a nicotine-containing solution would create an inhalable aerosol. However, while Project Ariel was patented, it never took off, likely because, despite increased awareness of the dangers of smoking, cigarettes were still enormously popular and completely unregulated, and hence, there was little need for a substitute [5]. In 1988, Philip Morris developed a similar product, the "Premier" Capillary Aerosol Generator, which heated liquid to an aerosol in a small capillary tube [6]. While this product was similarly unsuccessful, Philip Morris' 2009 electronic cigarette patent employs similar technology. Since their commercialization and widespread introduction on the US market in 2007, e-cigarette design and function has evolved rapidly, with tremendous product variability.

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S. C. Walley, K. Wilson (eds.), *Electronic Cigarettes and Vape Devices*,
https://doi.org/10.1007/978-3-030-78672-4_3

Electronic Cigarettes and Related Vaping Products

Basic Structure

The function of all e-cigarettes and other vaping products is similar: to heat a liquid to produce an aerosol for inhalation. The act of inhaling aerosols generated from e-cigarettes is commonly referred to as *vaping*. The overall structure of e-cigarettes, common to all generations of the product, includes a battery, atomizer, and a reservoir containing liquid (Fig. 3.1).

When the user inhales through a plastic or metal mouthpiece, a sensor is activated, either manually or automatically. Activation of the sensor then leads to heating of a filament (a coil) in the atomizer. Coils may differ by the metal type, coil design, number of coils, orientation, and dimensions. The coil then heats the liquid, turning it into an aerosol which is inhaled through the mouthpiece [7–10].

Most e-cigarettes use lithium-ion batteries, which are re-chargeable and commonly found in a large array of products, including laptops, mobile phones, and electric cars. Generally, lithium-ion batteries are considered to be safe; however, if the separator between the poles is breached, the poles short-circuit causing an increase in temperature which in turn causes an explosion. Although rare, explosions of e-cigarette devices, resulting in second or third degree burn injuries, or even death, have been reported [11–14].

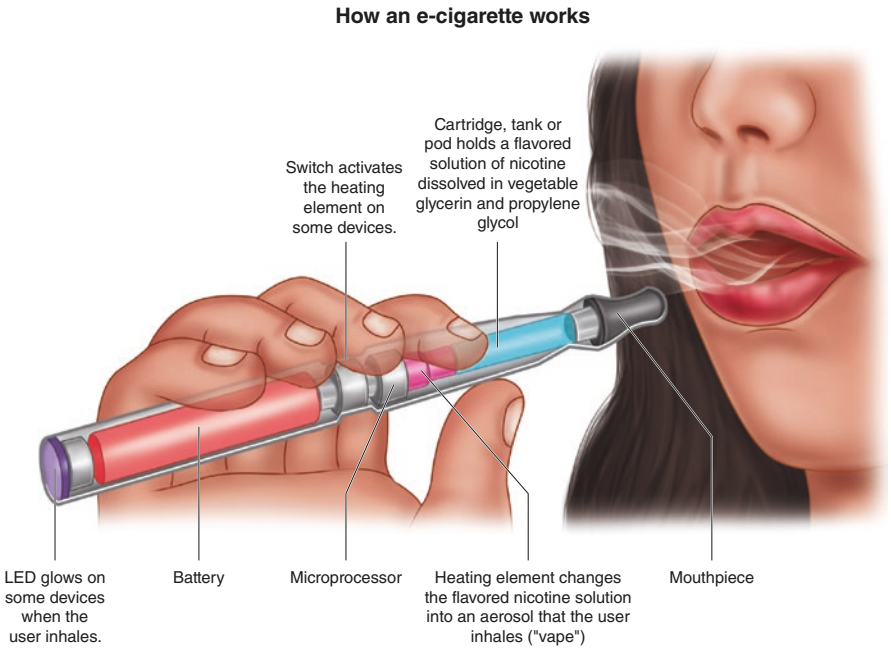

Fig. 3.1 How an e-cigarette works

Beyond the basic conceptual and structural similarities, there is wide variability among e-cigarette devices, both in the manufactured design and in the user's ability to modify the device. A "closed-system" device is not intended to be modified by the user (the most popular of this type is JUUL). By contrast, an open-system e-cigarette device offers the user the freedom to change many of the device features. For example, the liquid reservoir may be refilled by a multitude of different liquids; the power of the device may be increased by increasing the battery output voltage or replacing the heating coil with a low-resistance material.

Although some liquids used in e-cigarettes have been reported to be nicotine-free, most products currently available on the market contain and emit nicotine. The amount of aerosol emitted from e-cigarette devices and the aerosol's chemical composition depend on several device features and characteristics. For example, increasing the battery power or liquid nicotine concentration have both been shown to increase nicotine emissions and nicotine delivery to users [15]. Increasing the battery power has also been shown to increase other non-nicotine toxicants such as carcinogenic carbonyl compounds (including formaldehyde, acetaldehyde, and acrolein) [16–18], free radicals, and oxygen reactive species [19–21].

Below, we describe each generation of e-cigarettes. This commonly used classification is useful for summarizing the evolution of e-cigarettes over time (Fig. 3.2).

First Generation E-cigarettes

The first generation of e-cigarettes emerged on the market in 2007. They were commonly called "cig-a-likes," due to their close resemblance to conventional cigarettes. Many of these products even had an LED light at the end, simulating the glow

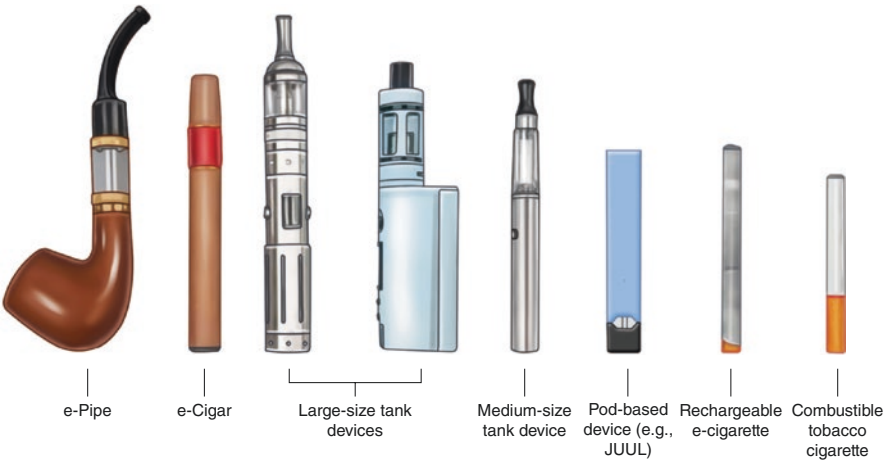

Fig. 3.2 Various vaping devices

of a lit cigarette. In earliest models (no longer available), the atomizer, battery, and fluid reservoir comprised three separate components. Subsequent two-piece models (still available) combine the atomizer and fluid reservoir (which is usually prefilled) into one piece, with a separate battery, which may be recharged. In 2013, one-piece disposable models were introduced. All first-generation e-cigarettes use a fixed, low-voltage battery [7].

Second Generation E-cigarettes

Second generation e-cigarettes are generally larger than first generation products; most resemble a pen or a laser pointer. E-cigarettes in this category are re-chargeable rather than disposable, and many features are customizable. Batteries in this group have significantly larger capacity than batteries in cig-a-like models, maintaining a charge for one to two days. Additionally, some second-generation e-cigarettes may allow the user to adjust the battery output voltage and device power, providing more aerosol for inhalation. Cartridges for liquids (commonly referred to as "clearomizers") may be prefilled or refillable, and compatible batteries may be sold separately. Users of second and third generation e-cigarettes often modify and customize their devices to produce large clouds, change levels of nicotine delivery, alter the taste of liquids, and experience different throat hits [22].

Third Generation E-cigarettes

Third generation e-cigarettes bear no resemblance to traditional cigarettes; they are much larger and more variable in shape than first- and second-generation products. Known as "mods," third-generation e-cigarettes are highly customizable. The battery output voltage can be adjustable by the user and the heating coil can be replaced with low-resistance material. Those modifications lead to an increase in the device's power (wattage) that generally results in an increased production of aerosols. Within the mod family of e-cigarettes, there are three types of atomizers: various styled atomizers, which may be larger than those in prior generations, replaceable dripping atomizers, in which the user builds their own filaments, and coils, onto which the refill fluid may be directly dripped. Alternatively, the atomizer is encased in a fluid tank. Sub-ohm atomizers have low resistance and can be used at higher voltage and wattage, which allows for inhalation of more aerosol – and therefore inhalation of all its components (nicotine, flavoring, humectants). Such advanced sub-Ohm devices also provide the user with a high degree of control over many features. For example, users can regulate the power and/or temperature limit or even replace the heater coil. The options for liquid refills are tremendously variable (see below), including different nicotine concentrations and flavors.

Fourth Generation E-cigarettes

Fourth generation e-cigarettes, also known as "pods," are sleek with a high-tech design. Within this category, there are three subtypes: devices with replaceable pods, devices with refillable pods, and disposable pod systems. They tend to be significantly smaller than prior generations, easily fitting in the palm of one's hand. These products often resemble common tech objects, such as flash drives, and so are not only easily concealed, but also easily disguised. In place of the refillable tank found in prior generations, the e-liquid in fourth generation models is sold in disposable pods, which contain highly concentrated nicotine in a protonated (nicotine salt) form, rather than the free-base nicotine found in prior nicotine solutions (see liquids, below).

The most popular and well-known of this class is JUUL, which came on the market in 2015. By 2019 JUUL accounted for 73.4% of all e-cigarette sales [23]; its popularity has been associated with the steep rise in current (past month) e-cigarette use among high school students, from 11% in 2017 to 27.5% in 2019 [24]. Other similar products such as Suorin Drop, myblu, and Vuse Alto utilize the same technology. Some pods may be refillable; many pods are sold separately and can be used with JUUL devices. Use of these products (including those that are JUUL imitations) is often called "juuling" rather than "vaping" [25]. On February 6, 2020, a nationwide ban on flavored e-cigarettes (excluding menthol and tobacco flavors) went into effect. However, this ban applies only to cartridge or prefilled pod devices like JUUL. Subsequently, similar refillable products such as Suorin Drop and Smok, left on the market, have become more popular, as have the disposable pod-mod, Puff-Bar [26–28].

Related Vaping Products

Vaporizers are similar to e-cigarettes in that they deliver an aerosol for inhalation through a noncombustible heating process. However, rather than liquid, substances such as loose tobacco, marijuana or other dry herbs, dab wax, and oil are used.

Dab rigs or dab pens are similar to vaporizers in that they are used to heat up highly concentrated wax (marijuana). Dabbing releases highly concentrated THC (see below). E-cigars and e-pipes are similar to e-cigarettes but look like traditional cigars and pipes. Hookah, also known as water pipe, narghile, argileh, shisha, hubble-bubble, and goza, is used for smoking flavored tobacco [29]. Hookah has been used in some cultures for centuries. Traditional hookah is combusted, but some newer electronic hookah devices (e-hookah) have emerged and are gaining in popularity [30]. Components of e-hookah include the head containing flavored solution with or without nicotine, metal body, water bowl, hose, and mouthpiece.

Liquids

Liquids used in e-cigarettes are usually (but not always) composed of nicotine, as well as at least one solvent, usually propylene glycol (PG) and/or vegetable glycerin (VG), flavorings (tobacco, menthol, candy or beverage themed, and more) and additives (e.g., sweeteners or antibacterial agents). As described previously, liquid content, combined with device characteristics, influences the nicotine and toxicant levels in the aerosol that is emitted from the e-cigarette device and inhaled by the user. While prefilled e-cigarettes come with standardized liquid characteristics such as PG/VG ratio and nicotine concentration, open systems accommodate a diversity of liquids with myriad characteristics. Since comprehensive regulation on manufacturing and sale of liquids has not yet been implemented, there are numerous manufacturers and retailers of e-cigarette liquids and a lack of labeling standards. Most liquids are sold commercially; however, some are do-it-yourself (DIY) formulations that users customize from individual ingredients purchased from shops and/or online retailers [31]. Kits (mixing bottles, measuring syringes) and instructions aimed at making the practice easy, and measurements precise, are also widely available online and in vape shops.

Nicotine

The majority of adults and adolescents who use e-cigarettes do so for the purpose of inhaling nicotine, though some use products advertised as nicotine-free. Nicotine is among the most addictive substances, comparable to heroin and cocaine [32]. The amount of nicotine in e-cigarettes is variable, and difficult to quantify for a number of reasons. First, labeling of liquids is inconsistent: Some are marked % per volume (e.g., 2.4%, 3.6%, 5%, 6.5%), others by concentration (mg/ml) [33]. Furthermore, nicotine concentrations in e-liquids may be inconsistent with stated concentrations on the label [34–36]. Finally, the type of product used and the user may impact nicotine delivery [15, 37]. For example, as stated above, increasing the voltage increases nicotine delivery by greater aerosol generation; "dripping," by placing the liquid directly onto the coil, increases the concentration of nicotine received by the user [38]. Some, more experienced e-cigarette users may be able to inhale more efficiently, increasing their nicotine intake [39–41].

Fourth generation e-cigarettes contain the highest nicotine concentrations of all e-cigarettes, from 5% to over 6.5% nicotine per pod [42]. As a point of reference, one 5% pod delivers nicotine approximately equivalent to a pack of cigarettes. Normally such highly concentrated nicotine would be irritating to the user. However, pods usually contain nicotine in a form of salts (protonated). Nicotine salts are lower in pH and consist of nicotine conjugated with a weak organic acid (e.g., benzoic acid, levulinic acid, salicylic acid). The addition of acid in nicotine salts allows manufacturers to greatly increase the concentration of nicotine while apparently

avoiding harshness and bitterness of generated aerosols – and therefore, fourth generation e-cigarettes containing nicotine salts are easier to use compared with the first three generations of e-cigarettes, which contain a free-base form [43]. As of 2020, the availability of highly concentrated nicotine-salt solutions seems to be an increasing market trend.

The steep increase in e-cigarette use among adolescents between 2015 and 2019 has been attributed to their overall appeal, flavors, and advertising [24, 44–49]. However, perhaps another possibility is that the high and easily palatable nicotine content of pod products contributes to their continued usage and promotes symptoms of dependence among regular users, particularly among those who may have never smoked traditional cigarettes [50–52]. While it may be difficult to quantify how much nicotine adolescents are using with e-cigarettes, levels of urinary cotinine, a metabolite of nicotine, may be as high or even higher in adolescents who use e-cigarettes, when compared to those who smoke cigarettes [42, 51]. In one study, more frequent e-cigarette use and use of pods was associated with higher urinary cotinine levels [50]. However, despite pod products' high nicotine content, as many as 40–63% of adolescents may be unaware that their e-cigarettes contain nicotine [44, 53, 54].

Adolescents are particularly susceptible to nicotine dependence and addiction, as evidenced by the fact that in the United States almost 90% of smokers initiate smoking as teenagers, under 19 years of age [32, 55, 56]. This vulnerability is thought to be due to adolescents' immature neural circuits, leading to upregulation of nicotinic receptors in the prefrontal cortex, which prime the brain for nicotine addiction [57–60], and possibly other addictive substances [61]. Studies of adolescent smokers have shown dependence to nicotine with sporadic and even infrequent use, with eventual progression to established addiction [62–64].

Solvents

Propylene glycol (PG) and glycerol (vegetable glycerin; VG) are vaporizing solvents (humectants) used in almost all e-cigarettes [33]. The volumetric ratio of PG and VG can affect the vaporization process in e-cigarettes, nicotine delivery, and the sensory experience among users. For example, higher levels of PG generally result in a stronger sensation on the back of the throat (so-called "throat hit"), whereas higher levels of VG produce more aerosol. Common ratios of VG/PG include 70/30 and 60/40 but can vary depending on the manufacturer and user preference. Both solvents, commonly found in cosmetics, pharmaceutical products, and food, are labeled by the FDA as GRAS (generally recognized as safe) when used in approved levels topically or for ingestion. The GRAS classification does not apply to inhalation, however. Robust data on the effects of inhaled PG and VG are limited, but both substances are known to be respiratory irritants. When heated, PG and VG may lead to the formation of carcinogenic carbonyl compounds (formaldehyde, acetaldehyde, acrolein) [33, 65, 66]. Liquids with higher VG

proportions may lead to the formation of more oxygen radicals than liquids with a larger proportion of PG [19, 67].

Flavorings and Sweeteners

There are over 15,000 e-cigarette flavors, even though some states have implemented total or partial restrictions on sale of flavored e-cigarettes since early 2020. Flavors are extremely common among e-cigarette users and are often named as a primary reason for their use. In liquids, flavor combinations are common, and their classification is not straightforward. Commonly marketed flavors include tobacco, mint/menthol, fruits/candy (grapes, mango, melon, strawberry, apple, peach, berry), crème/butter cinnamon, cheesecake, coffee/tea/chocolate, alcoholic beverages, and nonidentifiable flavor varieties (e.g., "Dark Side of the Moon", "Cosmopolitan"). Data from 2020 indicate that among high school students in the USA who currently used any type of flavored e-cigarettes, the most commonly used flavor types were fruit (73.1%); mint (55.8%); menthol (37.0%); and candy, desserts, or other sweets (36.4%) [68]. Among middle school students who currently used any type of flavored e-cigarettes, the most commonly used flavor types were fruit (75.6%); candy, desserts, or other sweets (47.2%); mint (46.5%); and menthol (23.5%) [68]. Underlying these flavors are particular chemicals or classes of chemicals that are used to impart a taste or odor (e.g., vanillin, limonene, isoamyl alcohol), some of which have known respiratory toxicity (e.g., diacetyl, cinnamaldehyde). As with PG and VG, many flavors are classified as GRAS for ingestion, but not for inhalation. While a lot is still unknown about the health effects of inhaling flavors, certain flavors are known to be toxic. Diacetyl (2,3-butanedione) came to attention when factory workers who inhaled diacetyl developed bronchiolitis obliterans, or "popcorn lung." Similar substances (diketones such as 2,3-pentanedione, 2,3-hexanedione, and 2,3-heptanedione) have been used in the place of diacetyl but may be just as toxic to lung tissue [69, 70]. Cinnamaldehyde, responsible for cinnamon taste, has been shown to be cytotoxic and genotoxic, with adverse effects on cell processes and cell survival [71, 72]. Saccharides and other sweeteners, found in sweet liquids, produce aldehydes and furans when heated [73].

Other Toxicants Emitted from E-cigarettes

In addition to the toxicants produced by aerosolization of flavorings, humectants, and other liquid components detailed above, e-cigarettes have the capacity to deliver numerous toxicants formed during heating and aerosolization, as chemical reactions may result in the formation of new harmful compounds. Specifically, at temperatures within the range of most e-cigarette products (150°–350 °C), formaldehyde, acetaldehyde, and acrolein have been detected at levels related to cancer and

cardiovascular disease [66]. Heavy metals, such as tin, lead, and nickel, have also been discovered in e-cigarette aerosols [74–76]. Benzene and other toxic solvents (toluene, xylenes, and styrene) may be present in e-cigarettes because of their use as solvents for nicotine extraction from tobacco leaves or decomposition of flavorings during vaporization processes [77–79]. Traces of carcinogenic tobacco-specific nitrosamines have been detected in liquids and aerosols mostly due to the extraction processes of nicotine from tobacco leaves or the addition of tobacco flavorings [80, 81]. Additionally, concerns have been raised about potential contamination of liquid by phthalates, organophosphate flame retardants, and pesticides for which respiratory safety has not been routinely evaluated [82].

Cannabis Vaping Products

Nicotine and cannabis share a common route of administration (inhalation by smoking or vaping), and many devices used to deliver these substances are identical. Although many states have decriminalized cannabis-derived products, products containing tetrahydrocannabinol (THC) or a mixture of cannabinoids are still classified as Schedule 1 substances under the United States Drug Enforcement Agency Controlled Substances Act [83]. However, products that only contain cannabidiol (CBD) are promoted and marketed without restrictions based on a claim that CBD-only products are derived from hemp, and not from cannabis.

While e-cigarettes have become highly effective in delivering nicotine, population-based studies have shown that these products have also been used to vaporize other psychoactive substances, including THC and CBD; indeed, the use of e-cigarette devices to vape cannabinoids has become increasingly common among adolescents [84]. A 2015 study found that 19% of 18- to 24-year-old ever cannabis users had vaped cannabis products, including oils, tinctures, concentrates, wax, and dried leaves [85]. More recent studies have found that 10% of high school students overall and 14% of 12th graders vaped cannabis [86, 87]. Vaping devices used for inhaling cannabis or hemp-derived liquids generally consist of the same elements and function in the same way as those products used for vaping nicotine. However, liquids containing cannabis and hemp extract are often more viscous than nicotine-containing products. Although PG and VG are commonly used solvents for cannabis extracts, highly concentrated solutions of THC and CBD sometimes contain oily (lipophilic) solvents like vitamin E acetate, medium-chained triglycerides, and coconut oil. Inhalation of oil-based ingredients used in THC vaping products has been suggested as potential cause of the e-cigarette or vaping associated lung injury (EVALI) outbreak in mid-2019 [88–90] (see Chap. 4). “Dabbing” refers to a more traditional practice of heating a highly THC-concentrated cannabis wax on a nail and directly inhaling the aerosol; now vaping devices are designed and marketed specifically for “dabbing.” Additionally, e-cigarettes not intended to be used with THC may be “hacked” by teens, by adding THC to prefilled or refillable reservoirs [91].

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Chapter 4
Acute and Chronic Health Effects of E-Cigarette Use

Ana Lucia Fuentes and Laura E. Crotty Alexander

Introduction

Electronic cigarettes (e-cigarettes), first became widely available in the United States in 2007 and were initially marketed without evidence as a safer alternative to conventional smoking. However, over the last several years, the harmful effects of these devices have risen to prominence. Although the effects of long-term, chronic use are not yet known, vaping has been associated with acute and subacute effects on virtually every organ system in human users. In addition, animal models of chronic use have detected numerous effects across the body, making it highly likely that long-term use of vaping devices will cause effects both similar to and disparate from those of conventional tobacco.

EVALI

The emergence of e-cigarette or vaping product use-associated lung injury (EVALI) rapidly changed the narrative of e-cigarettes and vaping in general. EVALI was recognized as a new and unique disease entity in the summer of 2019. More than 2000 cases have required hospitalization and more than 50 deaths have been attributed to EVALI [1]. These numbers underestimate of the number of e-cigarette users affected, as EVALI cases and outcomes stopped being consistently tracked due to the global SARS-CoV-2 pandemic.

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S. C. Walley, K. Wilson (eds.), *Electronic Cigarettes and Vape Devices*,
https://doi.org/10.1007/978-3-030-78672-4_4

Clinical Presentation

EVALI most commonly presents with a combination of respiratory, gastrointestinal, and systemic (fever and fatigue) symptoms. Based on the largest case series of EVALI patients, the most common findings are hypoxemia, tachycardia, and tachypnea [2]. Laboratory findings most often include leukocytosis, elevated inflammatory markers (erythrocyte sedimentation rate and c-reactive protein), and transaminitis (Table 4.1). Bilateral infiltrates including ground glass opacities are seen by X-ray and CT imaging [2]. Presentation varies dramatically, based on disease severity. Mild cases can often be managed in the outpatient setting, while severe cases often require an intensive care unit admission with invasive mechanical ventilation or even extracorporeal membrane oxygenation (ECMO) [1].

Mechanism of Injury

The mechanism by which lung injury occurs in EVALI is incompletely understood, but has been linked to vitamin E acetate (VEA) in cannabinoid containing vaping liquids [3]. It is likely that multiple variables contribute to pathogenesis. Most patients use multiple devices, which are made up of different materials and set to different configurations [1]. The vaping liquids themselves also vary, with different active agents (THC, nicotine, etc.), solvents, and flavorants. All of these variables play a role in absorbability and mechanism of injury, making research in this area challenging.

Nonetheless, there are multiple hypotheses for the mechanism underlying EVALI, two of which are described in detail by Crotty Alexander et al. [3]. The first postulates that chemicals within the vaping aerosols are directly cytotoxic to lung epithelial cells. This cytotoxicity leads to cell death, alveolar damage, and acute respiratory distress syndrome (ARDS), all of which are often seen in

Table 4.1 Overview of the presentation, evaluation, and treatment of EVALI

Clinical presentation of EVALI	
Symptoms	Respiratory – shortness of breath, cough, chest pain Gastrointestinal – nausea, vomiting, abdominal pain, diarrhea Systemic – fevers, chills, weight loss, fatigue
Vital signs	Hypoxemia Tachycardia Tachypnea
Laboratory	↑ WBC ↑ CRP and ESR ↑ AST and ALT
Radiology	Bilateral ground glass opacities Pneumothorax Pneumomediastinum
Treatment	Supportive treatment Consider glucocorticoids

EVALI. Alternatively, the second hypothesis advocates for a "two hit phenomena." In this thought process, the inhalation of these chemicals does not cause direct cytotoxicity. Rather, they cause an alteration of the inflammatory state of the lungs, leading to the release of inflammatory cytokines and causing pro-inflammatory changes to alveolar macrophages. At this point, the lung is primed so that a second insult to the lung (i.e. a new inhalant or infection) will lead to a pathologic inflammatory response, ultimately resulting in EVALI.

As of November 2020, vitamin E acetate remains the prime suspect as the causal agent, as it has been identified in e-liquids and bronchoalveolar lavage (BAL) samples from EVALI patients [3, 4].

Treatment and Outcomes

The primary treatment in EVALI is supportive care and cessation of vaping and dabbing. Steroids can also be considered, given benefits seen in case reports [5–9]. Long-term outcomes are not yet known, and studies including lung function and imaging are ongoing to determine whether lung damage is permanent. However, given documented cases of relapsed disease with recurrent vaping, a focus on vaping cessation is warranted [5–9].

Impact on the Pulmonary System

Vaping devices work by heating and aerosolizing a liquid compound made up of lipophilic carriers (propylene glycol and vegetable glycerin), chemical flavorants, tetrahydrocannabinol (THC), and/or nicotine. The combination of these chemicals has been associated with detrimental effects to the lung including interstitial lung diseases (ILDs), ARDS, and diffuse alveolar hemorrhage (DAH) [10–13]. Inhalation of e-cigarette aerosols has also been linked to exacerbation of preexisting lung diseases, specifically asthma and chronic obstructive pulmonary disease (COPD) [14, 15].

Conventional cigarette smoking is well known to cause multiple forms of ILD [2]. This is thought to be due to the strong inflammatory stimulus induced by cigarette smoking, leading to the recruitment of macrophages, inflammatory cytokines, and tumor necrosis factor (TNF) to lung tissue [10]. Studies have shown that vaping leads to similar cytokine stimulation (IL-6 and IL-8) and inflammation, thereby providing a mechanism by which e-cigarettes may induce specific ILDs, such as eosinophilic pneumonia and hypersensitivity pneumonitis [10, 11]. Meanwhile, it is thought that components in the liquid compound, specifically propylene glycol, lead to irritation, and inflammatory reactions ultimately causing lipoid pneumonia. Various case reports have implicated e-cigarettes as the causative factor in the development of various subtypes of ILD, including eosinophilic pneumonia, hypersensitivity pneumonitis, lipoid pneumonia, and diffuse alveolar hemorrhage [15–18].

Additionally, vaping has been implicated in other severe forms of lung injury, including ARDS and DAH [20]. Thus, both smoking and vaping cause a variety of ILDs.

E-cigarette use has also been shown to play a role in asthma, COPD, and bronchitis, with inhalation of vaping aerosols leading to worsening airway obstruction and increased airway hyperresponsiveness in individuals with mild asthma [17]. Meanwhile, other studies have shown that e-cigarette users were approximately twice as likely to have COPD. Recent animal data have shown that chronic inhalation of e-cigarette aerosols directly damages pulmonary structures, leading to emphysematous changes in animal lungs [16, 17]. Finally, e-cigarettes have also been shown to cause immune system depression, associated with increased risk of the development of chronic bronchitis [19].

Impact on Sleep Health

E-cigarette use, much like traditional cigarette use, has a detrimental effect on sleep health. This has been demonstrated through several studies, although it is not yet clear if this is due to the stimulant effects of nicotine, or if it has a separate mechanism of action. One group surveyed more than 1500 college students, half of whom were current e-cigarette users. They found that current users reported more sleep difficulty, as well as greater use of sleep medication than nonusers [21]. Similarly, a retrospective cross-sectional study involving 2889 participants found that e-cigarette users had decreased sleep duration when compared to nonusers. Finally, a small social media-based survey study found that dual use of e-cigarettes with conventional tobacco increased sleep latency [22]. These data confirm that e-cigarettes adversely impact sleep, but more work remains to be done to differentiate the role of nicotine vs other e-liquid components (i.e., THC).

Impact on the Cardiovascular System

E-cigarette exposure has also been shown to have negative effects on the cardiovascular system[3]. Studies have shown several different mechanisms by which this may occur including direct cytotoxicity, platelet dysfunction, oxidative stress, and endothelial dysfunction [23–25]. All of these can potentially lead to vascular injury and are strongly associated with cardiovascular compromise.

The majority of studies have been done using animal models; however, there are associations that have been identified in humans. For example, a large cross-sectional survey of more than 50,000 adults found that daily e-cigarette use was associated with myocardial infarction (MI), with an odds ratio of 1.7 for e-cigarette users relative to nonusers of e-cigarettes [26]. Although this is certainly not

causation, it is a starting point for future prospective epidemiologic studies and may be explained by the mechanisms stated above.

Additionally, e-cigarette use has been associated with hemodynamic changes, affecting cardiac physiology. Yan et al. showed that e-cigarette use resulted in an increase in heart rate and systolic blood pressure, albeit these changes were noted in the short-term, as vitals were taken only 20 minutes post vaping. Other studies have shown similar effects on hemodynamics, as well as an overall increase in sympathetic predominance [27–29].

The effects of chronic e-cigarette use have not been well established due to the lack of long-term studies. However, there are multiple animal studies that have been published which can give us insight. Olfert et al. used mouse models to show that exposure to e-cigarettes over a period of 8 months leads to increased aortic stiffness [27]. Crotty Alexander et al. showed increases in systolic blood pressure and cardiac fibrosis in mice similarly exposed to e-cigarette aerosols [28]. Finally, Espinoza-Derout et al. use mouse models to demonstrate a decrease in ejection fraction and left ventricle shortening in mice exposed to e-cigarette aerosols [29]. Ultimately, these findings demonstrate the mechanisms by which chronic e-cigarette exposure negatively impacts cardiovascular health.

Impact on Oncogenesis

Currently, there is no epidemiological data on the association of e-cigarette use and human cancer. However, research has demonstrated that e-cigarettes play a role in cell damage and repair mechanisms, both of which can ultimately lead to cancer. One study found that e-cigarette aerosol induces DNA damage in several mouse organs, including the lungs, bladder, and heart. They also found that DNA repair functions and proteins were significantly decreased in the lungs [30]. Meanwhile, Tang et al. found that mice exposed to e-cigarettes for a prolonged period of time (54 weeks) developed lung adenocarcinoma and bladder urothelial hyperplasia, which is extremely rare in mice exposed to filtered air [31]. Although these studies are based on mouse models, it is plausible that these same mechanisms affect humans in a similar fashion. Because of this, numerous organizations, including the American Cancer Society and Forum of International Respiratory Societies, recommend against using e-cigarettes, as their potential for harm outweighs any possible benefit [32].

Impact on the Renal System

E-cigarette aerosol has also been shown to cause negative effects on the kidneys, which is not surprising given the well-known toxicity of nicotine and conventional tobacco smoke. In mouse models, daily inhalation of these e-cigarette aerosols has

been shown to lead to kidney fibrosis, likely due to the activation of profibrotic pathways systemically [28]. Additionally, one study showed that intraperitoneal exposure to e-liquids leads to oxidative stress and alteration of the renal collecting ducts. Ultimately, more work needs to be done to further elucidate the effects of e-cigarette use on human kidneys.

Impact on Oral Health

E-cigarette use has also been found to have an impact on oral health, as well as the oral microbiome. Sundar et al. found that much like its effects on the lung, e-cigarettes induce inflammatory cytokine release and oxidative damage in periodontal cells, leading to pathologic changes in the oral cavity. Additionally, survey data that included over 20,000 participants found that those who used electronic nicotine products were at increased odds of being diagnosed with gum disease, despite controlling for conventional cigarette smoking. They also found that these participants have increased odds of having bone loss around teeth, further supporting the relationship between e-cigarettes and periodontal disease [34].

In regards to the oral microbiome, Pushhalkar et al. found that e-cigarette use increased the abundance of specific bacteria in the oral microbiome, leading to dysbiosis in microbial communes. This dysbiosis is associated with increases in the inflammatory response, evidenced by cytokine release [35]. This can have profound effects on the oral microbiome that may extend down to the respiratory tract. More remains to be studied on the long-term effects of this dysbiosis and the potential health risks it can cause.

Impact on Addiction

The negative effects of nicotine have been well studied in conventional cigarette smoking. It is known that prolonged smoking leads to physiologic dependence and behavioral compulsion [33]. This occurs due to the rapid absorption of nicotine through the blood brain barrier and binding to nicotinic acetylcholine receptors, which are believed to play a primary role in nicotine addiction [33]. Inhalation of e-cigarette aerosols generated from different devices and e-liquids has been proven to activate addiction pathways within the central nervous system. When e-cigarettes emerged on the market, many were hopeful that they would play a role in tobacco cessation. Unfortunately, they have been linked with numerous detrimental effects, as detailed above. Additionally, multiple randomized control studies, as well as observational studies, have shown that they are not beneficial in the treatment of nicotine or tobacco dependence [36, 37].

It is important to note that nicotine concentration varies dramatically amongst e-liquids. One cartridge of e-liquid can contain up to 200 puffs, which contains the

nicotine equivalent of three packs of cigarettes [38]. Different devices, temperatures, and Wattages applied can lead to higher levels of nicotine in the aerosols generated. Although nicotine absorption is also dependent on vaping frequency and volume, higher concentrations place vapers at risk for the addictive effects of nicotine. Adolescents and young adults in whom brain development is ongoing are more sensitive to the additive effects of nicotine, and addiction during brain development predisposes to altered responses to addictive substances as an adult.

Conclusion

E-cigarette use is known to cause adverse health effects, particularly in the acute and subacute setting. Although the long-term effects are not yet known, there is sufficient *in vitro, in vivo,* and *ex vivo* evidence to conclude that vaping is detrimental to overall health.

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Chapter 5
Health Effects of E-Cigarettes and Other Vaping Devices on Non-users

Joseph M. Collaco and Sharon A. McGrath-Morrow

Introduction

The health effects of combustible tobacco products on non-users have been reported as early as the 1970s [1, 2] and have been associated with premature death and disease in non-smoking children and adults. These health effects include sudden infant death syndrome (SIDS), acute respiratory infections, otitis media, more severe asthma, slowed lung growth, cardiovascular disease, and lung cancer [3]. Although research regarding the health effects of electronic cigarettes and other vaping devices on non-users is still in a nascent phase, it is not unreasonable to hypothesize that these exposures, similar to conventional tobacco exposure, would have some detrimental health effects. Although sidestream electronic cigarette exposures are considered minimal, exhaled emissions from the users of electronic cigarettes and other vaping devices can contain harmful chemicals that can be absorbed through the respiratory tract and skin of non-users [4]. In this chapter, we discuss the science behind secondhand exposures to electronic cigarettes and other vaping devices, groups experiencing secondhand exposure, effects on various organ systems, regulations protecting non-users, non-inhalational exposures, and the potential for thirdhand exposure.

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S. C. Walley, K. Wilson (eds.), *Electronic Cigarettes and Vape Devices*,
https://doi.org/10.1007/978-3-030-78672-4_5

Secondhand Exposure Potential

Although frequently incorrectly described as harmless "water vapor," the emissions from electronic cigarettes and other vaping devices are actually a complex mixture of aerosols, volatile organic compounds, and particulates [5]. For breath-actuated devices, a significant source of emissions is exhaled from the primary user. Particle modelling suggests that 7–18% of particles remain in the user's alveoli and 9–19% are absorbed into the user's blood, but 73–80% are exhaled [6]. In contrast, pharmacokinetic studies suggest that the rates of retained nicotine and vaping carrier liquids by the primary user range from 84% to 94% [7]. Nevertheless, measurements of air nicotine and particle concentrations do detect levels higher than that of background, albeit less than those associated with conventional cigarettes [8]. These emissions can result in significant absorption in exposed non-users. Levels of salivary and urinary cotinine (a nicotine metabolite) in non-using adults residing with an electronic cigarette user have been found to be similar to those found in non-users residing with conventional smokers [9]. Additionally, indoor air monitoring from a vape convention reported found that electronic cigarette emissions were a major source of PM_{10} particles, total volatile organic compounds, and air nicotine levels [10].

Secondhand Exposure Groups

Health effects from secondhand exposure to electronic cigarettes and other vaping devices may vary throughout the lifespan. Fetuses are subject to maternal use and potential use by others who vape around pregnant women. Rates of electronic cigarette use during pregnancy have been reported to range from 1% to 15% in the United States [11]. Infants and young children are primarily exposed to parental use and may be at higher risk for thirdhand exposure as described below due to their propensity to touch or lick a variety of surfaces. Nearly 5% of US adults living with children use electronic cigarettes suggesting that up to 5% of children may be exposed to emissions in the home setting [12]. Non-using adolescents and young adults are subject to exposure from peer use, and may be at higher risk for initiating use compared to individuals whose peers do not use. A national (US) survey from 2017 suggest that a quarter of youths are exposed to secondhand emissions, and youth use has increased since that time [13]. Finally, non-using adults may be exposed within the workplace depending on local regulations or in the home if they reside with a user. In general, exposures in early life may carry more significant long-term consequences for developing organs compared to similar exposures in adults.

Health Effects of Secondhand Exposure

Prenatal Exposure: Data in humans regarding the health effects to fetuses of maternal use/exposure to electronic cigarettes and other vaping devices are sparse. Effects are extrapolated from animal studies, predominantly murine, and appear to affect multiple organ systems. These effects may occur through direct end organ effects or through effects on the placenta [14]. Additionally, the presence or absence of nicotine in the electronic cigarette can alter the health effects as nicotine can independently adversely affect the developing nervous, respiratory, immune, and cardiovascular systems [15]. Some of these effects could potentially be intergenerational as studies have demonstrated epigenetic effects in mice exposed to electronic cigarette emissions prenatally [16, 17]. *Growth:* Several studies have demonstrated decreased weight in mice exposed to electronic cigarette emissions prenatally suggesting an effect on somatic growth [18–20]. In contrast, limited human data have been mixed regarding the effects of electronic cigarettes on fetal growth. One study of 218 women in Ireland found no difference in birth weight for infants born to electronic cigarette users versus mothers who did not use [21]. Another US-based study of 248 pregnant women found 5.1-fold increased risk of small-for-gestational-age births for women who used electronic cigarettes solely compared to non-users [22]. *Neurocognitive:* Mice that are prenatally exposed to electronic cigarette emissions have been demonstrated to show increased hyperactivity and changes in anxiety-related behaviors, which may be related to neuroimmunological alterations, perhaps mediated through nicotine [16, 23, 24]. *Respiratory:* Prenatal exposure to electronic cigarettes in a mouse model has been demonstrated to result in altered lung architecture with larger airspaces, perhaps mediated through an observed downregulation of genes involved in the Wnt signaling pathway associated with lung organogenesis [25]. *Gastrointestinal:* Maternal mouse exposure while pregnant and lactating to non-nicotine e-cigarette emissions has resulted in hepatic injury in the not directly exposed offspring, whereas nicotine-containing emissions resulted in hepatic steatosis in the adult offspring [26]. *Other:* In vivo craniofacial models (Xenopus) and mammalian neural crest cell lines demonstrate that prenatal electronic cigarette exposure could result in midline facial clefts and midface hypoplasia [27].

Respiratory Effects: The lung is uniquely susceptible to secondhand exposure from electronic cigarettes and other vaping devices due to the inhalational nature of the exposure. Health effects have been described in both the developing lung and in individuals with underlying lung disease. *Postnatal lung development:* One study of neonatal mice demonstrated that exposure to nicotine-containing electronic cigarette emissions led to diminished alveolar cell proliferation and a modest impairment in postnatal lung growth [20]. These findings include increased airspace size

with e-cigarette exposure similar to prenatal exposure as mentioned above. *Asthma:* Secondhand exposure to electronic cigarettes has been associated with an increased risk (adjusted odds ratio: 1.27) of an asthma exacerbation in adolescents with asthma [28]. In addition, flavoring of vaping solutions may also impact bronchoreactivity of immature airways; one in vitro study of ovine bronchial rings found bronchodilation occurring with exposure to non-nicotine-containing solutions of common flavors, such as menthol, strawberry, tobacco, and vanilla [29]. *Hypersensitivity pneumonitis:* Electronic vaping lung injury (EVALI) has been reported in primary users with a variety of pneumonitis presentations often, but not exclusively, associated with vitamin E acetate or tetrahydrocannabinol [30, 31]. There is at least one case of an adult with a prior history of bronchopulmonary dysplasia presenting with hypersensitivity pneumonitis after secondhand exposure in the home setting, suggesting that in a susceptible host, secondhand emissions can lead to EVALI-like presentations [32]. *Airway clearance:* Cough and throat-respiratory irritation have been reported in adults exposed to electronic cigarette emissions in a controlled setting [33]. Some of these chronic respiratory symptoms may be mediated by reduced mucociliary clearance (MCC) as at least one murine study has demonstrated a decrease in clearance with chronic exposure to nicotine-containing electronic cigarette emissions [34]. Another study examining the effects of nicotine e-cigarette emissions on MCC in human bronchial epithelial cells and sheep trachea found that nicotine e-cigarette vapors impaired MCC through inhibition of the TRPA1 receptors [35]. Of note, mice exposed to electronic cigarette emissions have been shown to have decreased pulmonary clearance of *Streptococcus* after intranasal infection [36].

Immunological Effects and Infections: Secondhand smoke exposure has been associated with an increased frequency of respiratory infections in children [3], and it is possible that secondhand exposure to electronic cigarettes and other vaping devices could have similar effects, but direct human data are limited. *Respiratory infections:* Exposure to electronic cigarette emissions, independent of nicotine content, has been found to lead to downregulated innate immunity and increased lung injury and mortality with influenza in mice [36, 37]. Human airway epithelial cells from non-smokers in vitro have been shown to have increased IL-6 production and rhinoviral infection load after exposure to electronic cigarette liquid, both nicotine and non-nicotine containing [38]. Increases in biofilm production and cytokine secretion have been seen in airway cell models with pathogenic bacteria (*Haemophilus influenzae, Streptococcus pneumoniae, Staphylococcus aureus,* and *Pseudomonas aeruginosa*) after exposure to electronic cigarette emissions [39]. *Microbiome:* A pilot study of smokers, electronic cigarette users, and non-using controls found changes in the gut microbiome of smokers compared to controls, but not between electronic cigarette users and controls [40]. In contrast, some studies have reported detrimental changes to the oral microbiome with electronic cigarette use [41, 42], but one study did not [40]. There are no published studies on whether non-users experience any microbiome changes with secondhand exposure to electronic cigarettes.

Neurocognitive Effects: Multiple studies have demonstrated the effects of nicotine exposure on neurocognitive outcomes [15]. However, data concerning the neurocognitive effects of secondhand electronic cigarette exposure are limited. One murine study found that a combination of prenatal and early-life postnatal exposure resulted in durable changes in adult behavior, specifically increased "hyperactive" behaviors [43]. This may be mediated through changes in gene expression in the frontal cortex [44].

Cardiovascular Effects: The use of electronic cigarettes on cardiovascular health over the long term is unknown, but multiple studies have demonstrated at least temporary changes in pathways related to oxidative stress, inflammation, vascular dysfunction, and thrombogenesis with primary use [45]. Data on the cardiovascular effects of secondhand exposure are extremely limited. Of note, use of electronic cigarettes has been associated with acute increases in heart rate and blood pressure secondary to nicotine [46]. Similarly, a crossover study found acute autonomic changes in heart rate variability and Qt_c interval in non-users exposed to electronic cigarette emissions [47].

Malignancy Risk: While secondhand smoke exposure is associated with an increased risk for malignancy [3], evidence is lacking for secondhand exposure to electronic cigarette and other vaping devices due to the limited timeframe of consumer availability to date and lag time associated with many cancers. Overall, the risk may be lower than with exposure to conventional cigarette smoke, but is likely not zero. One respiratory particle deposition model suggests that the malignancy risk associated with secondhand cigarette smoke is five times that of being exposed to secondhand electronic cigarette emissions [48]. Several tobacco-specific nitrosamines biomarkers, mostly notably 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and its metabolite, NNAL, are associated with malignancy, but urinary NNAL concentrations in electronic cigarette primary users are a fraction (1–10%) of those observed in cigarette smokers [49]. Limited data suggest that these carcinogenic compounds can be detected in non-users exposed to secondhand electronic cigarette emissions, but likely at lower levels than if they were exposed to conventional cigarettes [50].

Regulation of Secondhand Exposure

Regulations restricting secondhand exposure to electronic cigarettes and other vaping devices are more limited than those for conventional cigarettes. In 2016, the World Health Organization's Framework Convention on Tobacco Control recommended for signatories to ban indoor e-cigarette use to prevent secondhand exposure [51]. Indoor secondhand exposure may be banned by default in countries that forbid the sale of electronic cigarettes or nicotine-containing electronic cigarettes. Other countries may have nationwide bans for public indoor use, but often banning

of indoor use is by state or locality [52]. In the United States, use of electronic cigarettes on commercial air flights was banned in March 2016 by the Department of Transportation (www.transportation.gov); many other airlines around the world ban their use aboard as well.

Non-inhalational Exposures

Potentially hazardous exposures to electronic cigarettes and vaping devices are not limited to solely inhalational exposures. Analysis of telephone calls to poison centers in the United States and its territories between 2010 and 2018 identified over 17,000 calls reporting exposure to electronic cigarettes or the associated liquid with 64.8% involving a child less than 5 years old [53]. The majority of reported cases involved ingestion (77.5%), followed by dermal (13.0%), inhalational or nasal (10.4%), and ocular exposure (7.1%). Where severity of symptoms was reported, 42.7% did report adverse health effects, including 5.7% with moderate or severe symptoms, and 2 deaths; the most commonly reported symptoms were nausea, emesis, and ocular pain/irritation. At least 11 deaths associated with ingestion of electronic cigarette liquid have been reported in the literature [54]. These deaths are related to unintentional ingestions in young children, and frequently intentional ingestions (likely suicide attempts) in adolescents and adults. Universal child-resistant packaging in the United States as of July 2016 may have led to a decrease in some exposures [53]. Finally, burn injuries have been reported with ignition or explosion of the lithium batteries present in electronic cigarettes and other vaping devices, either with recharging or spontaneously [55, 56]. These injuries are associated with primary users who are carrying the devices in a clothing pocket [56], rather than non-users.

Thirdhand Exposure

Thirdhand exposure can be described as the residual tobacco smoke contamination within a space after smoking has ceased [57]. These residual products may be involuntarily inhaled, ingested, or dermally absorbed [58]. For example, nicotine and cotinine can be detected in infants and their incubators/cribs in a NICU setting (and thus never exposed to secondhand smoke) whose mothers smoke [59]. Likewise, nicotine from hands can be detected in children whose parents are current smokers [60]. With regard to electronic cigarettes, residual nicotine levels after use have been found not to reach background levels until 4 days later for glass and 16 days for terrycloth, suggesting that thirdhand exposure is possible [61]. However, levels of thirdhand exposure with electronic cigarette use are likely lower than that related

to conventional cigarette use [62]. Exposure levels may differ by surface location, and the highest nicotine levels are found on the floor [63], which may be especially problematic for crawling infants. In addition, different electronic cigarette products may carry different levels of risk for thirdhand exposure, dependent on generated particle characteristics [63]. Limited animal data from a juvenile mouse model suggest that thirdhand exposure to electronic cigarettes can result in suppression of brain growth, changes in immune function, and airway hyporesponsiveness [64]. Interestingly enough, some of these changes were also observed in mice with thirdhand exposure to non-nicotine-containing electronic cigarettes. This suggests that non-nicotine components of e-cigarette aerosols, including flavors, may be detrimental to the health of the exposed non-user.

Unintended Consequences

In addition to the health effects from electronic cigarettes and other vaping devices associated with secondhand, non-inhalational exposures, and thirdhand exposures, non-users who reside with e-cigarette users, particularly children, may be subjected to other unintentional consequences. For example, increased expenditures on electronic cigarettes could result in a decrease in other household expenditures, which could adversely affect non-users. Food insecurity has been associated with conventional cigarette smoking, although it should be noted that this relationship may be confounded by socioeconomic status [65]. In addition, adolescents residing in households where parents or older siblings vape are more likely to use electronic cigarettes or other vaping devices than if they were in a non-using household [66]. Also, initial use may also be facilitated by the ready access to such devices within the household [66]. Long-term multigenerational studies of smoking certainly demonstrate an elevated risk of smoking in children of smokers with a 1.7 increased odds ratio in one meta-analysis [66–68].

Conclusion

Although data concerning the health effects of secondhand exposure to electronic cigarettes and other vaping devices in humans are limited, the combination of animal studies, related studies in primary users of electronic cigarettes, and similar studies in those exposed to secondhand tobacco smoke suggest that there is the potential for long-term injury and developmental consequences. Ongoing efforts to raise public awareness of the potential hazards, education for clinical providers, and legislation to restrict secondhand exposure may reduce the health consequences for non-users.

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Chapter 6
Recommendations for Prevention and Treatment of E-Cigarette Use Among Youth in the Clinical Setting

Deepa R. Camenga and Nicholas Chadi

Introduction

Electronic (E-) cigarettes are a rapidly evolving class of tobacco products that can deliver nicotine or other substances through aerosolization. Since their introduction to the US market, e-cigarettes have exponentially increased in popularity among US youth, with 19.6% of high school students and 4.7% of middle school students reporting current use in 2020 [1]. Pediatric healthcare visits are a prime opportunity for youth e-cigarette prevention and treatment [2]. The US Preventive Services Task Force (USPTF) recommends that all primary care physicians provide interventions, such as education or brief interventions, to prevent tobacco use among children and adolescents [3]. Similarly, the American Academy of Pediatrics (AAP) recommends pediatricians screen for e-cigarette use and provide preventive counseling [4]. The USPTF also notes that there is currently insufficient evidence to recommend primary care interventions for youth who already use tobacco [3]. Although data are currently lacking on evidence-based practices for vaping cessation, there is an urgent need for healthcare providers to better understand how to address e-cigarette prevention and treatment during routine clinical practice.

Both the 5As and SBIRT (Screening, Brief Intervention, and Referral to Treatment) frameworks provide useful tools to help guide the clinical approach to vaping [5, 6]. The 5As approach was originally developed by the United States Public Health Service to address cigarette smoking cessation, but it can be applied to all tobacco products, including e-cigarettes. The 5As mnemonic refers to the 5 steps for cessation counseling: *Ask* about tobacco use, *Advise* patients to stop using

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S. C. Walley, K. Wilson (eds.), *Electronic Cigarettes and Vape Devices*,
https://doi.org/10.1007/978-3-030-78672-4_6

tobacco, *Assess* readiness to quit, *Assist* in quit attempt, and *Arrange* for follow-up [5]. SBIRT is defined by the Substance Abuse and Mental Health Services Administration as a comprehensive approach to the delivery of early intervention for risky substance use and timely referral to more intensive treatment for those who have substance use disorders [6]. Both the 5As and SBIRT frameworks contain steps for screening, counseling, and formulating a treatment plan, and either approach can be used to systematically address youth vaping in clinical practice [7].

This chapter provides recommendations for the prevention and treatment of e-cigarette use among youth in clinical settings. Clinical strategies for screening, counseling, and treatment will be reviewed, as informed by expert guidance and the adaptation of evidence-based clinical strategies for youth cigarette and marijuana smoking prevention and treatment.

Screening

Current data suggest that many pediatric healthcare providers do not routinely screen for use of e-cigarettes [2, 8]. However, screening provides an important opportunity to detect tobacco use early and provide essential health information and intervention. Screening for e-cigarette use should occur in primary care during routine preventive visits, during visits with mental health or behavioral health specialists, and as part of universal or selected screening in inpatient and emergency department settings.

Screening for tobacco use should include questions about both combustible tobacco products and e-cigarettes. The AAP recommends that screening for tobacco use starts around age 11 or 12—when many youths enter middle school. Screening should occur in a confidential manner, wherein the adolescent is asked about tobacco and e-cigarette use without the parent present. All healthcare providers who care for adolescents should be familiar with the state-specific and federal minor consent laws relevant to substance use. Healthcare regarding substance use may be considered confidential, meaning that the adolescent can consent to their own care and the relevant healthcare information is protected under state or federal privacy laws [9]. Providers are more likely to ask about tobacco use and adolescents are more likely to answer questions honestly with the assurance of confidentiality [10, 11].

Screening for e-cigarette use can be incorporated into general validated substance use screening instruments, such as the Car-Relax-Alone-Forget-Friends--Trouble (CRAFFT, available at https://crafft.org/get-the-crafft/) version 2.1 + N, Screening to Brief Intervention (S2BI, available at https://www.drugabuse.gov/ast/s2bi/#/) or Brief Screener for Tobacco, Alcohol or Other Drugs (BSTAD, available at https://www.drugabuse.gov/ast/bstad/#/) [12–15]. These screening instruments can be interviewer-administered or self-administered via written or electronic forms. Because e-cigarettes are comprised of a variety of products with many different names and adolescents generally do not view e-cigarettes as a type of tobacco product, screening questions should include e-cigarette specific terminology such as

"vaping" or "JUULing," or names of different product types/commercial brands, such as "vape pens," "vapes," or "JUULs" to accurately ascertain e-cigarette use. Ideally, adolescents should be screened for e-cigarette use at least once a year and at any time they present with an illness or injury that may be exacerbated or caused by vaping (e.g., lower respiratory tract symptoms). In emergency or inpatient settings, the provider should consider specifically screening for e-cigarette use if the adolescent drinks alcohol or uses any other tobacco products or drugs, as e-cigarette use is associated with other substance use [16–18].

Responding to a Negative Screen

If an adolescent does not report past use of e-cigarettes, healthcare providers can provide anticipatory guidance to reduce future risk of initiation. Providers can ask adolescents what they have heard about e-cigarettes or vaping, provide information to correct any misperceptions, and advise about the negative health effects of e-cigarette use. Additionally, providers should stress that remaining tobacco/e--cigarette-free is the healthiest choice. Adolescents may feel that "everyone vapes." Although a sizable minority of teens have tried e-cigarettes, the majority of teens do not report current e-cigarette use [19]. It also may be helpful to remind adolescents that it is, in fact, socially normative *not* to vape and to help teens find ways to say *no* to vaping.

Clinical Approach to Counseling the Adolescent Who Vapes

Detailed E-Cigarette Use History

If an adolescent reports a history of e-cigarette use, the provider should take a detailed e-cigarette use history to obtain the necessary information that would guide further counseling and treatment (see Table 6.1). Recognizing that providers may have limited time in the office, at a minimum, an assessment of vaping frequency and e-liquid content should be assessed: Topics that should be covered include the following:

- *Vaping frequency:* Whereas cigarette smoking is often quantified by assessing cigarettes/smoked per day, a standard clinical measure to assess the intensity of vaping currently is not available. One approach to characterize the frequency of vaping is to first assess how often the adolescent vapes per month or week; and if the patient reports daily vaping, characterize how many times per day they vape. To characterize whether the adolescent has a habitual pattern of daily use, the provider may consider asking how many times the adolescent vapes on the days they do use e-cigarettes. It is also possible to assess how many disposable

Table 6.1 Sample questions to ask during the detailed e-cigarette use history[a]

Questions	Rationale
Vaping frequency[b]*:* How many days do you vape per week/month? On days that you vape, how many times do you vape/day?	Understanding the context in which youth vape can help providers offer effective cessation counseling. Frequent use throughout the day places youth at risk for developing withdrawal symptoms.
E-liquid content[b]*:* What type of cartridges or liquids do you put in your vape? What is the nicotine concentration of the e-liquid? What flavors do you use? Do you ever vape tetrahydrocannabinol (THC) or cannabidiol (CBD)? What concentration of THC do you use?	Vaping nicotine and THC place youth at risk for nicotine and cannabis use disorders; higher concentration cartridges may be associated with greater risk of developing dependence. Vaping THC may also be associated with EVALI.
Cartridges/refills: How long does a cartridge last you? How many cartridges do you go through in a typical week? If not using cartridges, how often do you refill your vaping device?	More frequent use places youth at risk for dependence and withdrawal.
Brands: What type and brand of vape do you use?	Although data are still emerging, preliminary reports suggest that illicit market products may be associated with lung injury and other vaping-related harms.
Access/obtaining products: Where and how do you obtain your cartridges or vaping liquid? Do they come from a legal source (i.e., a store), or were they produced and sold in the illicit market?	
Dependence/craving/withdrawal: How long after you wake up do you start vaping? Are you vaping at school and/or work, and if so, are you doing so regularly throughout the day? What happens if you stop vaping? Do you experience cravings (a strong feeling that you want to use again)? If vaping nicotine: Do you develop symptoms of nicotine withdrawal (i.e., irritability, depressed mood, difficulty concentrating, feeling restless, increased appetite)? If vaping THC: Do you develop symptoms of cannabis withdrawal (i.e., anxiety, hostility, difficulty sleeping, low appetite, depressed mood)? Have you had episodes of persistent vomiting? Paranoia? Psychotic symptoms like hearing voices or seeing things that are not really there?	

Table 6.1 (continued)

Questions	Rationale
Vaping initiation and motivation When and at what age did you start vaping? Why did you start? Why do you continue to vape? What are some downsides of vaping for you?	Early onset of substance use is associated with greater lifetime risk of substance use disorder. Motivations for initiating and continuing vaping can help inform cessation counseling.
Quit attempts: Have you tried quitting on your own?	Cessation attempts are likely to be hampered by cravings and withdrawal. For nicotine, these symptoms can be reduced with pharmacotherapy.

[a]Adapted from Hadland SE, Chadi N (2020) [7]; [b]High yield-questions

e-cigarettes, cartridges, or pods are used per week or how often the vaping device is refilled.

- *Type of e-liquids used*: The provider should assess the flavors and nicotine concentration used in the e-cigarette device and whether tetrahydrocannabinol (THC) or other substances are vaped. Some adolescents are unsure of the nicotine concentration of the e-liquids they use or believe they are vaping nicotine-free e-liquids [20, 21]. However, the majority of e-liquids consumed by youth contain some nicotine, and popular device types, such as pod systems, may contain high-concentration salt-based nicotine, which has been shown to decrease the harshness and increase the palatability of the e-liquid [22]. Given these misperceptions about nicotine-containing e-cigarettes, the provider may consider calculating the amount of nicotine consumed by identifying the product used and nicotine concentration online during the visit. Of note, some e-liquid manufacturers may report nicotine concentrations as percentages, whereas others report the concentrations as mg/ml [23]. It therefore may be helpful to educate the adolescent and their family that each percentage point is equal to at least 10 mg/ml of nicotine, so a nicotine concentration of 3% would be around 30 mg/ml or more of nicotine. Additionally, it may be helpful to compare the nicotine contained in e-cigarettes and traditional cigarettes by explaining that the tobacco industry has reported that a 0.7 ml pre-filled nicotine-containing e-liquid pod with a concentration of 3% to 5% is roughly equivalent to the nicotine contained in 1 pack of traditional cigarettes [23].

If the visit allows for a more extensive history to be taken, the provider should obtain additional history to better characterize the types of products used and how the adolescent obtains them:

- *Device type:* Providers should ask what type and brand of e-cigarette product the adolescent uses. Recognizing that there are thousands of brand names associated with e-cigarette products, the provider may have to search the internet to determine the characteristics of the brand name product. E-cigarette device types include disposable e-cigarettes, vape pens, pod systems, and mods or advanced personal vaporizers. Heat-not-burn devices are tobacco products that heat

tobacco at lower temperatures than combusted cigarettes, producing a "smoke" [24]. These devices form a separate category of tobacco products and are not usually considered vaping devices. Providers should ask if more than one device type is used by the adolescent as they may use different device types in different settings (e.g., a pod system at school and a mod at home) [25, 26]. The provider may also want to ask which device type is preferred or used most often by the adolescent.

- *Source of vaping device:* Adolescents obtain vaping devices from a variety of sources, including peers, online, retail stores, vape shops, family, and from the illicit "black" market [27]. Understanding where the adolescent obtains e-cigarettes can help the provider provide tailored information about the potential risks of obtaining e-cigarettes from legal or illicit sources. As demonstrated by the E-cigarette, or Vaping, product use-Associated Lung Injury (EVALI) outbreak of 2019–2020, vaping THC-containing e-liquids obtained from the illegal "black" market may be associated with increased risk of lung injury or death [28, 29]. Providers should warn adolescents about some of the risks associated with acquiring e-cigarettes from retail or online sources. In the United States, it is illegal for a retailer to sell tobacco products, including e-cigarettes, to youth under the age of 21. Schools have been reported to expel students who are found to buy or sell vaping devices on school property.

To inform counseling and the development of a vaping cessation plan, the provider should assess for facilitators and barriers for vaping cessation by asking about vaping motivations, previous quit attempts, and symptoms of dependence, craving, and withdrawal.

- *Reasons for vaping*: Understanding the adolescent's motivations for vaping may help the provider formulate a tailored cessation strategy. Common reasons for e-cigarette use include curiosity, palatable flavors, peer use, and the "buzz" obtained from the nicotine [30, 31]. Some adolescents may use e-cigarettes with nicotine, THC, or other substances because they perceive that it can help with mood, concentration, or weight control. If this is the case, the provider may need to assess for symptoms of depression, anxiety, attention deficit hyperactivity disorder, or body image distortion to determine whether a co-occurring mental health disorder may be contributing to the e-cigarette use.
- *Quit attempts:* Many adolescents expect that they will eventually stop vaping, and some have attempted to quit vaping in the past [32]. Determining whether and how the adolescent has attempted to quit previously can help identify potential barriers/facilitators to quitting. Further, reassuring adolescents that a higher number of past quit attempts is predictive of future success may help encourage them in case of relapse [33]. Finally, assessing for withdrawal and or craving symptoms during a quit attempt can help the provider start to assess whether the teen is experiencing dependence.
- *Dependence/craving/withdrawal*: Adolescents may experience symptoms of nicotine and/or THC dependence. Unlike cigarettes, wherein the dependence

can be partly measured by assessing the frequency of cigarette smoking (i.e., cigarettes smoked per day), e-cigarette frequency does not reliably correlate with nicotine exposure, as nicotine absorption is affected by a multitude of factors such as device type, e-liquid nicotine concentration, and the depth and number of puffs [34]. Thus, it is important for the provider to assess for dependence by specifically asking about withdrawal and craving symptoms, as well as whether adolescents are experiencing a "loss of control" over vaping wherein they need to vape during school/work hours. The Hooked in Nicotine Checklist (modified for e-cigarettes), the Patient-Reported Outcomes Measurement Information System Nicotine Dependence Scale for Electronic Cigarettes (PROMIS-E), and e-cigarette Fagerstrom Test of Cigarette Dependence (e-FTCD) are questionnaires that can be used to assess for nicotine dependence in adolescents who vape nicotine [35–37]. Alternatively, the provider can assess whether the adolescents have mild, moderate, or severe tobacco or cannabis use disorder per the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria [38].

Of note, it is also important to assess whether vaping is resulting in signs or symptoms of respiratory, cardiovascular, gastrointestinal, or neurologic illness due to the associations between vaping and asthma symptoms, cardiovascular outcomes, EVALI symptoms, and seizures [28, 39–43]. The provider may obtain this information during the e-cigarette use history or as part of the broader review of systems. If the patient is currently experiencing symptoms, further relevant history may need to be obtained to determine whether they are due to vaping or another etiology, and acute management of symptoms should be prioritized.

Counseling Adolescents About Vaping Cessation: A Motivational Interviewing Approach

After obtaining a detailed e-cigarette use history, the provider can use motivational interviewing techniques to guide subsequent education and treatment efforts. Brief motivational interventions are especially appropriate for adolescents because they promote independent decision-making, rapport, and collaborative therapeutic relationships instead of "lecturing" or confrontation [44, 45]. A more detailed description of motivational interviewing is beyond the scope of this book, but readers may find additional information on this topic through the Elsevier ScienceDirect platform available at https://www.sciencedirect.com/topics/nursing-and-health-professions/motivational-interviewing. As a first step, the provider can set the tone by conveying that they respect the adolescent's autonomy: "*Our conversation today may be different than others you have had about vaping. I am not here to tell you what to do, but rather to help you make the changes that you decide to make.*" To further show respect for autonomy, the provider could then ask: "*Is it OK if we talk*

a bit more about your vaping?". The provider could then briefly summarize what they learned from the previous conversation and share what they believe are the most salient and immediate risks to the adolescent: "*We know that nicotine causes addiction, especially in teens with developing brains. I am concerned that if you continue vaping, you might develop an addiction*" or "*We now know that ingredients in e-cigarettes could be harmful to the lungs. I am concerned that you might develop a very serious lung disease*" [46]. In some cases, stressing that the tobacco industry targets youth through social media and advertising might help teens realize that they are being "taken advantage of" by corporations when they vape, a sentiment that directly opposes the adolescent's natural desire for independence and autonomy.

After reviewing the medical risks of vaping, the provider should then assess the teen's motivation to stop vaping completely, using the readiness ruler or another similar technique: "*On a scale of 1-10 (1 being not ready and 10 being very ready), how ready are you to quit?*" The provider can then ask why the adolescent chose the number they did rather than a lower number (i.e., eliciting reasons to change), and why the adolescent chose the number rather than a higher number (i.e., eliciting barriers to change). The readiness ruler can help the adolescent increase motivation to make a quit attempt or seek further treatment. The provider may need to encourage the adolescent to identify reasons to change by suggesting positive short-term effects of quitting, such as saving money, avoiding school or parental punishment, or potential improvements in their athletic or musical performance. If the adolescent expresses motivation to quit, the provider can assist them in quitting by formulating a personalized treatment plan that uses the behavioral and pharmacologic strategies outlined below. On the other hand, if the teen is not ready to quit, it is important that the provider encourages the adolescent to start thinking about cutting down or quitting and assures them that help is available whenever they are ready to talk more about vaping cessation [47].

Behavioral and Pharmacological Strategies for E-Cigarette and Vaping Cessation

Research on evidence-based strategies designed specifically for e-cigarette and vaping cessation remains extremely limited. Given the absence of youth-focused vaping-specific cessation strategies, providers are encouraged to adapt evidence-based strategies used for cigarette smoking [7, 33]. In general, cessation strategies can be divided in two main categories—behavioral and pharmacological. First, behavioral strategies, which should be considered first-line treatment for all youth, apply to all types of e-cigarettes and vaping products and devices [48]. Pharmacotherapy can be considered as a complement to behavioral strategies in cases of more severe addiction to vaping substances (see Table 6.2 for overview) [47].

Behavioral Strategies

Once it has been established (i.e., during an individual counseling session) that an adolescent is interested in quitting or cutting down e-cigarettes or vaping, a useful first step is to set a quit date. This quit date could be close in time for adolescents with high levels of motivation and readiness to quit, or further away, for adolescents who may feel more comfortable with a more gradual, or stepwise approach [49]. In both cases, providers should help the adolescent develop a plan for success that will build on their own motivators and incentives [50]. It is often helpful to discuss more practical details which include how to safely dispose of vaping products (to limit temptations), how to avoid common triggers (e.g., spending time with people who vape, walking in front of vape shops, browsing vaping-related social media content, and using alcohol or drugs) and what to do if a friend offers to share an e-cigarette. To maximize chances of success, the provider should work with the adolescent to formulate treatment plan from a menu of options that includes evidenced-based behavioral interventions such as: (a) individual or group counseling based on the principles of motivational interviewing; (b) structured forms of individual therapy, for example cognitive-behavioral therapy, which can help identify and address key thoughts, emotions, and behaviors associated with vaping [51]; (c) contingency

Table 6.2 Medications for management of nicotine use disorder[a, b]

Characteristics	Nicotine replacement	Bupropion sustained-release (SR) (Zyban®)	Varenicline (Chantix®)
Mechanism of action	Full agonist that binds to nicotinic cholinergic receptors	Mechanism incompletely understood; modulates dopaminergic transmission in the brain	Partial agonist that binds to nicotinic cholinergic receptors
Age considerations	In the United States: Approved for adults ≥18; off-label use for youth <18	In the United States: Approved for adults ≥18; off-label use for youth <18	In the United States: Adults ≥18
Administration and length of treatment	Can use a nicotine patch with a short-acting NRT for breakthrough cravings Can administer nicotine patch for 4–6 weeks, then administer the next lowest dose patch for 2–4 weeks and continue wean until patient tolerates no nicotine In general, treatment should begin with more frequent use of short-acting NRT (e.g., 1 piece/lozenge every 1–2 hours) and then attempts should be made to increase interval between doses	Begin treatment at least 1 week before target quit date After 2–3 months, may consider discontinuing medication; however, continued treatment with bupropion may support ongoing cessation for up to a year, and some patients may choose to remain on the medication even longer	Begin treatment at least 1 week before target quit date Continue for a total of 12 weeks of treatment; a second 12-week course of treatment may support ongoing cessation

(continued)

Table 6.2 (continued)

Characteristics	Nicotine replacement	Bupropion sustained-release (SR) (Zyban®)	Varenicline (Chantix®)
Dosage	*Nicotine patch (for maintenance dose)*: Apply to skin every 24 hours (change site daily)[d] <1/2 cartridge/day (= 0–25 mg of nicotine salts): 7 mg patch 1/2 to 1 cartridge/day (= 25–50 mg of nicotine salts): 14 mg patch 1–2 cartridges/day (= 50-100 mg of nicotine salts): 21 mg patch *Gum or lozenge (short-acting nicotine[e] for breakthrough cravings)*: For those who vape within 30 minutes of waking: start with 4 mg For those who start to vape >30 minutes after waking: start with 2 mg Use 1 piece every 1–2 hours for first 6 weeks Use 1 piece every 2–4 hours for 3 additional weeks Use 1 piece every 4–8 hours for 3 additional weeks (After chewing nicotine gum and tasting nicotine, gum should be "parked" between oral gums and cheek for best absorption)	Bupropion SR 150 mg by mouth once daily for 3 days, then increase to 150 mg by mouth twice daily	Varenicline 0.5 mg by mouth once daily for days 1–3, then increase to 0.5 mg by mouth twice daily for days 4–7, then increase to 1 mg by mouth twice daily
Other considerations	In the United States, NRT is available over the counter for adults. Data suggest that for adults, cessation is most likely following *combination therapy* of nicotine replacement with varenicline (preferred), or of nicotine replacement with bupropion	May be beneficial in patients with underlying depression. Due to elevated risk for seizure, contraindicated in individuals with a seizure disorder or eating disorder, or who have abruptly discontinued alcohol, benzodiazepines, or anti-epileptic drugs	Previously had a black-box warning in the United States due to concern for risk of increased suicidality and agitation; warning was dropped in 2016 after clinical trial data showed no significant increase in risks. If patients experience these symptoms, the medication should be discontinued, and the patient closely monitored

[a]Adapted from Hadland SE, Chadi N (2020) [7]

[b]Listed medications have been studied for cigarette smoking cessation; their use among youth who vape has not been extensively studied

[c]Based on US Food and Drug Administration recommendations and available clinical trial data; use of medications in younger ages than those listed here can be considered

[d]Patches can be worn during the daytime only or overnight; wearing the patch overnight may help reduce morning cravings

[e]Short-acting nicotine inhalers and nicotine oral/nasal sprays are also available; their use in youth is discouraged due to concerns regarding potential misuse and reinforcing effect

management (e.g., the use of incentives to promote smoking cessation) [52]; (d) mindfulness-based or other mind-body interventions [53]; (e) self-help interventions including online materials [54] and smoking/vaping quit lines (e.g., *Smokefree Teen*, and *1–800 QUIT-NOW*) and; (f) interactive app, social media, or text-message-based interventions (e.g., *This is quitting, My Life My Quit)* [33, 48, 55]. Cessation plans should also include a strong focus on personal wellness and self-care, including sleep hygiene, healthy nutrition, and physical activity which can all contribute to reduced cravings and increased motivation to quit [56]. Finally, youth should be encouraged to seek help and support from friends and trusted family members by notifying them about their plans and intentions to quit (including informing them of their quit date) and asking them if they can help them stay on track if things get more difficult.

Pharmacotherapy

Nicotine Replacement Therapy: Although nicotine replacement therapy (NRT) and use of bupropion and varenicline have been shown highly effective in increasing adult cigarette smoking cessation rates, evidence of effectiveness among adolescents is much less robust [33]. In fact, a recent meta-analysis suggests that the benefits of pharmacotherapy are unclear, and that its use, alone or in combination with behavioral strategies, may only lead to minimal increases in long-term *adolescent* smoking quit rates [57]. When it comes to vaping cessation specifically, there are currently no placebo-controlled studies testing the effectiveness of NRT, bupropion, or varenicline. Nonetheless, healthcare providers across North America have been using NRT off-label on a case-by-case basis for treatment of nicotine withdrawal symptoms (e.g., during hospitalization where smoking/vaping is not permitted) and as part of a multipronged vaping cessation approach combining behavioral strategies and pharmacotherapy, an approach that is supported by the American Academy of Pediatrics [4, 58].

As detailed in AAP Nicotine Replacement Therapy and Adolescent Patients webpage at https://services.aap.org/en/patient-care/tobacco-control-and-prevention/youth-tobacco-cessation/nicotine-replacement-therapy-and-adolescent-patients/, there are currently three forms of NRT that can be recommended for adolescents: patches, gums, and lozenges [58, 59]. Patches, which provide continuous low-dose nicotine throughout the day, are best used in combination with shorter acting gums and lozenges, which can help reduce cravings, especially in situations that are triggering for the adolescent. Nicotine inhalers and nasal sprays are not recommended for adolescents due to potential misuse and reinforcing effect [60]. Although NRT is available over the counter for adults, NRT is available by prescription in the United States for adolescents less than age 18. The prescription can be used to reduce the costs of the medication (through insurance coverage) and help tailor treatment dosing and duration an adolescent's daily nicotine intake. Certain

insurance plans may require a pre-authorization for the prescription of NRT to adolescents, and adolescents should be informed that their prescription may not be confidential if their parents are informed of the NRT via their insurance companies' explanation of benefits [61]. If it is felt the adolescent can safely self-administer a short-acting NRT during school hours, the provider may need to provide a written authorization for medication self-administration in school.

Although nicotine absorption may differ significantly based on types of vaping devices and liquids, the tobacco industry has reported that 30 to 50 mg of nicotine salts, as found in a 0.7 mL pre-filled nicotine-containing e-liquid pod with a concentration of 3% to 5%, is roughly equivalent to the nicotine contained in 1 pack of traditional cigarettes [23, 34]. Knowing that people who smoke greater than a ½ pack per day (10 cigarettes) generally require a full-strength 21 mg nicotine patch (patches are available in strengths of 7, 14, or 21 mg), equivalences can be calculated for youth who vape (i.e., 1 × 0.7–1.0 mL 3–5% nicotine pod/day = 21 mg patch). The patch can be used for 8–10 weeks, with instructions to use the first dose for 6 weeks, and to "step down" to lower doses for 2 weeks. For instance, a patch regimen could consist of 6 weeks with a 21 mg patch, followed by 2 weeks with a 14 mg patch and 2 weeks with a 7 mg patch [58]. Nicotine gums and lozenges can be prescribed as needed every 1 to 2 hours for the first 6 weeks, then every 2–4 hours for 3 weeks, and every 4–8 hours for 3 additional weeks [58]. We recommend that providers consider starting adolescents who vape within 30 minutes of waking start with the 4 mg gum/lozenge, and those who vape more than 30 minutes after waking start with the 2 mg dose. In our clinical experience, some adolescents who vape require a slower taper for the NRT with dose adjustment guided by the adolescent's symptoms. Of note, nicotine replacement products are considered safe to use in youth with minimal side effects (mainly skin irritation for the patch, and dry mouth/mouth irritation for gums and lozenges) [58, 62]. Providers may consider starting with lower strength patches/lozenges/gums for youth <45 kg [63].

Additional Medications for Nicotine Cessation: In adults, bupropion and varenicline can be used alone or in combination with nicotine replacement therapy and have been shown to significantly increase smoking quit rates [33, 64]. However, data on the effectiveness of these agents in adolescents and young adults who smoke cigarettes remain highly limited (and non-existent for youth who consume nicotine primarily through vaping). Bupropion is considered safe to use for the treatment of depression in adolescents 12 years and above, but varenicline is only recommended in youth 18 and above due to lack of effectiveness in younger youth [65, 66]. Main contraindications include seizure disorders and eating disorders for bupropion and active suicidal ideation for varenicline. Nonetheless, these medications could be considered on a case-by-case basis in combination with behavioral interventions, as part of a comprehensive vaping cessation plan [7].

Cannabis Cessation: If it is found that an adolescent primarily vapes cannabis, the provider should consider a brief intervention around cannabis use and a referral to a treatment provider that is comfortable managing cannabis use. There is currently no

FDA-approved treatment for management of cannabis withdrawal symptoms or for the support of cannabis cessation or reduction, regardless of the form of consumption.

Summary

E-cigarette use is common among adolescents and healthcare providers should be prepared to address their use during the clinical encounter. Both the 5As and SBIRT frameworks can help embed routine screening and counseling in clinical practice. If an adolescent reports e-cigarette use, it is important for the provider to obtain a detailed e-cigarette use history and use motivational interviewing techniques to help inform adolescents about the risks of e-cigarette use and enhance motivation to quit. Evidence-based strategies for e-cigarette and vaping cessation are lacking; however, both behavioral and pharmacologic strategies for cigarette smoking can be adapted for vaping.

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Chapter 7
Evaluation of Evidence of E-Cigarettes as a Smoking Cessation Treatment for Adult Smokers

Robert McMillen

As e-cigarettes entered the US market in 2006, many of us had questions about the public health impact of these new nicotine delivery devices. Although e-cigarettes have not been FDA approved as a smoking cessation device, questions arise about their public health impact. Do e-cigarettes provide a public health benefit as an aid to promote smoking cessation and reduction with adult smokers? Or, do these products create a public health harm by attracting new users, who might then transition to combustible cigarettes? Or, both? Researchers have devoted a lot of attention to these questions over the past decade. Regarding the question of a potential public health benefit, over 90 studies examining the impacts of e-cigarettes on smoking cessation or reduction [1] have produced disparate and often contradictory findings [2–5]. By contrast, prospective studies addressing e-cigarette and subsequent combustible cigarette smoking have produced more consistent findings [6–13]. This chapter comments on this research and the potential public health benefits and harms of e-cigarettes.

Do E-Cigarettes Facilitate Smoking Cessation and Reduction?

A Chinese pharmacist invented the first e-cigarette in 2003 as a potential cessation device [14]. As e-cigarettes entered the US market, some public health researchers proposed these products to be a less harmful alternative to combustible cigarettes and a potential tool to help people to stop smoking combustible cigarettes. Others worried that e-cigarettes would reduce smoking cessation rates by providing a way to inhale nicotine in smokefree environments, thereby reducing quit attempts [15].

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S. C. Walley, K. Wilson (eds.), *Electronic Cigarettes and Vape Devices*,
https://doi.org/10.1007/978-3-030-78672-4_7

Despite the vast amount of research on this topic, we have yet to reach a consensus on the question of whether e-cigarettes can help adults to quit smoking cigarettes. Among the reasons for a lack of resolution, three challenges stand out. First, the landscape for e-cigarettes continues to evolve. Second, observational research on this topic has produced inconsistent and contradictory findings. Third, randomized controlled trials (RCTs) could produce the most compelling evidence, but there are only 13 published articles looking at e-cigarettes and smoking cessation and/or reduction based on RCTs at the time of this writing.

The Evolving Landscape of E-Cigarette Products

As e-cigarette design evolved over the past decade, researchers developed a classification system to characterize these changing products. First-generation e-cigarettes were designed to look like cigarettes, had low-voltage batteries, and were inferior in delivering nicotine to the brain compared to future products. Second-generation e-cigarettes had larger variable voltage batteries and refillable nicotine filled reservoirs. These products are also known as tank systems. Third-generation products use modifiable batteries that provide the user with the ability to vary voltage, wattage, and power in order to manipulate nicotine levels and other aspects of the vaping experience. Fourth-generation e-cigarettes include pod-based systems and the voltage is typically not modifiable [16]. These products deliver a high dose of nicotine at low pH levels, which is less harsh compared to the higher pH nicotine found in previous generations of e-cigarettes [17, 18].

The evolving landscape of e-cigarette products presents a challenge to addressing this issue. E-cigarettes on the market today are very different than the products examined in most of the published research addressing these questions. Current e-cigarettes deliver much more nicotine to the brain, and do so more quickly than previous generations [19, 20], a feature that could possibly make these newer products more effective as a cessation tool (but also has the potential to addict youth more quickly). Indeed, UK researchers found that users of first-generation e-cigarettes were less likely to quit cigarette smoking than those who used second-generation tank systems [21]. These improvements in the ability to deliver nicotine to the brain reduce the generalizability of earlier studies suggesting that e-cigarettes are not effective in promoting smoking cessation.

Inconsistent Results from Observational Research Addressing E-Cigarettes and Smoking Cessation

Most of the published research examining e-cigarettes and smoking cessation is based on observational studies; these present a second challenge in that they have produced inconsistent and contradictory results. A literature search can produce

published studies that find that e-cigarettes can be effective aids to promote smoking cessation [22, 23], or find that e-cigarette use reduces smoking cessation rates [24–26], or that e-cigarette use has no impact on smoking cessation [23, 27].

Methodological variation across these observational studies is likely responsible for some of the conflicting findings regarding the cessation question. Choices about populations sampled, measures used to assess e-cigarette use, reasons assessed for e-cigarette use, inclusion of different covariates, and analytical approach may impact the estimated association between e-cigarette use and cessation [1, 28].

Another critical limitation of many observational studies on this topic concerns the timeline of survey development, approval, and administration. The product and regulatory landscape for e-cigarettes and our understanding of how to ask the right questions continue to evolve as studies transition from design to administration. We may be asking the wrong questions about outdated products by the time a survey goes in to the field.

A Lack of Randomized Control Trials Addressing E-Cigarettes and Smoking Cessation

Randomized controlled trials (RCTs) are the gold standard for testing causal hypotheses. However, lack of RCTs testing the hypothesis that e-cigarettes facilitate smoking cessation is often cited as a barrier to resolving this question [1, 29, 30]. The lack of RCTs is due in part to the e-cigarette manufactures not administering these trials to test the efficacy of their products. Scholarly research on cessation is hampered by a funding policy issue. Federal guidelines regulate how the National Institutes of Health (NIH) can fund nicotine cessation RCTs. NIH-funded human subject nicotine cessation studies must have Investigational New Drug approval from the Food and Drug Administration (FDA) in order to investigate an e-cigarette product as a potential medical product for smoking cessation. In other words, the FDA would have to approve an e-cigarette product as a drug before the NIH can fund an RCT to test whether or not that product helped people to quit smoking. And, no e-cigarette manufacturer has applied for Investigational New Drug approval. The cost for an e-cigarette manufacturer to conduct an RCT for an investigational new drug and apply to the FDA for approval is high, and these companies' revenues are sufficiently high without going through the time and expense necessary to get into this health space. Due to this policy, federally funded RCTs cannot address e-cigarettes for smoking cessation. However, this policy does not apply to RCTs that assess reductions in smoking as an outcome measure, rather than smoking cessation.

To date, only 13 RCT studies looking at whether e-cigarettes can facilitate cigarette smoking cessation or reduction are in the literature [5, 31–42]. Nine of these are based on non-US participants, whereas the NIH funded two trials with US participants. Reduction in cigarettes smoked per day, rather than smoking cessation, served as the outcome measure in the two NIH trials. Two other trials in the United States used regional participants and were not funded by the NIH.

EffiCiency and Safety of an eLectronic cigAreTte (ECLAT) as Tobacco Cigarettes Substitute: A Prospective 12-Month Randomized Control Design Study

The first RCT began in 2010 and it examined e-cigarettes on cigarette smoking cessation and reduction included 300 Italian participants who were smokers with no intent to quit [32]. The trial included three arms, with 100 smokers in each arm. The first arm provided 7.2 mg nicotine cartridges for 12 weeks; the second arm provided 7.2 mg nicotine cartridges for 6 weeks, and then 5.4 mg nicotine cartridges for 6 weeks; and the third arm provided cartridges with no nicotine for 12 weeks. The trial did not include a control group that received evidence-based cessation therapy. Participants reported cigarettes smoked per day and exhaled carbon monoxide was assessed over nine visits during a 12-month period (baseline, weeks 2, 4, 6, 8, 10, 12, 24, and 52). Daily consumption dropped sharply from baseline to week 2 in all three arms, but increased slightly over each of the following assessments. Exhaled carbon monoxide levels mirrored this pattern of the nine assessments. At week 52, smoking reduction was found among 10.3% of participants and complete abstinence from smoking was found among 8.7% of participants, with 26.9% of former smokers continuing to use e-cigarettes. These results of this trial using first-generation e-cigarettes suggested that e-cigarettes could impact smoking cessation and reduction, at least for some smokers; but the findings are somewhat limited due to lack of a control group that used an FDA-approved cessation method.

Effect of Electronic Cigarettes on Smoking Reduction and Cessation in Korean Male Smokers: A Randomized Controlled Study

Conducted in 2012, this RCT of South Korean male workers from a motor company included two arms [37]. Participants in the treatment arm received a 12-week supply of GO-C Ovale second-generation e-cigarettes, those in the control arm received a 12-week supply of nicotine gum. Eligible subjects had smoked at least 10 cigarettes per day during the preceding year, had smoked for at least 3 years, and were motivated to stop smoking entirely or to reduce their cigarette consumption ($n = 150$). Outcome measures included smoking reduction and smoking cessation. E-cigarettes were as equally effective as nicotine gum for facilitating smoking cessation at each follow-up and were associated with higher proportions of subjects with reduced daily cigarettes at week 24.

Electronic Cigarettes for Smoking Cessation: A Randomized Controlled Trial

New Zealand researchers produced the next RCT examining e-cigarette use and smoking cessation – A Study of Cessation using Electronic Nicotine Devices (ASCEND) [34]. The trial, conducted in 2011–2013, included 657 New Zealand smokers who wanted to quit smoking. The trial included three arms; participants either received a first-generation e-cigarette with 16 mg of nicotine ($n = 289$), a

21 mg nicotine patch once a day ($n = 295$), or a placebo e-cigarette ($n = 73$). Analyses of exhaled breath carbon monoxide measurements (a biomarker for cigarette smoking but not e-cigarette use) at 6-month follow-up found that e-cigarettes, with or without nicotine, were modestly effective at helping smokers to quit, with similar achievement of abstinence as with nicotine patches, and few adverse events.

Effectiveness of the Electronic Cigarette: An 8-Week Flemish Study with 6-Month Follow-Up on Smoking Reduction, Craving, and Experienced Benefits and Complaints

In 2013, Flemish smokers with no intention to quit smoking participated in a three-arm RCT to examine the effect of e-cigarette use on acute craving-reduction in the lab and smoking reduction at 6-month follow-up [35]. The three arms included two groups in which participants were provided with a second-generation e-cigarette and could vape or smoke cigarettes during the study period (two different e-cigarette products were selected in order to examine potential product-related variation) and participants in the control arm could only smoke. For the 8-week period during the lab study, subjects participated in lab visits at weeks 1, 4, and 8 in which researchers assessed craving and withdrawal symptoms of using an e-cigarette after being 4 hours abstinent from smoking or vaping. After the lab study component of the study, all participants were provided with an e-cigarette and smoking cessation and reduction was assessed at 6-month follow-up.

In the lab study, participants found second-generation e-cigarettes to be immediately and highly effective in reducing abstinence-induced cigarette craving and withdrawal symptoms. At 6-month follow-up, almost half of subjects had reduced (23%) or quit their smoking (21%). However, randomization only existed during the initial laboratory phase of this study; there was no longer an unexposed control group during the phase of the study in which the smoking cessation outcomes were observed [1].

E-Cigarettes Versus NRT for Smoking Reduction or Cessation in People with Mental Illness: Secondary Analysis of Data from the ASCEND Trial

Secondary data analysis of data from the RCT of New Zealand adult smokers [34] found that the use of first-generation e-cigarettes for quitting appears to be equally effective, safe, and acceptable for people with and without mental illness [36].

A Randomized Trial Comparing the Effect of Nicotine Versus Placebo Electronic Cigarettes on Smoking Reduction Among Young Adult Smokers

In 2014, US young adult smokers (ages 21–35) who were interested in reducing cigarette consumption participated in a two-arm RCT in which subjects either received 3 weeks of disposable, first-generation e-cigarettes (4.5% nicotine) or

placebo e-cigarettes [31]. The primary outcome measure was self-reported reduction in the number of cigarettes smoked per day at the end of week 1 and week 2. Subjects in both arms smoked significantly fewer cigarettes per day at both study time periods than at baseline. Comparisons across study arms found significantly fewer cigarettes per day in the intervention arm than in the placebo arm at week 3, but not at week 1. However, no differences in exhaled CO were detected at any time point in the study. Logistic regression models demonstrated that using e-cigarettes more frequently was associated with smoking fewer cigarettes per day.

A Pragmatic Trial of E-Cigarettes, Incentives, and Drugs for Smoking Cessation

This US-based RCT examined sustained smoking abstinence for 6 months among 6006 employees and their spouses at 54 companies that used Vitality wellness programs [38]. Eligible participants were at least 18 years old and reported current smoking on a health risk assessment within the previous year. The paper did not include motivation to quit smoking as an eligibility requirement. Conducted in 2014 and 2015, this RCT included five arms: (1) usual care consisted of access to information regarding the benefits of smoking cessation and to a motivational text-messaging service (control arm); (2) usual care plus free cessation aids (nicotine-replacement therapy or pharmacotherapy, with e-cigarettes if standard therapies failed); (3) usual care plus free e-cigarettes, without a requirement that standard therapies had been tried; (4) usual care plus free cessation aids plus $600 in rewards for sustained abstinence; (5) usual care plus free cessation aids plus $600 in redeemable funds, deposited in a separate account for each participant, with money removed from the account if cessation milestones were not met. The first three arms addressed the role of e-cigarettes and smoking cessation. Participants in the third arm did not demonstrate higher rates of sustained smoking abstinence for 6 months than those who received usual care or those who received usual care plus free cessation aids.

E-Cigarettes Versus Nicotine Patches for Perioperative Smoking Cessation: A Pilot Randomized Trial

Conducted in San Francisco in 2015 and 2016, this RCT involved 30 preoperative patients who were current cigarette smokers of more than two cigarettes per day having smoked at least once in the last 7 days [39]. Motivation to quit was not an eligibility requirement. All patients received brief counseling, a brochure on perioperative smoking cessation, and referral to the California Smokers' Helpline. The trial included two arms: (1) patients in this arm were provided with a 5-week supply of NRT patches, followed by a 1-week supply of placebo patches; and (2) patients in this arm received a 5-week supply of first-generation e-cigarettes, followed by a 1-week supply of placebo e-cigarettes. Results revealed no differences across arms in biochemically confirmed smoking cessation or smoking reduction at 30-day, 8-week, and 6-month follow-up.

Benefits of E-Cigarettes in Smoking Reduction and in Pulmonary Health Among Chronic Smokers Undergoing a Lung Cancer Screening Program at 6 Months

This RCT included 210 Italians, 55 years old or more, who smoked an average of 10 cigarettes or more a day for at least the past 10 years and were undergoing a lung cancer screening program [40]. Motivation to quit was not an eligibility requirement. All participants received a 3-month cessation program that included a cognitive-behavioral intervention. There were three arms, each with 70 participants: (1) participants were provided with an e-cigarette kit that included 12 liquid cartridges and instructed to dual use e-cigarettes and cigarettes for 1 week and then use e-cigarettes exclusively for the remaining 11 weeks; (2) same as arm 1, but the e-cigarettes were nicotine-free; and (3) the control group that only received support. At the end of 6 months, participants who received e-cigarettes smoked slightly fewer cigarettes per day than those who received nicotine-free e-cigarettes or just support. There were no differences in 6-month smoking abstinence.

A Feasibility Study with Embedded Pilot Randomized Controlled Trial and Process Evaluation of Electronic Cigarettes for Smoking Cessation in Patients with Periodontitis

This feasibility RCT examined patients from 2015 through 2018. Patients at Tyne Hospitals NHS Dental Clinical Research Facility in the UK, who were tobacco smokers, had periodontitis, and not currently using an e-cigarette were eligible [41]. Motivation to quit was not an eligibility requirement, and 80 patients were enrolled into this trial. There were two arms. The first received standard non-surgical periodontal therapies and brief smoking cessation advice. The second received the same protocol, as well as an e-cigarette starter kit with brief training. The starter kit included a tank-based e-cigarette with a 2 week of supply of e-liquid. At 6-month follow-up, rates of carbon monoxide-verified continuous abstinence did not differ across arms. Although more participants in the e-cigarette arm were abstinent, the difference was not significant.

Nicotine Patches Used in Combination with E-Cigarettes (With and Without Nicotine) for Smoking Cessation: A Pragmatic, Randomized Trial

This RCT examined the impact of combining NRT with e-cigarettes on smoking cessation [42]. Between 2016 and 2018, 1124 New Zealand adults who were motivated to quit smoking participated in this trial. All were offered 6 weeks of telephone-delivered behavioral support and received a 14-week supply of their allocated treatment. Participants in the first arm received nicotine patches, those in the second arm received nicotine patches plus a second-generation e-cigarette starter kit with an e-liquid that had a nicotine content of 18/mg/l, and those in the third arm received

nicotine patches and the same e-cigarette but with a nicotine-free e-liquid. Participants who received patches plus nicotine e-liquids had higher self-reported continuous smoking abstinence at 1-month, 3-month, and 6-month follow-up than those received patches only or patches plus nicotine-free e-liquids. The same outcome was found for CO-verified quit rate at 6 months.

A Randomized Trial Comparing the E-Cigarettes Versus Nicotine-Replacement Therapy

Published in the *New England Journal of Medicine*, this RCT of UK smokers enrolled in smoking cessation programs from 2015 to 2018 [5] provides some of the strongest support of the hypothesis that e-cigarettes can help people to quit smoking in a proctored smoking cessation treatment plan. In this two-arm trial, smokers were provided with the nicotine replacement therapy of their choice for up to 3 months, or a second-generation e-cigarette starter kit and asked to purchase future e-liquid. In both arms, treatment also included weekly behavioral support for at least 4 weeks. The primary outcome was confirmed cessation at 1-year follow-up. Smokers in the e-cigarette arm remained abstinent for 1 year at nearly twice the rate as those using nicotine replacement options, 18% of the e-cigarette users were no longer smoking at 1 year compared to 9.9% of the nicotine replacement users. However, the e-cigarette users were also more likely to still be using their devices at 1 year compared to the nicotine replacement users—80% compared to 9%. This was the first randomized trial to find that cessation rates were higher among people who were treated with e-cigarettes compared to those who received NRT, and generated enthusiasm about their harm reduction potential. It should be noted, however, most people use e-cigarettes as recreational products and not as part of a clinically supervised cessation attempt that, most important, includes intensive counselling [43].

A Randomized Clinical Trial Examining the Effects of Instructions for Electronic Cigarette Use on Smoking-Related Behaviors and Biomarkers of Exposure

Administered from 2014 to 2018, this trial of US adult daily smokers with no immediate interest in quitting included four arms: dual use of e-cigarettes (second-generation) and cigarettes, complete substitution of cigarettes with e-cigarettes, complete substitution of cigarettes with NRT, and continued smoking of usual brand cigarettes [33]. Protocol compliance for participants in the substitution arms was assessed by CO measurements at each clinic visit during the study period. The primary outcome variable was cigarettes smoked per day over the 8-week study period. No differences in cigarettes smoked per day were found between the e-cigarette substitution arm and the NRT substitution arm. However, more participants experienced CO-verified end-of-treatment 7-day point prevalence abstinence in the e-cigarette arm than in the NRT arm.

Of these 13 RCTs, five did not include NRT as a control arm [31, 32, 35, 40, 41], one combined NRT with e-cigarette use—so there was no NRT control [38], four found that e-cigarettes were no more effective than NRT for facilitating smoking cessation [34, 36, 37, 39], one trial found that e-cigarettes were associated with higher rates of 7-day smoking abstinence than NRT [33], one trial found that e-cigarettes (paired with behavioral support) plus NRT were modestly more effective than NRT alone for facilitating smoking cessation [42], and one trial found that e-cigarettes (paired with behavioral support) were more effective than NRT for cessation [5]. This last RCT provides the most compelling support for e-cigarettes as a cessation strategy. However, it is important to note that most of the people who were able to successfully substitute e-cigarettes for cigarettes were not nicotine-free. They continued to use e-cigarettes.

Attempts to Synthesize These Studies

At least 16 reviews have attempted to synthesize these 90 studies, and these have also reached disparate conclusions [12, 15, 29, 30, 44–48]. Most reviews, however, agree that existing observational research limits the certainty of any conclusions and more randomized controlled trials examining smoking cessation and reduction are needed to resolve this issue. As noted previously, only 13 of the more than 90 research studies on this topic are based on RCTs. Most of the published research utilized observational methods and has yielded inconsistent results for the association between e-cigarette use and smoking cessation and reduction. These inconsistencies may arise from the evolving landscape of e-cigarette products, the analytical approach used to examine the relationship [28], and the poor quality of much of the literature [44]. Two recent reviews established quality inclusions standards and the number of studies that met these standards was in the single digits for both reviews [1, 44].

Many of the observational studies that were considered to provide a low quality of evidence were conducted as our understanding of how to ask the right questions was evolving. A research team from the Truth Initiative recently proposed six assessments that a well-designed study on e-cigarettes and smoking cessation and/or reduction must include, namely, (1) the outcome of interest must be cigarette smoking cessation and/or reduction in smoking, (2) confirmation that the respondent is using e-cigarettes for the purpose of smoking cessation, (3) a control or comparison group and measures to address the potential impact of e-cigarette use on smoking cessation or reduction with minimal confounds, (4) a design that can establish that e-cigarette use preceded the outcome, (5) a dose and duration of e-cigarette use measure, and (6) an assessment of e-cigarette product used [1].

One recent meta-analysis framed the observational research on this topic as studies on the effects of e-cigarettes as consumer products and how they are actually used in the general population, whereas most RCTs examined the effects of e-cigarettes as administered under medical supervision [48]. Within the

observational studies analyzed, the authors found no evidence that e-cigarettes used as consumer products were associated with smoking cessation (among all smokers and smokers who were motivated to quit smoking). However, their analyses did reveal that the provision of free e-cigarettes was associated with increased smoking cessation in RCTs of e-cigarettes administered as smoking cessation therapy. The authors conclude that e-cigarettes as consumer products have no public health benefit, but may have some merit as therapeutic interventions if delivered to patients under medical supervision.

In summary, the lack of RCTs examining e-cigarettes as effective aids to promote smoking cessation and the limitations of inconsistent observational research on this topic limit the ability to make strong conclusions. That said, observational studies do seem to suggest that more frequent use of e-cigarettes predicts successful cessation [12].

Do E-Cigarettes Create a Public Health Harm by Attracting New Users, Who Might Then Transition to Combustible Cigarettes?

Any potential harm-reduction benefit of e-cigarettes to adult cigarette smokers must be weighed against the risk that these products might also be attractive to adolescents and young adults with no history of nicotine use. That is, do e-cigarettes attract users who were otherwise unlikely to be smoking combustible cigarettes [49]? The features and marketing designed to make e-cigarettes more attractive to smokers than other nicotine replacement therapies also appeal to nonsmokers [50].

And indeed, we are experiencing an e-cigarette epidemic among our youth. Past 30-day e-cigarette use nearly doubled among US adolescents from 2017 to 2018. Both the Monitoring the Future Survey [51] and the National Youth Tobacco Survey (NYTS) [52] found skyrocketing rates of adolescent vaping. Past 30-day use increased again in 2019 to 27.7% from 20.8% in 2018. Use appeared to drop the following year. Although 19.6% of high school students reported past 30 day use in 2020, NYTS administration was halted due to COVID-19-related school closures [53] and this 1-year downward trend may not continue in future years. According to former FDA Commissioner Scott Gottlieb, this dramatic spike of youth vaping was driven by pod-based e-cigarettes [54]. Several features of these fourth-generation e-cigarettes are problematic for adolescent public health. The tech sleekness, ease of discreet use, and flavors of pod-based e-cigarettes contain design elements known to be attractive to nonsmoking youth. Improved nicotine delivery, coupled with the ability to discreetly use e-cigarettes more frequently, could also accelerate an addiction trajectory for adolescents and young adults.

Increased e-cigarette use among adolescents may also undo years of progress in reducing youth smoking, given the prospective evidence that e-cigarette use is associated with subsequent initiation of cigarette smoking [6–8, 10, 11, 55–57] and

current smoking [10] among young never smokers, even after adjusting for psychosocial predictors of smoking. E-cigarettes may provide an onramp to cigarette smoking among youth who would be the least expected to start smoking. This association appears to be strongest among adolescents who were least susceptible to smoking combustible cigarettes at baseline [7, 56, 57].

In summary, the debate over whether or not e-cigarettes are effective aids to promote cessation remains unsettled. Lack of randomized controlled trials and the evolving landscape of e-cigarette products reduce the generalizability of studies and hamper a strong consensus concerning the impact of e-cigarettes on smoking cessation, although several reviews agree that e-cigarettes can have at least a modest impact on smoking reduction. However, any potential harm-reduction benefit of e-cigarettes to adult cigarette smokers is offset by sharp increases in e-cigarette use among adolescents and by the consistent prospective research demonstrating that nonsmoking adolescents and young adults who initiate e-cigarette use are at increased risk of transitioning to combustible cigarette use.

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Chapter 8
Marketing and Advertising of E-Cigarettes and Pathways to Prevention

Susanne E. Tanski

As has been noted in other chapters, the science is clear: there is no "safe vape". Vaping/e-cigarette use is unfortunately common among young people, however, and a major public health issue. Vaping nicotine has been shown to affect brain development leading to issues with attention, behavior, cognition, and mood, and vaping of any substance has been shown to cause lung injury and disease. Adolescent use of e-cigarettes can establish a pattern of life-long nicotine addiction and has been linked to subsequent combusted tobacco use. So what can we do to prevent it?

Why Do Young People Vape? Marketing and Advertising

Vaping initiation specifically by youth has skyrocketed since the introduction of these products to the US market. While the drivers of initiation are multifactorial, this increase has been in large part due to advertising and marketing, which includes design characteristics and accordingly product appeal. The most recent generations of vaping devices deliberately moved away from any resemblance to a traditional cigarette or other combusted product, which accordingly has attracted a different market audience: youth and young adults.

These differences and product characteristics have been heavily emphasized in direct advertising and promotion (paid media) as well as "earned media." "Earned media," which is not directly paid for by a company, includes publicity in general such as social media mentions and recommendations, memes, blog posts, shares and retweets of content, and articles in magazines, newspapers, and digital formats. The distinction between company-paid advertising and earned media is difficult to detect, as company-paid

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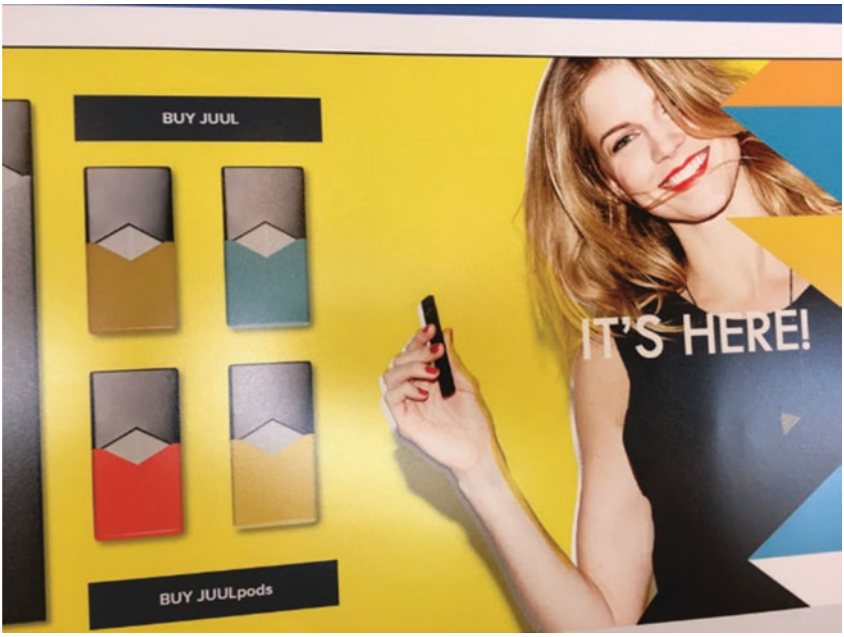
S. C. Walley, K. Wilson (eds.), *Electronic Cigarettes and Vape Devices*,
https://doi.org/10.1007/978-3-030-78672-4_8

influencers and brand ambassadors have been increasingly used to promote products such as vaping products, and their social media content may be indistinguishable from other consumer-made content. Similar to the tobacco industry's advertising and promotions over the twentieth century that were so effective in driving other tobacco use (e.g., cigarettes) [1, 2], tactics used for promotion of vaping products have been designed to change social norms, create social identities that include vaping as a lifestyle, and generate brand loyalty. JUUL provides a highly effective example with their "Vaporized" advertising campaign and earned media across multiple platforms [3], achieving market dominance within 3 years of product launch. Looking at the Instagram platform alone, a study in 2018 identified nearly 15,000 JUUL-relevant posts with related hashtags from more than 5000 unique users [4]. Themes included lifestyle and social norms, youth-related content, promotional content, and nicotine and addiction. More than half of posts referenced online and offline communities or peer groups (e.g., "JUUL gang is the cool gang"), including posts referencing JUUL use during social activities and events and as part of people's cultural or social identity. Posted content heavily incorporated memes and cartoon imagery, referenced musicians or celebrities, and showed schools and other youth contexts as places where JUUL was used. While much of the content within these posts could not be directly related to paid company advertising, 1/3 of the content was promotional in nature, including direct user engagement strategies such as incentivized "friend-tagging" (e.g., tag your friends, tag your JUUL partner) or giveaways to promote the products. Such tactics reinforced vaping and "JUULing" as socially normal and part of a desired image and culture [4]. While JUUL closed their own Instagram account *@juulvapor* and took action to remove specific content targeting underage consumers in mid-2018, vendors and users continued to promote on Instagram, with the number of JUUL-related posts increasing year over year following JUUL's official halt to the social media platform [3].



An example of JUUL marketing provided by Massachusetts Attorney General Maura Healey's office

Beyond social media, the promotional activities and sponsorships of JUUL and others mimic previous successful tobacco industry tactics [2]: celebrity endorsements, glamorous models, event sponsorships, and with youth-appealing flavors. While event sponsorships are expressly prohibited in the Family Smoking Prevention and Tobacco Control Act of 2009 for cigarettes and smokeless tobacco [5], e-cigarettes are not yet restricted. An investigation released by Senator Rockefeller and other members of Congress in 2014 identified that e-cigarette companies "sponsored dozens of athletic, musical, social and cultural events that appeal to youth" [6]. Thematically, e-cigarettes are promoted across all platforms, sponsorships and promotions with a variety of messages that are appealing to youth: freedom, rebellion, and independence. There are also implicit and incorrect messages that e-cigarettes are a healthier alternative to smoking, again, a concept that is attractive to youth. The 2014 Surgeon General's report clearly stated: "The evidence is sufficient to conclude that advertising and promotional activities by the tobacco companies *cause* the onset and continuation of smoking among adolescents and young adults" [2] (emphasis added). As a whole, these tactics have been highly successful to create curiosity, interest, and positive affect around vaping products, which contributes to behavioral willingness and susceptibility to initiation. The marketing, branding, advertising, and normalization of vaping has undermined decades of tobacco control efforts.

Marketing: Product Appeal

As noted, e-cigarettes have substantially different product characteristics than traditional combusted tobacco that have significant appeal to youth and young adults. Modern e-cigarettes and pod-mod devices such as JUUL have been noted for their sleek design elements: on its release day, a reviewer described JUUL as "the iPhone of e-cigarettes…Once you get used to how to use it, it's all foggy bliss" [7]. Other factors of appeal include user-friendly functions, the "element of fun" associated with their use (e.g., vape tricks) [8], a less aversive use experience (as comparing to smoking) [9], concealability due to small size and low vapor [10], less stigma (than cigarettes) [11], lower perceived risk [11], and a nearly unlimited range of desirable flavors.

While advertising and changes in social norms are first steps in developing the positive attitude toward e-cigarettes, the myriad of flavors are plausibly the next driver of e-cigarette use. The body of evidence from cigarettes has been clear: flavors in tobacco products attract young users [12]. Notably, characterizing flavors other than tobacco and menthol have been banned from cigarettes since the Family Smoking Prevention and Tobacco Control Act of 2009 [5] due to the link between flavored cigarettes and youth initiation. The availability of flavors is a commonly noted reason for vaping initiation [13–17]. The flavors help mask the harsh taste of nicotine, making repeated use more likely. With the thousands of flavor combinations on the market, there is been concern that flavors may also modify the addictiveness of e-cigarettes even beyond masking the harshness: if a pleasurable flavor

is linked with a rapid hit of nicotine, this may be more behaviorally and biologically reinforcing to drive addiction. The appeal of flavors for youth is well understood by e-cigarette manufacturers: a parent education website sponsored by blu e-cigarettes noted in 2014 that "kids may be particularly vulnerable to trying e-cigarettes due to an abundance of fun flavors such as cherry, vanilla, pina-colada and berry." Despite understanding that these products appeal to children, that same company was marketing e-cigarettes at the time in cherry, vanilla, piña colada, and other candy flavors. Refillable e-cigarette liquids come in flavors such as "cotton candy" and "gummy bear," clearly aiming at youth users. Once an adolescent user has tried a vape, there is high risk for ongoing use and escalation due to the addictiveness of nicotine. Many vaping products have high nicotine content, as high as 69 mg/mL [18], leading to rapid blood levels of nicotine [19], and a nicotine "buzz" [4, 8].

What Works for Vaping Prevention?

Youth tobacco prevention has been a focus of public health interventions for decades, with lessons learned over time. As early as 1994, the US Surgeon General's report concluded that educational interventions alone were insufficient to prevent smoking among youth [20]. More promising interventions include teaching social and self-management skills, and changing social norms around tobacco use. All best practices require a multipronged approach. Today, there is a robust evidence base of effective strategies to prevent tobacco use in youth and young adults. These include *policy approaches to restrict youth access to tobacco* through tax increases (to reduce access to price-sensitive youth and young adults), age-of-purchase laws with enforcement actions for businesses, and smokefree public and workplace laws (to reduce locations where smoking is allowed as well as establish smokefree norms); *policies to reduce the impact of marketing* including advertising bans; *mass media campaigns* and *statewide, community-wide, and school-based programs* that educate and change social norms around tobacco use [21]. Since e-cigarettes are a tobacco product, each of these strategies should apply to e-cigarette use and vaping prevention; however, it is also critical to consider regulating other aspects of product appeal, including flavors.

Vaping Prevention in Action: 2015–2020

The various policy approaches to reduce access and regulate product characteristics such as flavors are discussed in detail in Chap. 9. These policy approaches arguably hold the greatest promise in reversing the vaping epidemic, as they impact large populations and do not require individual actions or advocacy. Also

influencing large populations and as described as a key component of the "Tobacco Control Vaccine" (a population-based framework for preventing tobacco-related disease and death) [22], mass-media campaigns have been repeatedly proven to prevent initiation of tobacco use among young people. The most recent major public education campaign for tobacco prevention is "The Real Cost." Initiated by the FDA in 2014 and targeting middle and high school students through internet, social media and television, a focus on vaping started in 2019 [23]. While on school premises, targeted prevention messages are delivered to phones and tablets using geofencing. The FDA also partnered with Scholastic, the world's largest publisher and distributor of children's books, delivering print materials and posters into every public and private high school in the United States to extend the reach of the program.

Such efforts are working but can be threatened. Prevalence data tracking patterns of vaping product use have demonstrated temporal associations between education programs and policies to restrict access with decreased vaping rates. According to data from the National Youth Tobacco Survey, between 2011 and 2014, there was a 900% increase in current (past 30-day) vaping among high school students (1.5% to 13.4%), with further increase to 16% in 2015 [24]. Concerted public health messaging about the risks of vaping for youth and young adults was initiated, with implementation of policies at the national, state, and local levels, and a decrease in vaping prevalence was noted through 2016 and 2017. This progress was thwarted by the introduction of the new class of "pod-mod" products including JUUL as described previously. The skyrocketing sales of JUUL and similar pod-mod products corresponded with a dramatic 78% increase in adolescent use in a single year from 2017 (11.7%) to 2018 (20.8%) [24]. As documented by the National Institute of Drug Abuse Monitoring the Future survey, this reflected the single greatest year-over-year increase for any substance ever measured over the 44-year period of tracking [25].

At the time of this chapter's writing, however, a recent report of vaping use from the National Youth Tobacco Survey of 2020 demonstrated a decline in past 30-day vaping prevalence among high school students, from 27.5% in 2019 to 19.6% in 2020 [26]. A similar study from Monitoring the Future found no change from 2019 to 2020, (22.5% to 21.8%, respectively) [27], supporting a halt to the rapid acceleration of adolescent vaping seen since 2017. These data were collected with a shortened 2-month survey period in early 2020 [26] due to the COVID pandemic closing schools in March 2020; within weeks to months of a federal law increasing the age of sale for all nicotine-containing products to 21 years (December 20, 2019); following many months of heightened media activity in response to the fall 2019 outbreak of E-cigarette or Vaping-Associated Lung Injury (EVALI) which may have deterred use by increasing perception of harm [28]; in the context of the FDA's ongoing targeted mass media "The Real Cost" Youth E-cigarette Prevention campaign [23], and coincident with a policy change February 7, 2020, enforcing against the manufacture, distribution, and sale of flavored prefilled pods or cartridge-based e-cigarettes (excluding tobacco flavors and menthol) [29].

These data are cause for cautious optimism given they reflect a short-term measure that may be immediately responsive to decreased access by the change in law and enforcement and changes in behavior that may have been spurred by health concerns over the EVALI epidemic. Additional data will be needed to assess if this is a sustained decline in vaping prevalence, however, which may be difficult to assess with many schools continuing to be in hybrid or remote schooling formats due to the ongoing COVID-19 pandemic.

Ongoing Policy Advocacy Is Needed for Effective Vaping Prevention

In 2020, the US House of Representatives passed the *Reversing the Youth Tobacco Epidemic Act*; however, this was not taken up in the Senate. This Act would prohibit flavors in all tobacco products, including e-cigarettes, menthol cigarettes, and flavored cigars; prohibit online sales of tobacco products; hold e-cigarettes to the same marketing restrictions as traditional cigarettes; and increase penalties for retailers that sell tobacco products (including e-cigarettes) to those under age 21 [30]. Until this or a similar bill passes into law, there remain significant policy gaps in preventing vaping. Online retailers, in particular, are often ineffective at verifying the age of tobacco product purchasers. Behind a computer screen or smartphone, young people can easily gain access to products where in-person age verification at brick-and-mortar retail stores would have prevented purchase.

Regarding advertising, while there are voluntary self-regulations, there currently are limited controls on the marketing of e-cigarettes and as noted there is significant penetration of e-cigarette marketing to youth audiences, including on broadcast and cable television. TV and radio ads for cigarettes were banned in 1971 to limit exposure to impressionable children. TV advertising creates a halo effect: since cigarettes are not legal to advertise on TV, allowing e-cigarettes to be advertised creates a false dichotomy that "e-cigarettes must be ok if they can be advertised on TV." A critical opportunity was lost when e-cigarettes were allowed to evade the cigarette TV advertising ban: youth today are no less impressionable than the children of the 1970s, 1980s, 1990s, etc. In response to the EVALI epidemic, several networks stated in 2019 that they would no longer allow e-cigarette advertising, including CNN, WarnerMedia, CBS, and Viacom [31]. These voluntary standards are non-binding, however, and could be reversed. Advocacy remains important to hold e-cigarettes and all other deemed tobacco products to the same advertising limitations as traditional cigarettes, which would importantly include prohibition of brand sponsorship of athletic, music, and concert events and distribution of branded non-tobacco merchandise, creating advertising and sales parity across all tobacco products.

Beyond this existing federal action, ongoing advocacy approaches are also needed to extend smokefree public and workplace laws to include prohibition of vaping products.

Other Effective Prevention Interventions: Statewide, Community-wide, and School-Based Programs That Educate and Change Social Norms Around Tobacco Use

As noted, tobacco prevention efforts can be derailed with disruptive innovations such as new product entries to the market (as seen with JUUL), requiring vigilance in product surveillance. Further, each new successive generation of youth needs to be exposed to effective and fresh information to educate regarding the harms of vaping to prevent initiation. School-based programs, in particular, have been found to reduce or postpone the onset of tobacco use, working best if integrated into community or state-wise prevention efforts. In 1994, the Centers for Disease Control and Prevention (CDC) released Guidelines for School Health Programs to Prevent Tobacco Use and Addiction, which synthesized research, theory, and current practice. These guidelines suggested that schools implement seven recommendations to effectively prevent tobacco use among youth: (a) develop and enforce a school policy on tobacco use; (b) provide instruction about the short- and long-term negative physiologic and social consequences of tobacco use, social influences on tobacco use, peer norms regarding tobacco use, and refusal skills; (c) provide tobacco-use prevention education in kindergarten through 12th grade; (d) provide program-specific training for teachers; (e) involve parents or families in support of school-based programs to prevent tobacco use; (f) support cessation efforts among students and all school staff who use tobacco; and (g) assess the tobacco-use prevention program at regular intervals.

With regard to more detailed content, health risk information is not enough. Adolescents today are engaged consumers and digital natives who often seek information on their own, and believe that they can interpret it and assess risk. Focus groups conducted for The Real Cost campaign identified that vapes are viewed as the "lowest risk" of the available substances [32]. Adolescents have created a false narrative, built largely on advertising and social media, that vapes are a healthier alternative to smoking, that they are edgy and cool and more compelling than combusted tobacco. Through message testing with adolescents around vaping and smoking, key themes to prevent vaping and other tobacco use have been identified: the predatory nature of the vaping (and tobacco) industries, and teaching about industry marketing and countermarketing, addiction, social norms, and social influences.

One exemplar highly effective program is the *Stanford Tobacco Prevention Toolkit*, funded in part by California's Tobacco-Related Disease Research Program, the California Department of Education, and CVS Health Foundation. The toolkit includes theory-based and evidence-informed multimedia resources, created by educators, parents, and researchers with the goal to prevent middle and high school students' use of tobacco and nicotine. Available at no cost, this customizable curriculum includes a broad menu of modules that can be used across a range of ages to develop refusal skills, build knowledge and resilience, and prevent tobacco use. Modules and units include printable posters, PowerPoints with teacher talking points, fact sheets, sample curricula, FAQs, activities, quizzes and games,

discussion guides for parents, as well as in-depth lesson plans and information for teachers. Modules can be scaled for time, with recommendations how to tailor materials accordingly and technical assistance as needed. Importantly, there are specific modules regarding vaping prevention. To date, this curriculum or aspects of it have been delivered to over 700,000 students in the United States over a 2-year period. https://med.stanford.edu/tobaccopreventiontoolkit.html.

Another exemplar program is the *Taking Down Tobacco Program* created by the Campaign for Tobacco Free Kids, a comprehensive youth advocacy training program geared to middle and high school students. This program teaches transferable advocacy skills using experience-based advocacy courses on messaging, media advocacy, and decision-maker engagement, with the goal of equipping youth to change their local communities. www.TakeDownTobacco.org.

Many other reputable programs are available; however, it is important to consider the source [33]. The 2012 Surgeon General's report, *Preventing Tobacco Use Among Youth and Young Adults*, reviewed tobacco industry-sponsored, youth prevention initiatives in depth, including school-based programs. The report found that "the tobacco industry's youth smoking prevention activities and programs have not provided evidence that they are effective at reducing youth smoking. Indeed, unpublished internal industry documents available to the public because of litigation, and published academic studies, indicate that they are ineffective or serve to promote smoking among youth" [21]. In spite of such warnings, JUUL created a school vaping education curriculum and paid schools and camps for the opportunity to deliver "anti-vaping" messaging directly to students [34]. In congressional testimony, JUUL was shown to have taken content directly from the Stanford Tobacco Prevention Toolkit, modifying it to remove portions relating to flavors, how the e-cigarette industry markets to youth, and the impact of nicotine on the brain [35, 36]. Industry-sponsored programming should not be used in effective efforts for tobacco prevention.

The Role of Health Professionals in Vaping Prevention

As trusted health providers providing health supervision, it is critically important that pediatricians, family physicians, and advanced practice providers also play their role in tobacco prevention by talking with patients and parents about tobacco. Parents should be encouraged to express disapproval of all tobacco use (including vaping), and to keep the home tobacco free and make tobacco products inaccessible (even if parents smoke or vape themselves). Parents should be supported and provided assistance in quitting tobacco using evidence-based techniques and FDA-approved medications. Parents should be aware of vaping products and their risks and speak with other parents and community stakeholders about creating vape-free and tobacco-free expectations for their communities. Kids should be counseled about the risks of all tobacco use and screened for peer or personal use. If identified,

every patient at any stage of use should be appropriately helped with cessation as described in Chap. 6.

Tobacco prevention is possible, and our first tobacco-free generation within reach if the trend can be reversed on the vaping epidemic among youth.

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Chapter 9
The E-Cigarette Regulatory Landscape: Policy and Advocacy Approaches

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Introduction

Electronic cigarettes (e-cigarettes) entered the US marketplace around 2006 [1, 2]. At the time, traditional cigarettes were subject to regulations established decades prior. E-cigarette producers strategically circumvented those tobacco ordinances and have been able to market, sell, and dramatically expand the use of e-cigarettes in a largely unregulated market [3].

Regulatory delays have been fueled by legal controversies regarding how to classify electronic cigarettes; well-funded industry challenges to campaigns to regulate the manufacture, import, and sale of said products; legislative loopholes; aggressive advocacy efforts of lobbyists and pro-vaping groups; deceptive marketing; and controversial claims that e-cigarettes are harm-reducing products [3]. All of these missteps have worked in tandem, continuing to play a crucial role in the rapidly evolving youth vaping crisis.

As Big Tobacco companies own a substantial portion of the e-cigarette market, it is perhaps not surprising that the e-cigarette industry's current product growth strategies mirror those tobacco companies used years ago [2, 4, 5]. These tactics are designed to encourage youth smoking initiation and foster a lifetime of nicotine addiction, without regard for potential health consequences. Recent data underscores the industry's marketing success and disregard for the public's health. In less than a decade, rates of e-cigarette usage and associated disease have rapidly skyrocketed, particularly among adolescents. In 2011, 1.5% of high school students reported e-cigarette use in the past 30 days [6]; in 2016, high school student use had

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S. C. Walley, K. Wilson (eds.), *Electronic Cigarettes and Vape Devices*,
https://doi.org/10.1007/978-3-030-78672-4_9

risen to 11.3%. By 2020, rates of high school student e-cigarette usage rose to 19.6%; 4.7% of middle school students also reported e-cigarette use in the last 30 days. Based upon these statistics, it is estimated that in 2020 over 3.5 million high school and middle school students used electronic cigarettes [7, 8].

In 2018, after delaying to impose e-cigarette regulations that had been written into federal law, Dr. Scott Gottlieb, Commissioner of the Food and Drug Administration (FDA) at the time, declared e-cigarette use among adolescents an "epidemic," noting that "E-cigs have become an almost ubiquitous–and dangerous–trend among teens" [9]. In fact, large numbers of e-cigarette users have become addicted to nicotine; many will eventually turn to traditional cigarettes, vape other substances, and suffer acute or chronic adverse health consequences [10, 11]. Thousands of e-cigarette users have been hospitalized with the acute lung disease electronic cigarette or vaping-associated lung injury (EVALI), and numerous individuals are known to have died of e-cigarette-related illnesses [12–15].

Federal Regulations

The Federal Government's efforts to regulate e-cigarettes have been marked by legal battles, recurrent federal delays, loopholes, and only limited success. The first federal attempt to assert authority over these products occurred in 2008, when the FDA issued an import alert guiding districts to seize shipments of electronic cigarettes from China and ban the goods from entering the United States [16, 17]. Classifying e-cigarettes as "unapproved drug-device combination products," the FDA claimed that without FDA approval the products, like all FDA unapproved drug-devices, are prohibited under the Federal Food, Drug, and Cosmetic Act (FD&C Act) [17, 18].

FDA efforts to ban e-cigarette entry into US markets resulted in multiple drawn-out court battles [18]. Electronic cigarette manufacturers Smoking Everywhere and Sottera (now NJOY) challenged the FDA in court, arguing that in fact their products did not meet the criteria of "unapproved drug-device combination products" (*Sottera v FDA)* as they did not provide therapeutic effects [19, 20]. While the legal battles played out in court, e-cigarettes were aggressively marketed, distributed, and sold throughout the United States and their use continued to increase.

Advocacy groups such as Action on Smoking and Health and a coalition that included the American Medical Association, the Campaign for Tobacco Free Kids, the American Cancer Society, and the American Heart Association campaigned to grant the FDA authority over e-cigarettes based on law written into the *Federal Food, Drug, and Cosmetic Act (FD&C Act)* [21]. Some state and government officials, including the National Association of Attorney Generals, also advocated in favor of granting the FDA power to regulate e-cigarettes as well as to ban e-cigarette sales and use [22]. In September 2009, California passed a bill banning the sale of e-cigarettes in the state, yet Governor Schwarzenegger overruled the bill [23]. In 2010, legislators in New York and Illinois also submitted bills to ban e-cigarettes;

those bills failed to pass [3, 24, 25]. Supporting anti-smoking groups and electronic cigarette legislation, internet giant Amazon banned the sale of e-cigarettes on their website in 2009 and PayPal froze all e-cigarette vendor accounts that same year [21].

Nevertheless, in December 2010, the courts ruled in favor of the e-cigarette manufacturers, determining that electronic cigarettes cannot be classified as "drug-device combination products" or regulated as such. The courts further ruled that e-cigarettes must be classified and regulated as "new tobacco products" [18], while recognizing that they contain tobacco-derived substances, such as nicotine, rather than actual tobacco [19, 26].

In June 2009, prior to the court's ruling, President Barack Obama signed the *Family Smoking Prevention and Tobacco Control Act* (*Tobacco Control Act*). This legislation amended the *FD&C Act* and granted the FDA authority to regulate "the manufacturing, distribution, and marketing of tobacco products," including cigarettes, cigarette tobacco, and smokeless tobacco products [27, 28]. In 2010, when the courts classified e-cigarettes as "new tobacco products," the courts also determined that the FDA's authority to regulate those products required formal revision of the *FD&C Act*, through the addition of the Deeming Rule [29]. During the period of time from 2010 (when the courts granted the FDA jurisdiction over e-cigarettes as new tobacco products) until 2016 (when the FDA finally published the Deeming Rule), e-cigarettes were intensely marketed and sold in a federally unregulated market; their use soared.

A draft of the Deeming Rule was first proposed in 2014, some 4 years after the court's ruling [29]. It was not until August 2016 that the FDA released the final Rule, extending the authority granted to the FDA to regulate "all tobacco products," including electronic cigarettes and other electronic nicotine delivery systems (ENDS), pipe tobacco, cigars, and hookah and waterpipe tobacco. The Rule grants the FDA oversight of e-cigarette ingredients, warnings regarding potential product health risks, and the registration of manufacturers [29, 30]. The Rule also sets a federal minimum age of sale of 18, requires retailers to obtain photo identification (ID) verification of the age of those under 27, prohibits distribution of free e-cigarette samples, and limits vending machine e-cigarette sales to adult only facilities [27, 29]. Importantly, the rule establishes an FDA premarket tobacco product application (PMTA) review process that requires the FDA's approval of all e-cigarettes prior to a product's sale in the marketplace [14, 29]. When submitting an application to market an e-cigarette product, manufacturers must "provide scientific data that demonstrates a product is appropriate for the protection of public health" [29, 31].

Two years after the passing of the Deeming Rule, the PMTA review process had still not been implemented. In fact, in August 2017 the FDA extended the deadline for the industry to submit a PMTA to August 2022 while continuing to allow e-cigarettes to be marketed and sold. In response to this extension, in 2018 a coalition of the American Academy of Pediatrics, the American Medical Association, the American Cancer Society Cancer Action Network, the American Heart Association, the American Lung Association, the Campaign for Tobacco Free Kids, and the Truth Initiative sued the FDA and the Department of Health and Human Services [32]. After

many court battles, the application deadline was changed to September 9, 2020 [33]. The FDA has nearly 1 year to review submitted applications and determine whether products are proven to be safe and can be legally marketed and sold [31]. During this review period, products can remain on sale in the marketplace. As such, the e-cigarettes on the market at the time of this writing have not been evaluated or approved by any government regulatory agency, nor have they been determined to be safe.

State and Local Tobacco Regulations

The 2009 *Tobacco Control Act* grants states and localities the explicit authority to enact tobacco control policies in addition to those established under federal law, specifically in areas in which the FDA has not been granted authority to set regulations [27, 28]. By law, states and municipalities can legislate smoke- and aerosol-free zones, increase tobacco taxes, establish product prices, raise the minimum legal sales age above 18, and even prohibit the sale or use of certain categories of tobacco and vaping products [18, 26].

While state governments play a crucial role in protecting the public's health through legislation, earlier tobacco control efforts illustrate that policy-based campaigns that begin at the local level are often more effective and efficient than those initially promoted at the state level [3, 34]. State-level tobacco control campaigns can be hindered by well-funded tobacco industry lobbying and targeted campaign contributions to key legislators [3, 35]. By contrast, local governments tend to be more responsive to their constituents, health professionals and community organizations than they are to lobbyists. In many instances, local government has been shown to offer a viable avenue for successful tobacco control legislation, as grassroots efforts launched at the local level can mobilize constituents and lead to statewide or even national legislation (Table 9.1) [3, 34]. As described below, many states and localities have passed tobacco control legislation, though e-cigarette regulations continue to lag behind those of traditional tobacco products.

Tobacco-Free Policies

Combustible Tobacco Smoke-Free Policies

Long before the arrival of e-cigarettes in the United States, for much of the mid-twentieth century, smoking was a centerpiece of American culture; smokers were free to light-up almost anywhere. Individuals were commonly found smoking combustible cigarettes in public spaces such as workplaces, hospitals, doctors' offices, restaurants, and on buses, trains, and airplanes. Images of cigarettes and smokers were prevalent, seen on billboards and magazine covers and in newspapers, television shows, and movies [37, 38].

Table 9.1 Strategies and operationalization for public health advocacy [34]

Strategy type	Operationalization
Local advocate/change agent	Recruit respected members of local community, who can coordinate with local and national advocacy groups and use vignettes to illustrate the importance of proposed legislation. Include nurses, pediatricians, counselors, school administrators, teachers, etc.
Geographic proximity	Enlist leaders from locations that have already passed the proposed legislation to approach bordering jurisdictions yet to pass. Work with more progressive border towns of major cities to pass the legislation first, in order to "surround" locations where passage might be more challenging.
Simple messaging	Develop a one-page document with the key arguments for the proposed legislation concisely summarized. Poll jurisdictions and ask if they would like more information regarding the proposed legislation. Start advocacy with those jurisdictions expressing greatest levels of interest.
Youth advocacy	Work with youth advocates, such as high school and college students, to advocate for passage.
Inoculation against counterarguments	Understand the most common counterarguments and preempt those arguments with opposing research and data.
Press and media [36]	Develop op-eds and contact the press/media about meetings to provide local coverage.

It was not until the 1970s and 1980s that evidence of the harmful health effects of inhaling secondhand smoke emerged. While the tobacco industry and multiple smoker-advocacy groups pushed back on the scientific findings, national groups such as the American Nonsmokers' Rights Foundation and Action on Smoking and Health, and grassroots organizations such as the Group Against Smoking and Pollution actively petitioned for designated non-smoking areas in public places [39]. These early advocacy efforts launched the non-smokers' rights movement. This powerful coalition of individuals and organizations successfully campaigned at the state and local levels for smoke-free policies designed to protect non-smokers from the health consequences of secondhand smoke, effectively discouraging smoking initiation and a culture that embraces cigarette use [40].

The first smoke-free state legislation was passed in the 1970s, when states such as Minnesota began to limit smoking through the creation of smoking and non-smoking zones in public spaces [37, 39]. Over time, other states and localities enacted smoke-free ordinances, which varied in scope and in the nature of their restrictions. In 1990, San Luis Obispo, California, became the first municipality to pass major smoke-free legislation, banning smoking in buildings open to the public, including restaurants and bars. In 1995, Utah banned smoking in restaurants, becoming the first state to pass a statewide smoke-free law. California followed, banning smoking in restaurants in 1995 and in bars in 1998. In 2002, Delaware passed the first comprehensive smoke-free laws, laws that the CDC defines as prohibiting smoking in all indoor worksites, restaurants, and bars [41]. New York soon followed, passing comprehensive smoke-free restrictions in 2003 [42, 43].

As of April 2021, 27 states and the District of Columbia have passed comprehensive smoke-free laws. Nine additional states have passed more stringent legislation, limiting the restrictions to workplaces, restaurants, and/or bars, but not all three locations. Further, over 1000 cities and counties have enacted comprehensive smoke-free mandates, and an additional 450 localities have passed less inclusive smoke-free legislation [43]. Private organizations and industries, such as hotels and gyms, have also established rules that ban combustible cigarette use on private property or limit the usage of tobacco products to designated smoking areas. Some of these private locations that prohibit or limit smoking are found in states in which there are otherwise few smoke-free regulations [44, 45].

Although most efforts to enact smoke-free laws banning traditional tobacco product use have been left to states and municipalities, the Federal Government and its agencies have passed smoke-free policies that specifically focus on three types of locations: Federal Government buildings, airlines, and public housing. In 1997, President Clinton issued Executive Order 13058, banning smoking in all Federal Government buildings [46]. Tobacco control advocates had campaigned for such a policy as early as 1971, while previous presidents had drafted similar executive orders and multiple legislatures had proposed such a policy in the senate. However, responding to tobacco lobbyist pressures, the attempts of earlier administrations to sign such restrictions into law were defeated [47]; only at the end of the century was this Executive Order finally issued.

In the airline industry, federal restrictions were imposed only years after individual consumers and organized groups, such as flight attendants, voiced complaints to the industry and its leaders regarding dangerous exposures to secondhand smoke. Those who opposed the harms of secondhand smoke also advanced their agenda by joining the advocacy efforts of groups such as "the Group Against Smoking and Pollution and the American Nonsmokers' Rights Foundation, organizations that had battled for years with tobacco lobbyists and secured the support of the American Medical Association, the American Lung Association, and the American Heart Association [37].

In 1971, United Airlines became the first airline company to identify smoking and non-smoking zones on their aircraft. Soon, other airlines followed. By 1973, the Civil Aeronautics Board declared the establishment of non-smoking sections on all airplanes to be a federal requirement [37]. While the tobacco and airline industries joined forces to defeat all efforts to ban smoking on airlines, the first such ban went into effect in 1988, eliminating smoking on all flights of 2 hours or less. By early 1990, legislation had passed banning smoking on all domestic flights [37, 44]. In 1995, after Delta Air Lines banned smoking on all domestic and international flights, other airlines also adopted this smoke-free policy. By 2000, a comprehensive federal law was finally passed banning traditional cigarette smoking on all flights entering and leaving the United States, an important victory for individuals and groups that had championed non-smokers' rights since the early 1970s [48].

In 2016, a third federal smoke-free zone was established by the US Department of Housing and Urban Development (HUD) [49]. This action followed intense local, city, and state advocacy efforts that were accelerated by legal and ethical

arguments to ban smoking in all public housing authorities [50]. HUD passed a rule requiring all public housing agencies to implement a smoke-free policy banning the use of tobacco products—excluding e-cigarettes—in low-income public housing units by July 2018 [49]. This ordinance was encouraged by a study that found that children in multi-unit housing complexes had significantly higher rates of cotinine biomarkers in their blood, even when no one in their personal housing unit smoked [51]. The successes of tobacco control activists, who battled with the tobacco industry and lobbyists regarding regulating smoke-free zones, illustrate an effective model in which public health action at the grassroots level spurs important legislative and even industry-wide change [34].

E-Cigarette Clean Air Policies

Notably, while states, municipalities, federal agencies, and industries have gradually endorsed smoke-free rules regulating traditional tobacco products, e-cigarettes are not automatically subject to these same prohibitions. In fact, because smoke-free laws were written to prohibit "smoke" and e-cigarettes emit an aerosol that contains a suspension of fine particles and harmful chemicals rather than smoke, policy makers initially failed to prohibit smokers from using e-cigarettes in most locations [1]. The tobacco industry has taken full advantage of this legislative loophole, originally marketing e-cigarettes as devices that circumvent smoke-free zones and provide individuals with the "freedom to smoke anywhere" [52, 53].

As of 2021, some states and municipalities have amended their existing smoke-free policies to include e-cigarettes, supporting the health of those who choose not to inhale the toxic aerosol e-cigarettes produce. In 2009, Suffolk County, New York became the first community to update its smoke-free tobacco ordinance to include electronic cigarettes [54]. In 2010, New Jersey followed by North Dakota and Utah were the first states to impose these same restrictions. Additional states including Hawaii and Delaware passed comprehensive e-cigarette clean air legislation in 2015. California, Vermont, and New York followed in 2016–2017 [54]. As of April 2021, 15 states and the District of Columbia have passed comprehensive smoke-free laws that include electronic vaping devices. These states prohibit the use of both traditional cigarettes and e-cigarettes in worksites, bars, and restaurants [55, 56].

While more than a quarter of US states impose comprehensive e-cigarette restrictions, many other states impose regulations that are narrower in scope. For example, Maine bans e-cigarette use in restaurants and bars, while Nevada places restrictions on e-cigarette use in workplaces and restaurants [26]. Some states, such as Georgia and Illinois, only prohibit e-cigarette use in the buildings and on the grounds of state universities. Other states specifically prohibit electronic cigarette use in public schools, ambulances, correctional facilities, museums, hospitals, railways, and/or childcare facilities. As of April 2021, only Idaho, Indiana, and Mississippi have failed to pass any statewide restrictions on the use of e-cigarettes in particular locations [26, 56]. Although this data suggests an overall positive trend, it also indicates that nearly half

of the states that have comprehensive smoke-free ordinances that prohibit the smoking of traditional cigarettes in public spaces do not include e-cigarette use in those policies. This data highlights a significant regulatory gap and the urgent need for targeted advocacy efforts in many states.

In addition to state laws regulating aerosol-free zones, municipalities throughout the United States have passed ordinances that establish local e-cigarette clean air zones in public spaces [56]. These local regulations are particularly important in states that have not passed statewide policies regulating e-cigarette use. While some of these municipalities have comprehensive laws that include workplaces, restaurants, and bars, other municipalities have passed more stringent laws restricting the use of e-cigarettes in select locations. The number of localities that impose aerosol-free laws has increased dramatically in the last decade. In 2013, 181 municipalities had implemented such a law; 5 years later, e-cigarette clean air regulations had been implemented in 745 municipalities [54]. As of April 2021, nearly 1000 municipalities have passed restrictions on the use of e-cigarettes in certain public spaces [56]. Local e-cigarette clean air laws have been passed in municipalities in all states that do not otherwise have statewide smoke-free laws [56].

On the federal level, smoke-free ordinances that ban traditional cigarette use have recently been applied to the use of e-cigarettes on airlines. In 2016, the US Department of Transportation issued a rule banning e-cigarette use on all flights on which the use of traditional cigarettes is prohibited, including charter flights [57]. Although HUD has not announced a policy regulating e-cigarette use in public housing facilities, at the time of this writing the agency has granted individual public housing authorities jurisdiction to restrict the use of e-cigarettes in housing units and on surrounding property [58].

Smoke-free cigarette and e-cigarette zones are critical to safeguarding the public's health. History verifies that they are also crucial because of their potential to transform the culture of acceptance that now surrounds e-cigarette use, particularly among youth [37]. As they did for traditional cigarettes, clean air regulations for e-cigarettes can redefine the fundamental values and social assumptions that surround electronic cigarette use and assist in the establishment of healthier cultural norms.

Federal, State, and Local Tobacco Taxes

A strong body of evidence has shown that tax increases on traditional tobacco products are among the most effective policies to reduce smoking rates. The 2014 *Report of the Surgeon General* notes that "significant increases in tobacco taxes and prices reduce tobacco use by leading some current users to quit, preventing potential users from initiating use, and reducing consumption among current users" [40]. The 2016 report of The National Cancer Institute and World Health Organization entitled *The Economics of Tobacco and Tobacco Control* echoed similar findings: "A substantial body of research, which has accumulated over many decades and from many

countries, shows that significantly increasing the excise tax and price of tobacco products is the single most consistently effective tool for reducing tobacco use" [59]. As with the tax on traditional cigarettes, early research suggests a tax on e-cigarettes to be an effective strategy to reduce e-cigarette use, particularly among adolescents. For example, a 2018 study notes that a 10% increase in e-cigarette prices is associated with a 9.7% reduction in the number of days middle and high school students use e-cigarettes [60].

The federal excise tax on traditional cigarettes was first levied in 1864 as a means of raising revenue during the American Civil War [61]. Currently, the federal cigarette tax is $1.01 per pack, which represents an over 12-fold increase from 8 cents per pack in 1970 [62]. All US states also levy a state excise tax on cigarette packs. As of January 2021, the lowest state cigarette tax is $.37 per pack in Georgia, followed by $.44 in North Dakota. By contrast, Connecticut, New York, and the District of Columbia have the highest tax rates, at $4.35, $4.35, and $4.50 per pack, respectively [62].

Over the last two decades, 48 states and the District of Columbia have increased cigarette tax rates 141 times [62]. In addition to excise taxes, most states also apply a state sales tax to the cost of cigarettes. While the majority of counties and cities do not impose an additional local cigarette tax, more than 630 local jurisdictions do. Chicago, Illinois, has the highest combined state and local tax rate at $7.16 per pack. Evanston, Illinois, has the second highest rate at $6.48 per pack [62].

Notably, while the Federal Government imposes an excise tax on all traditional cigarettes, the government does not impose a tax on electronic cigarettes or other vaping products. Similarly, although every US state imposes a tax on cigarettes and some non-cigarette tobacco products (such as cigars or chewing tobacco), at the time of this writing only roughly half of states and a select group of localities impose a tax on e-cigarettes. Some of these states impose a tax through laws newly created to tax e-cigarettes; others have amended their tobacco tax laws to include e-cigarettes and other vaping products [63].

Review of the history of taxes on electronic cigarettes indicates that in 2010 Minnesota was the first state to impose a tax on e-cigarettes [64]. It was 5 years before other states followed: North Carolina, Louisiana, and the District of Columbia imposed such a tax in 2015 [26]. By the start of 2019, nine states and the District of Columbia had imposed an e-cigarette excise tax. By the end of that year, that number had more than doubled. As of March 2021, 29 states and the District of Columbia have enacted an excise tax on e-cigarettes. While Alaska does not impose state taxes on electronic cigarettes, municipalities within the state impose local e-cigarette taxes [26, 55].

Data confirms that there have been some increases in state efforts to regulate e-cigarettes through evidence-based economic strategies that can result in a decline in e-cigarette use while also raising revenue. However, the number of states and localities that impose e-cigarette taxes continues to significantly lag behind that of jurisdictions that tax traditional cigarettes, suggesting an important strategy that many states and municipalities have yet to adopt to affect a decline in youth e-cigarette use and reverse the current vaping epidemic.

Whereas taxes on cigarettes are uniformly imposed on a per pack basis, states and municipalities that levy taxes on e-cigarettes do so utilizing three different models. Some tax e-cigarettes based on a percentage of the items' wholesale prices; others tax a flat rate per millimeter of e-liquid or per e-cigarette cartridge; yet other states use a system that is a combination of these two approaches [65]. Of those states that tax based on a percentage of product value, Minnesota has the highest rate (95%) followed by the District of Columbia (91%) and Massachusetts (75%) [63].

Numerous public health advocacy groups, individual stakeholders, and community groups have launched campaigns to advocate for their state legislatures to implement an excise tax on e-cigarettes and other vaping products. For example, the Foundation for a Healthy Kentucky coordinated with the state Chamber of Commerce, the Cancer Foundation, the Health Collaborative, the Medical Association, and the Kentucky Youth Advocates to campaign for an excise tax bill on e-cigarettes, which successfully passed in April 2020 [66]. In Utah, parents, students, school staff and administrators, and numerous health, public health, and religious groups campaigned for a tax on e-cigarettes as a means to reduce youth e-cigarette use. These groups included the American Cancer Society Cancer Action Network, the American Heart Association, the American Lung Association, the Campaign for Tobacco Free Kids [67], Students Against Electronic Vaping, The Church of Jesus Christ of Latter-day Saints, and the St. George Interfaith Council [68]. Utah passed the tax bill in February 2020, though many legislators were displeased that the original proposed tax of 86% was reduced in the final passed legislation to a 56% tax on e-cigarettes [26, 69].

In the case of e-cigarette taxes, statewide legislative successes have often followed local advocacy efforts. This underscores the role that partnerships between local community leaders and state and national health and tobacco control organizations can play in campaigns designed to curb e-cigarette initiation and use. Because they have been shown to be an effective tobacco control measure, e-cigarette taxes should be a major target of advocacy efforts designed to combat the current youth vaping epidemic.

Regulation of E-Cigarettes and Characterizing Flavors

The 2009 *Family Smoking Prevention and Tobacco Control Act* bans the marketing and sale of all traditional cigarettes containing any characterizing flavor (e.g., fruit), with the exception of menthol [28]. Evidence shows that the 2009 Act contributed significantly to declines in youth smoking rates. A recent study found that the flavors ban led to a 43% reduction in underage smoking (ages 12–17) and a 27% decline in smoking among young adults (ages 18–25) [70]. An earlier study reports that after the signing of the 2009 Act the likelihood of youth initiating smoking declined significantly as did the number of cigarettes those who were smokers smoked [71]. These and similar findings demonstrate that the ban on flavored

traditional cigarettes is a necessary tobacco control policy to protect youth from smoking initiation, decrease the appeal of cigarettes, and ultimately reduce the societal harm of tobacco products.

Although banning the sale of flavored cigarettes was known to lower youth smoking rates, flavored e-cigarettes were left unregulated for years, largely due to tobacco industry pressure. The industry has taken full advantage of the regulatory gaps it helped create, steadily increasing the introduction of flavors into the e-cigarette marketplace [1, 72]. E-cigarette products have been distributed and sold in a panoply of enticing flavors, such as chocolate, cotton candy, gummy bear, peanut butter, whipped cream, banana split, fruit medley, and menthol, all of which target youth and encourage e-cigarette initiation and nicotine addiction [71]. By 2017, more than 15,500 e-cigarette flavors were available for purchase, up from slightly under 8000 flavors in 2014 [1, 71].

The menacing role of flavors in the current vaping crisis is confirmed by a 2019 study that reports that over 70% of high school students who use e-cigarettes use flavored products [73]. In 2016, fruit and candy were the most popular flavors among high school students; since then, fruit and mint/menthol have grown to be the first-choice e-cigarette flavors among youth [14, 74].

While the 2016 Deeming Rule grants the FDA the authority to regulate flavored vaping products, the agency has taken delayed and only limited action to do so [14]. In September 2019, the Federal Government announced a plan to ban all flavored e-cigarettes and nicotine pods [75]. After extensive tobacco industry and lobbyist pushback, the FDA rolled out the Government's final policy in January 2020 [76]. This ordinance prohibits the sale, distribution, and production of certain flavored cartridge-based e-cigarette products (such as JUUL), except for tobacco, mint, and menthol flavors. The weakened regulation also allows for the sale of flavors in non-cartridge-based vaping products, such as e-cigarettes that use refillable e-liquids. Additionally, it does not prohibit the sale of flavored disposable vaping products [76].

While the FDA restriction specifically bans the distribution and sale of flavored cartridge-based vaping products, none of the e-cigarettes on the market at the time of this writing have received the FDA's approval through the premarket tobacco application process. Given this current status, the FDA announced that the flavor restrictions are not a "ban," but rather an outline of the agency's enforcement priorities. The FDA notes, it "will make enforcement decisions on a case-by-case basis, recognizing that it is unable, as a practical matter, to take enforcement action against every illegally marketed tobacco product, and that it needs to make the best use of Agency resources" [76]. In July 2020, the FDA further announced restrictions on the sale of flavored disposable e-cigarettes such as Puff Bar® and ordered that they be removed from the marketplace. However, due to the FDA's limited enforcement capacity, those products remained widely available for sale throughout the United States through at least 2020 [77]. Numerous health and advocacy groups have protested the FDA's less-regulated version of the flavor ban, including the American Academy of Pediatrics, the American Heart Association, the American Lung Association, the American Cancer Society Cancer Action Network, the Campaign

for Tobacco Free Kids, and the National Association for the Advancement of Colored People [78].

Some advocates have turned their campaigns to the state level, where they have found that legislative efforts to enact a ban on flavored e-cigarettes have led to disappointing delays and legal battles. Michigan is one such state; notably, the courts blocked the Governor's 2019 efforts to ban the marketing and sale of all flavored vaping products [79]. As with other tobacco control efforts, a large percentage of the campaign to restrict flavors now focuses on the local level, where teens, parents, teachers, counselors, school administrators, religious groups, and community groups and leaders join with organized advocacy groups [3, 34].

Such an advocacy model has proven to be an effective public health strategy in Massachusetts, the first state in the nation to pass a comprehensive ban on all flavors, including mint and menthol. Public health advocates launched successful local campaigns throughout the state. In July 2014, Yarmouth was the first Massachusetts town to pass the ban on flavored e-cigarettes; Newton and then Sherborn followed in September of that same year [80]. By late 2019, over 161 municipalities in Massachusetts had passed local policies banning the sale of all flavored vape and tobacco products. These local advocacy efforts ultimately led to Governor Charlie Baker's November 2019 signing of a statewide comprehensive flavor ban applying to the sale of all tobacco products: *An Act Modernizing Tobacco Control* [81, 82]. This legislation asserts a ban on all flavors in electronic and traditional cigarettes and cigars (except tobacco flavor) and includes mint and menthol.

The movement to ban flavored electronic cigarettes at the local level has increasingly gained momentum. In 2018, San Francisco was the first major city in the nation to successfully ban all flavored e-cigarettes, including mint and menthol [83]. Since that time, many other municipalities have passed similar ordinances. Groups such as the American Cancer Society, the American Heart Association, the American Lung Association, and the Campaign for Tobacco Free Kids, and individuals such as former New York City Mayor Michael Bloomberg supported the San Francisco ban with aggressive funding, advocacy efforts, and pushback against the well-funded tobacco industry [84]. By the end of 2019, 274 localities had placed restrictions on some flavored vaping products; importantly, 88 of those localities had comprehensive bans, meaning they included menthol products. As of December 2020, the number of jurisdictions with flavor restrictions has increased to 331, including 7 states and 143 cities; 14 states have at least 1 jurisdiction with restrictions against flavored vaping products [85].

States that have passed comprehensive statewide flavor bans on e-cigarettes include Massachusetts, New York and Rhode Island; Massachusetts is the only state as of this writing to include regular menthol cigarettes in its flavor ban. Other states have imposed less broad restrictions. Maryland prohibits all cartridge-based and disposable e-cigarette flavors except for menthol. Utah similarly allows the sale of menthol as well as mint products, while prohibiting other flavors. Yet other states impose more limited flavor restrictions [85].

A recent study conducted after San Francisco banned flavors concluded that the overall use of flavored tobacco products in the city declined significantly and that local flavor bans can effectively reduce e-cigarette use [86]. Studies such as this provide strong evidence that the elimination of flavored vaping products is pivotal to policies designed to reduce adolescent and young adult initiation and use of those products [87]. As the nation awaits the FDA's actions on the electronic cigarette premarket tobacco application process, cities and municipalities are well situated to undertake campaigns to ban flavored tobacco products and defend against the youth vaping crisis.

Tobacco 21 Enactment and Enforcement

Tobacco 21 (T21) refers to state and federal legislation that raises the minimum legal age of tobacco sales from 18 to 21. This policy first emerged in the United States in Needham, Massachusetts, in 2003 [34]. At the time, the Needham Board of Health announced the policy as a response to community concerns regarding youth cigarette smoking rates; the policy went into effect in 2005. Some 7 years later, after data was published documenting a dramatic decline in smoking rates in Needham youth from 2006 to 2012, two pediatricians launched a movement throughout Massachusetts to raise the minimum age of tobacco sales from 18 to 21. Through strong advocacy efforts, T21 policy spread from town to town in Massachusetts, as well as to towns, cities, and states throughout the nation before passing at the federal level in 2019 [34].

Soon after the 2012 passing of T21 legislation in a number of towns in Massachusetts, the "Big Island" of Hawaii adopted the policy in November 2013. This was quickly followed by the passing of T21 legislation in New York City [34]. In 2015, Hawaii became the first state to pass Tobacco 21 legislation, followed by California in 2016, and New Jersey in 2017. The following year Massachusetts, Oregon, and Maine passed statewide T21 legislation. At the time that Massachusetts passed the statewide legislation, over 230 towns in the state had raised the minimum tobacco sales age from 18 to 21 [88].

Notably, in December 2019, the Federal Government amended the FD&C Act and raised the federal minimum age of sale of all tobacco products, including e-cigarettes, from 18 to 21 years [89]. At the time, 19 states had passed Tobacco 21 legislation. Since the federal passing of this tobacco control legislation, additional states have passed their own versions of T21 ordinances with state-specific enforcement parameters. As of June 2021, 37 states, the District of Columbia, and over 550 counties nationwide have adopted Tobacco 21 policy [90, 91].

Since the adoption of Tobacco 21 at the federal level, it has been officially illegal to sell tobacco products—including traditional cigarettes, cigars, and e-cigarettes—to anyone under the age of 21. However, when the policy was signed into law, the FDA and retailers were granted a transition period during which to formally adopt

and implement the new minimum age of sale law. That transition period ended in September 15, 2020. The FDA continued to use those under 18 as trained decoys in its compliance check program during this transition period [92] and has since been using those under 21 [93].

The current federal law prohibiting the sale of all tobacco products, including e-cigarettes, to those under 21 supersedes all established state and local ordinances. Notably, some of these ordinances align with the Federal Government's ruling and are supported by that mandate, while others do not. All states and localities have established legislation that minimally prohibits the sale of both traditional tobacco products and e-cigarettes to minors under the age of 18, in line with previous federal law. While 37 states have implemented T21 policy, states such as Alaska impose a sales age of 19 [90, 91]. The Department of Health and Human Services has given states 3 years to demonstrate compliance with the age 21 ruling; those states that do not comply will be in danger of losing federally available Substance Abuse Prevention and Treatment Block Grant funds [94, 95].

Confusion may abound regarding the enforcement of the minimum age of sale of tobacco products in those states where state legislation designates the minimum age to be under the federal law of age 21. In locations where the state-legislated minimum age of sale remains 18, trained decoys under the age of 18 continue to be used in state compliance checks, even though selling e-cigarettes or other tobacco products to persons under 21 violates federal law [94]. Similarly, in such locations state and local officials are unlikely to enforce federal law, raising the possibility that retailers in some states may continue to sell tobacco products to those under 21.

The recognition that certain states and municipalities have not raised the minimum sales age to 21 highlights the critical need for locations to align with the federal law in order for enforcement and compliance checks to play an effective role in controlling youth access to tobacco products including e-cigarettes. Strong partnerships among community and youth leaders, tobacco-control groups, departments of public health, boards of health, and local politicians can further the spread of Tobacco 21 policy throughout localities and encourage consistent enforcement of T21 regulations [1].

Tobacco Retail Licensing

Many municipalities, cities, and states require retailers to obtain a tobacco or e-cigarette retail license (TRL) before engaging in the sale of tobacco or e-cigarette products. This requirement helps to control the density, number, and location of tobacco and/or e-cigarette retailers and assists with the collection of fees that support some of the costs of enforcement. Retail license requirements also encourage retailers to abide by local, state, and federal tobacco regulations, such as minimum age of sale laws—if only so that retailers avoid penalties, fines, and potential suspension or revocation of a granted license [96].

As of March 2021, 38 states and the District of Columbia set licensing requirements for traditional cigarette retailers. By comparison, 36 states and the District of Columbia have passed laws requiring retailers to obtain a license in order to sell electronic cigarette products, either in store or online [26, 97]. Retailers who conduct business in municipalities where they are not obliged to obtain a tobacco or e-cigarette license cannot be mandated to abide by tobacco or e-cigarette control laws. For example, such retailers are not subject to Tobacco 21 compliance checks or penalties for sales to minors; nor are they limited in where or how they market or sell their products. States and municipalities that do not require retailers to obtain tobacco and/or e-cigarette licenses set the stage for a lucrative unregulated market in cigarette and e-cigarette sales as well as for increased youth access to these products. Advocating for laws that require all retailers of traditional tobacco and e-cigarette products to obtain a license could result in reduced physical access to those products and more limited opportunities for the e-cigarette and tobacco industries to market, sell, and distribute those products, particularly to vulnerable youth [96].

Future Directions

Leaders and organizations can play a critical role in mobilizing constituents and advocating for policies that fully ban the sale of all e-cigarette and vaping products, as occurred in San Francisco in June 2019 [98]. As an alternative to banning the marketing and sale of such products, action can focus on advocating to local and state governments to implement evidence-based policies that discourage youth initiation and use of electronic cigarettes (Table 9.2). In addition to such policy-based measures, school staff and healthcare providers can play important roles in educating adolescents about e-cigarettes' harmful effects, counseling youth to avoid e-cigarettes, and encouraging youth to become engaged in tobacco control advocacy efforts in their schools and local communities [99]. When coupled with strong enforcement efforts, public health policies and local initiatives effectively discourage youth initiation and use of e-cigarettes and can reduce the associated potential for a lifetime of nicotine addiction and adverse health consequences. Such policies are critical to reversing the current youth vaping crisis that is affecting communities across the nation.

Table 9.2 Targets for evidence-based e-cigarette policy

Comprehensive aerosol-free clean air zones
State and/or local e-cigarette taxes
Comprehensive flavor bans that include mint and menthol
Tobacco 21 laws and enforcement
Mandatory licensing requirement

History verifies that when federal and state government actions do not align with public health needs, campaigns at the local level can and should move forward. As they build community support and gain momentum, these advocacy efforts can influence municipalities and successfully advance to the state and even federal level [34], counterbalancing the ill-intentioned tobacco industry and filling those gaps in legislation and enforcement that continue to undermine the public's health.

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Conclusion

We hope that you have enjoyed and learned a great deal from this in-depth exploration of e-cigarettes and vaping devices. Returning again to Dr. Julius Richmond's framework presented in the Introduction for advancing public health policy, we hope that we have increased your knowledge base, given you ideas for social strategies to reduce the epidemic of youth nicotine addiction, and motivated you to engage in the activities to change political will.

The electronic cigarette and tobacco industry is a multi-million-dollar behemoth that has the resources to rapidly adapt their products to induce and capitalize on popular demand. Healthcare professionals have the responsibility to care for patients and parents who have nicotine addiction, and we hope that we have given you some practical tools for this in Chap. 6 and the Resources Section (below), but also to be aware of the broader context. Since the market is rapidly changing, keep asking the teenagers in your life what their friends are using—you may be surprised at what comes up. Keep up to date on the current epidemiology of electronic cigarette use—the CDC updates these data yearly. Healthcare providers, parents, and policy makers can all participate in advocacy to help protect children. Your voice is incredibly important in the activities we discussed in Chaps. 8 and 9. You can make a difference in your organization, town, state, nation, or in your professional organizations. As pediatricians, we both have been closely involved with the American Academy of Pediatrics and their tobacco control work. Our voices are amplified by the participation of the organization and harmonize with the voices from other important groups such as the Campaign for Tobacco Free Kids, American Lung Association, and Parents Against Vaping E-Cigarettes. Advancing this public health policy will take a chorus of passionate voices who believe in keeping youth free from nicotine and tobacco.

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https://doi.org/10.1007/978-3-030-78672-4

Resources Page

Adolescent tobacco cessation resources	How to connect	Program description	Notes
1-800-QUIT-NOW	Enroll by phone (toll-free), fax, or on-line	Provides individual counseling, self-help materials, and referral to resources by trained professionals and in some states, provides cessation medications (≥18 years)	Youth resources vary by state
1-855-DEJELO-YA ("quit now")	Enroll in Spanish by phone (toll-free)	Provides individual counseling, self-help materials, and referral to resources by trained professionals and in some states, provides cessation medications (≥18 years)	Youth resources vary by state
Asian Smokers Quitline	Enroll by phone (number differs by language) or at www.asiansmokersquitline.org/smokers/	Provides individual counseling, self-help materials, and referral to resources by trained professionals and in some states, provides cessation medications (≥18 years)	Available in Korean, Cantonese, Mandarin and Vietnamese
Smokefree Teen	Access Smokefree TXT by texting "QUIT" to 47848 or access at www.teen.smokefree.gov	6–8-week text-based program for teens who want to quit smoking	Smokefree TXT for teens 13–17 years old
This is Quitting	Text "DITCHJUUL" to 88709	Text-based messages for youth and young adults who want to quit vaping	Program length 4 weeks or longer
My Life My Quit	Text 1-855-891-9989 or www.mylifemyquit.com	Text (not available in all states) and web-based messages for youth who want to quit	Program length 4–6 weeks
QuitStart	Download free app on the app store	Provides personalized quit support for youth who want to quit smoking	Age 13 years and older

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Adult tobacco cessation resources	How to connect	Program description	Notes
1-800-QUIT-NOW	Enroll by phone (toll-free), fax, or on-line	Provides individual counseling, self-help materials and referral to resources by trained professionals and in some states, provides cessation medications (≥18 years)	Resources vary by state
Smokefree.gov	Access Smokefree TXT by texting "QUIT" to 47848 or access at www.Smokefree.gov	Access to quit smoking education and resources including a personalized quit plan	Resources vary by state
American Lung Association Freedom From Smoking	Access online at https://www.lung.org/quit-smoking/join-freedom-from-smoking	Web-based resources with personal quit plan. In some areas, Freedom From Smoking Group Clinics (8-week group sessions) are available	Resources vary by region
Become an EX	Text QUIT to 202-899-7550	Provides support to create a custom plan for adults to quit tobacco use	Sponsored by Truth Initiative

Resources for additional education for healthcare providers	Organization	Link
Surgeon General Reports on Tobacco	Health and Human Services (HHS)	https://www.hhs.gov/surgeongeneral/reports-and-publications/tobacco/2020-cessation-sgr-factsheet-key-findings/index.html
National and state-specific tobacco information	Centers for Disease Control and Prevention	https://www.cdc.gov/tobacco/index.htm
Policy statements on pediatric tobacco use and smoke exposure, including recommendations on treating teens	American Academy of Pediatrics Julius B. Richmond Center of Excellence	https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Richmond-Center/Pages/Electronic-Nicotine-Delivery-Systems.aspx
State-specific yearly evaluation and grades on tobacco control	American Lung Association State of Tobacco Control	https://www.lung.org/research/sotc
Motivational interviewing skills	Science Direct	https://www.sciencedirect.com/topics/nursing-and-health-professions/motivational-interviewing
Vaping Information, Solutions and Interventions Toolkit (VISIT)	Stanford Medicine and the co-founders of the Stanford Tobacco Prevention Toolkit	https://med.stanford.edu/visit/about.html
Screening tools for youth tobacco use	Car-Relax-Alone-Forget-Friends-Trouble version 2.1+N (CRAFFT)	https://crafft.org/get-the-crafft/

Resources for additional education for healthcare providers	Organization	Link
	Screening to Brief Intervention (S2BI)	https://www.drugabuse.gov/ast/s2bi/#/
	Brief Screener for Tobacco, Alcohol or Other Drugs (BSTAD)	https://www.drugabuse.gov/ast/bstad/#/

Advocacy and policy resources with focus on youth tobacco control and prevention	Link	Notes
American Academy of Pediatrics	https://services.aap.org/en/advocacy/	The largest organization of pediatric healthcare providers with information on child health issues, including tobacco and e-cigarette-specific resources. Some resources available only to members
Parents Against Vaping E-cigarettes (PAVE)	https://www.parentsagainstvaping.org/	Advocacy and education organization with specific recommendations by state
Campaign for Tobacco-Free Kids (CTFK)	https://www.tobaccofreekids.org/	Advocacy organization dedicated to reduce tobacco use through communications and policy
Truth Initiative	https://truthinitiative.org/	Organization committed to achieving a culture where young people reject smoking, vaping, and nicotine
Stanford Tobacco Prevention Toolkit	https://med.stanford.edu/tobaccopreventiontoolkit/about.html	An educational resource for educators and students with PowerPoints, worksheets, and activities available

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