



Annual Review of Public Health

Harm Minimization and Tobacco Control: Reframing Societal Views of Nicotine Use to Rapidly Save Lives

David B. Abrams,¹ Allison M. Glasser,²
Jennifer L. Pearson,³ Andrea C. Villanti,⁴
Lauren K. Collins,² and Raymond S. Niaura¹

¹College of Global Public Health, New York University, New York, NY 10012, USA;
email: David.B.Abrams@nyu.edu, niaura@nyu.edu

²Schroeder Institute for Tobacco Research and Policy Studies, Truth Initiative, Washington, DC 20001, USA; email: ag6507@nyu.edu, katz.laurenk@gmail.com

³School of Community Health Sciences, University of Nevada, Reno, Nevada 89557, USA;
email: jennipearson@unr.edu

⁴Vermont Center on Behavior and Health, University of Vermont, Burlington, Vermont 05401, USA; email: andrea.villanti@uvm.edu

Annu. Rev. Public Health 2018. 39:14.1–14.21

The *Annual Review of Public Health* is online at
publhealth.annualreviews.org

<https://doi.org/10.1146/annurev-publhealth-040617-013849>

Copyright © 2018 David B. Abrams et al. This work is licensed under a Creative Commons Attribution 4.0 International License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited. See credit lines of images or other third-party material in this article for license information



Keywords

harm minimization, nicotine, e-cigarettes, smoking, tobacco

Abstract

Inhalation of the toxic smoke produced by combusting tobacco products, primarily cigarettes, is the overwhelming cause of tobacco-related disease and death in the United States and globally. A diverse class of alternative nicotine delivery systems (ANDS) has recently been developed that do not combust tobacco and are substantially less harmful than cigarettes. ANDS have the potential to disrupt the 120-year dominance of the cigarette and challenge the field on how the tobacco pandemic could be reversed if nicotine is decoupled from lethal inhaled smoke. ANDS may provide a means to compete with, and even replace, combusted cigarette use, saving more lives more rapidly than previously possible. On the basis of the scientific evidence on ANDS, we explore benefits and harms to public health to guide practice, policy, and regulation. A reframing of societal nicotine use through the lens of harm minimization is an extraordinary opportunity to enhance the impact of tobacco control efforts.



Smoking:

the inhalation of the smoke from any combustible tobacco product

Alternative nicotine delivery systems (ANDS):

noncombusted refined nicotine (e.g., e-cigarettes, heat-not-burn and other emerging products, as well as smokeless and NRT)

E-cigarettes:

also called vape pens, personal vaporizers, e-hookahs, e-pipes, and e-cigs, among other names, are battery-operated and produce an aerosol instead of smoke

Combusted/combustible tobacco:

products that burn tobacco resulting in inhalation of the resultant smoke (e.g., cigarettes, cigars, pipes, roll-your-own products, and hookah)

Harm minimization:

Reducing harm as much as possible with the ideal being zero harm

Noncombusted/noncombustible tobacco:

nonburning tobacco products (smokeless tobacco, snus)

1. INTRODUCTION

The fiftieth-anniversary US Surgeon General's Report, in 2014, concluded, "The burden of death and disease from tobacco use in the U.S. is overwhelmingly caused by cigarette and other combusted tobacco products; rapid elimination of their use will dramatically reduce this burden" (117, p. 7). Globally, smoking-caused annual deaths will rise to 8 million by 2030 if current trends continue (137, 139). It is imperative to find additional ways to accelerate the decline in smoking because, if nothing changes, a billion lives will be lost prematurely by 2100 (136). Despite declines over the last 50 years, ~520,000 Americans annually die prematurely from smoking-related causes (116, 117). The Surgeon General stated, "The current rate of progress in tobacco control is not fast enough. More needs to be done" (117, p. 875). The US Food and Drug Administration (FDA) Commissioner endorsed the need for striking an appropriate balance between regulation and encouragement of the development of innovative nicotine or noncombustible tobacco products that are less dangerous than cigarettes (119). It is past time to add new and even radical approaches (13, 132).

The term alternative nicotine delivery systems (ANDS) encompasses a diverse class of non-combustible smokeless tobacco products or nicotine-containing products, primarily exemplified by e-cigarettes that are vaped not smoked (Figure 1). ANDS raise fundamental questions for society: Could ANDS be leveraged to effectively compete with cigarettes, eventually making smoking obsolete sooner than would otherwise be possible (2, 29, 57)? Can many types of ANDS, when decoupled from deadly toxins in combusted tobacco smoke, be accepted by the public and by its health, regulatory, and advocacy bodies as an extraordinary opportunity to save lives rather than as a threat to the success of past tobacco control efforts? These questions are contentious, and their answers are complicated. Addressing opportunities for ANDS requires reexamination of the role that nicotine plays in sustaining smoking and the role that nicotine can play in reducing smoking when delivered in a safer, yet appealing manner (36, 77, 85). In a major shift in FDA policy following the FDA Commissioner's announcement (119), a new national comprehensive nicotine management strategy was proposed (44): "The agency's new tobacco strategy has two primary parts: reducing the addictiveness of combustible cigarettes while recognizing and clarifying the role that potentially less harmful tobacco products could play in improving public health. . . .Reducing cigarettes' addictiveness could help users quit more easily and help keep those who are experimenting—young people, in particular—from becoming regular smokers. . . .The availability of potentially less harmful tobacco products could reduce risk while delivering satisfying levels of nicotine for adults who still need or want it" (p. 1).

Reexamination of nicotine's role in society requires reconsidering the harm minimization perspective within tobacco control (13, 46) (see the sidebar titled Harm Reduction or Harm Minimization). The primary goal of harm minimization is to prevent the use of nicotine-containing products among nonusers, while pragmatically acknowledging that less harmful noncombusted nicotine products either with tobacco (e.g., snus) or without tobacco (e.g., e-cigarettes) can dramatically reduce risk compared with smoking combusted products (1, 2, 13, 46, 57). Harm minimization is wholly consistent with tobacco control goals to prevent any use by underage youth (1) and encourage complete smoking cessation in both youth and adults and is responsive to the Surgeon General's admonition that more must be done to eliminate smoking tobacco (117).

We suggest a science-based reframing of nicotine use to inform current and future US and global tobacco control strategies. We use e-cigarettes as exemplars of ANDS, but newer types of ANDS products (e.g., that heat and do not burn tobacco) (102, 113) and accumulating scientific evidence will require continued discussions about managing nicotine's changing role in society. At times, our use of the term ANDS may also encompass classes of substantially less harmful

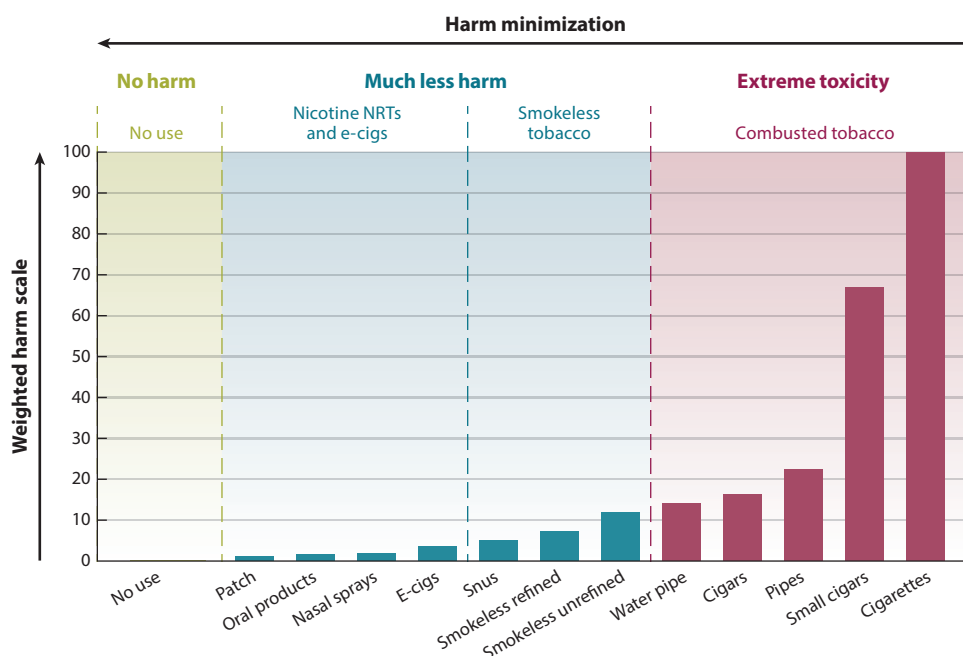


Figure 1

Products along the harm minimization continuum. Adapted with permission from Nutt et al. 2014 (89). The harm minimization continuum posits that all nicotine-containing products are not equally harmful and, instead, range from exceptionally low harm (e.g., NRT) to exceptionally high harm (e.g., combusted tobacco such as cigarettes, cigars, hookah, pipe). The figure depicts four panels representing classes of products. Products containing tobacco are depicted as combusted or smoked (panel 1, *right*) and noncombusted or smokeless (panel 2, *right middle*). Smokeless products are far less harmful than smoked tobacco, but there is variation in the smokeless tobacco category; low nitrosamine Swedish-type snus is lower in relative harm than unrefined tobacco. Heat-not-burn tobacco products (e.g., heat sticks) would fall into this panel. Panel 3 (*left middle*) depicts the class of nicotine delivery products without any tobacco (e-cigs/e-vapor products and NRTs). Panel 4 (*left*) depicts no use and thus no exposure. Abbreviations: e-cigs/e-vapor, electronic cigarettes; NRTs, nicotine replacement therapies.

noncombustible modes of nicotine delivery [i.e., medicinal nicotine replacement therapy (NRT), low nitrosamine Swedish snus, any smokeless tobacco, e-cigarettes] (30, 36, 38, 58, 60, 65).

The changing landscape of innovative reduced-harm products calls for a refocusing of tobacco control strategies, concentrating specifically on smoking control (57). Some traditional strategies will continue to be effective, whereas others may become ineffective or possibly iatrogenic (57) if

NRT: nicotine replacement therapy

HARM REDUCTION OR HARM MINIMIZATION

The term harm reduction implies any reduction in relative harm from a prior level, even a small reduction such as reducing smoking by one or two cigarettes per day. Harm minimization strives to reduce harms to zero (i.e., ideally to no use and thus no harmful exposure). When a consumer does not want to stop all nicotine use, then harm minimization implies striving for the complete elimination of smoked tobacco exposure by substituting it with the use of less harmful noncombusted forms of nicotine instead of smoking.

TCA (or FSPTCA):

The Family Smoking Prevention and Tobacco Control Act

CDER: FDA Center for Drug Evaluation Research

CTP: FDA Center for Tobacco Products

Vaping: the inhalation of e-cigarette aerosol

they slow rather than speed the demise of smoking (2, 77). Herein, we integrate science and policy analysis to address the critical questions that underpin public health practice, policy, regulation, advocacy, and communication on nicotine-containing products (128).

2. REFRAMING TOBACCO CONTROL AND NICOTINE USE

Decades of tobacco control interventions (e.g., age purchasing restrictions, taxation, media campaigns, cessation services) have significantly decreased smoking prevalence in the United States (20, 35, 54). The 2009 Tobacco Control Act (TCA) (120) and the newly promulgated nicotine management strategy (44) complements tobacco control efforts by giving the FDA statutory authority to regulate tobacco and ANDS products. The TCA includes a public health standard that requires regulators to consider the net impact of tobacco products on the population as a whole, including smokers and nonsmokers (1, 2, 41, 117, 128). Adding to the FDA's prior role [via the Center for Drug Evaluation Research (CDER)] of approving medicinal products (e.g., NRT) for smoking cessation, the FDA established the Center for Tobacco Products (CTP) to regulate the manufacture, distribution, and marketing of tobacco and emerging nicotine products for consumer use (i.e., recreational rather than medicinal) (2, 13, 57, 130).

Whereas the CTP's authorities seek to protect the public from products that could harm public health, the CTP can also promote public health by supporting products (e.g., using product standards) and encouraging behaviors that maximize net population benefits by displacing smoking (2, 44, 119, 120, 128). Public education by the CTP can change behavior by informing smokers about the harms of different classes of refined nicotine products (Figure 1), compared with both smoking (relative risk) and no use (absolute risk) (2, 13, 57, 103).

Both the emergence of ANDS products and the TCA provide an opportunity to enrich tobacco control with a harm minimization framework (2, 13, 44, 57, 119). The following sections use e-cigarettes as the main case example of the individual health and the population health potential of selected harm minimization strategies.

2.1. Decoupling Nicotine from Inhaled Smoke for Harm Minimization

The logic of smoking harm minimization is simple and compelling. As Michael Russell, a pioneer in the field, put it, "People smoke for nicotine but they die from the tar" (105, p. 1431). In getting the nicotine they seek, smokers are exposed to enormous harm, including from cardiovascular disease, cancer, and pulmonary diseases, due to the inhalation of toxic smoke from tobacco combustion products (117). For most smokers, there is little evidence that nicotine itself causes any of these classes of disease when decoupled from smoke [see details in Niaura et al. (85)]. Although nicotine use poses some risk for vulnerable groups (e.g., with cardiovascular disease or during pregnancy), this risk is substantially lower than the risk posed by continuing to smoke cigarettes (10, 29, 30, 85). Nicotine itself does not appear to cause cancer, even in former smokers who use low nitrosamine snus for decades (10, 30, 58, 60, 64–66, 85). Evidence also indicates that nicotine itself is relatively safe when obtained from FDA-approved NRT (85), which is widely used for smoking cessation (36, 38). E-cigarettes deliver nicotine without any tobacco in aerosol form (known as vapor) (30, 57, 103). Smokers switching to vaping have experienced improved lung capacity and less frequent asthma events (96–98). At the doses that smokers experience, nicotine itself carries minimal harm (38, 85). Thus, if smokers could be shifted from smoking to consuming clean nicotine (i.e., without smoke), many lives would be saved (24, 30). The safest course is to stop smoking or, better, never to start. But a harm minimization approach recognizes that demanding absolute perfection is often counterproductive and that, when a harmful behavior cannot be eliminated, it is necessary

to reduce its adverse health consequences (46). For those who are smoking and are unwilling or unable to quit nicotine use, moving to cleaner ANDS, including e-cigarettes, NRTs, or low nitrosamine snus, would reduce harm relative to smoking.

2.2. ANDS and the Harm Continuum: How Harmful Are E-Cigarettes?

The harm minimization continuum (**Figure 1**) posits that all nicotine-containing products are not equally harmful and, instead, range from exceptionally low harm (e.g., NRT) to exceptionally high harm (e.g., cigarettes, cigars, hookah) (41–43, 48, 61, 85, 90, 103). Smokeless tobacco is much lower on the risk continuum than combusted products but varies in risk within that class of products (e.g., low nitrosamine Swedish-type snus versus other smokeless tobacco with high nitrosamine levels) (30).

When nicotine is decoupled from the deadly toxins in inhaled smoke, it is substantially less harmful (10, 85, 103, 117). Most of the harm is due to the inhalation of combustion products [about 70 human carcinogens and other toxins in particulate matter (sometimes called “tars”) and carbon monoxide] (121). E-cigarette aerosol is very different. E-cigarettes do not contain any tobacco and do not produce carbon monoxide (103). The harm continuum (**Figure 1**) emphasizes a key point: It is not that e-cigarettes are completely safe, or even the safest nicotine-containing product available, but that they are much safer than smoking. NRTs are safe enough that CDER approved them for over-the-counter consumer use more than two decades ago. Long-term use of NRT has been endorsed as an acceptable strategy to reduce morbidity and mortality from smoking (23, 36, 122). CDER updated NRT labeling in 2013 to permit NRT use while smoking (also known as dual use) as part of the journey to cessation and permits sustained use for relapse prevention for a lifetime if need be (38).

Most reviews of toxicological, clinical, and epidemiological evidence indicate that the chemicals found in e-cigarettes, when used as intended, are far fewer and well below levels seen in cigarette smoke (10, 41, 42, 48, 85). According to the Royal College of Physicians in the United Kingdom, “[T]he available data suggest that they are unlikely to exceed 5% of those associated with combusted tobacco products” (103, p. 87). Studies in humans have also documented improved physiological outcomes, including reduced blood pressure, improved lung function, and lower disease symptoms, among smokers who switched to e-cigarettes (96, 97, 98). E-cigarettes are much less dependence-producing than are cigarettes (73, 109). Thus, the potential harm of e-cigarettes falls in the low range on the continuum. Harm levels do differ among e-cigarettes. Lab studies have documented some potentially toxic constituents in some devices, e-liquids, and flavors, especially when overheated to produce aldehydes (such as acrolein and formaldehyde) and an acrid “dry puff condition” unlikely to be tolerated by actual users (34). Nonetheless, prudent product standards can readily eliminate these unnecessary risks and ensure quality control over devices and liquids (2, 7, 30, 44, 119). In summary, the FDA’s Gottlieb & Zeller state: “Nicotine, though not benign, is not directly responsible for the tobacco-caused cancer, lung disease and heart disease that kill hundreds of thousands of Americans each year” (44, p. 1).

2.3. Rethinking Nicotine: A Three-Dimensional Framework for Harm Minimization

Nicotine and tobacco products can fit into a three-dimensional conceptual space (**Figure 2**): (a) harmfulness, (b) appeal, and (c) satisfaction including dependence. **Figure 2** provides a road map with which to envision how to optimize ANDS product use to successfully compete with and

Dry puff: conditions when vaping with a high wattage, too much airflow, old coils, or no liquid; not normally used

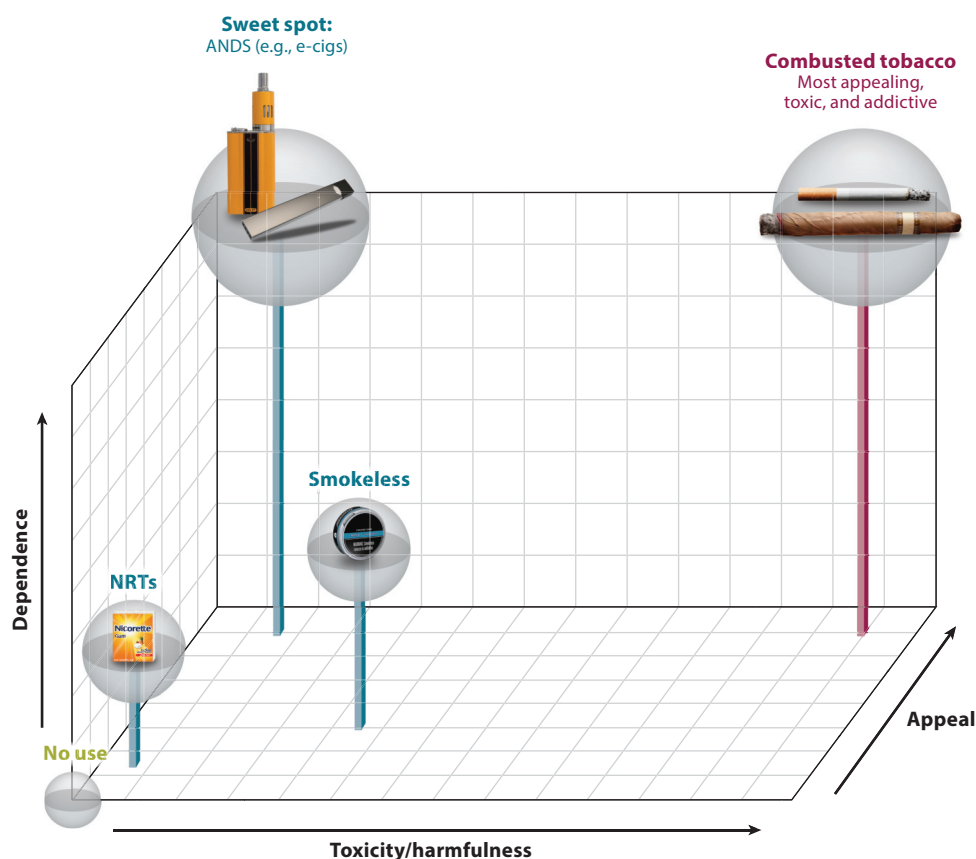


Figure 2

Multidimensional framework for nicotine-containing products. Nicotine and tobacco products can be depicted within a three-dimensional conceptual space: harmfulness (x -axis), appeal or popularity (z -axis), and satisfaction, which includes degree of dependence (y -axis). Appeal is a complex function of attractiveness, as well as cost, accessibility, and marketing practices, and appeal is related to satisfaction, including factors such as nicotine levels, taste, flavors, sensory characteristics, and dependence liability. This figure provides a roadmap with which to envision where a specific class of products can be placed. The top, back, right corner depicts the most popular (appealing), highly satisfying (dependence), and toxic space, whereas no use at all is zero on all three axes. Combusted products are, by far, the most appealing, satisfying, and toxic. The bottom, front, left space depicts products that have low toxicity but little appeal or satisfaction. NRTs are not used by many and are thus not appealing or satisfying and unlikely to displace cigarettes at a population level. Minimizing risk while making a net population health impact requires products to successfully compete with and replace smoking. Thus, the sweet spot, where ANDS products fall, is depicted by high appeal and satisfaction but low toxicity along with intermediate products such as Swedish-type snus, which has successfully displaced cigarettes in Sweden. Abbreviations: ANDS, alternative nicotine delivery systems; e-cigs/e-vapor, electronic cigarettes; NRTs, nicotine replacement therapies.

replace smoking, minimizing risk and making both an individual and a net population beneficial health impact.

As already depicted in **Figure 1** and described in Section 2.1, the toxicity of ANDS (e-cigarettes, smokeless nicotine, and NRTs) differs substantially from that of smoking (**Figure 2**, x -axis). The appeal or popularity of various types of ANDS also differs as does their degree of satisfaction

and thus their ability to displace smoking (**Figure 2**, *z*-axis), which contributes to the likelihood that ANDS will be adopted and its use sustained at a scale large enough to affect population-level outcomes (24). Appeal is a complex function of attractiveness, sensory characteristics, and subjective satisfaction (including nicotine level, taste, and flavors) as well consumer beliefs about relative harm, cost, accessibility, and marketing practices (2, 30, 32, 33, 57, 106). A product with minimal satisfaction will not be appealing and is unlikely to be adopted or used extensively, which has proven to be the case with over-the-counter NRT (45, 134). Ideally, less harmful products must be sufficiently appealing. The ANDS product must also be believed to be much less harmful than smoking to encourage switching from the high- to the low-harm products.

Dependence (**Figure 2**, *y*-axis) refers to the potential for the product to provide satisfaction and, relatedly, its potential to induce addiction, which is a function of both its pharmacological and its subjective rewarding and sensory properties. Dependence can also reflect a response to negative consequences of stopping smoking (withdrawal) and to wanting the positive and desirable effects that nicotine can have for some users (e.g., the satisfaction related to improved alertness, attention, concentration, memory, or mood) (49, 86, 110). Some degree of satisfaction, benefit from, and even dependence on much less harmful ANDS may have to be acceptable to society (i.e., recreational use of clean nicotine similar to the societal acceptance of adult alcohol use and marijuana use, rather than prohibition of all forms of nicotine primarily because of its addiction liability) as a means of speeding the demise of smoking and its attendant massive harms (2, 57). The limited evidence available suggests relatively little harm in secondhand vapor, as compared with secondhand smoke (41). Society will need to develop separate policies for secondhand vapor as was done in the United Kingdom (103).

Cigarettes and combusted tobacco products are the most appealing, most addictive, and most toxic of all nicotine delivery products and thus have dominated use for more than a century (12, 100). They are the perfect storm, occupying the space at the highest level on all three dimensions (highest on all axes in **Figure 2**).

The question arises: Where do ANDS fit? The dimensional space depicted in **Figure 2** can be helpful in locating what may be the sweet spot of an ideal e-cigarette or a future innovation of an ANDS. This sweet spot is depicted by both ANDS and by the success of snus in displacing cigarettes in Sweden (64–66). Appealing flavors, efficient nicotine delivery, and lower cost compared with cigarettes all play an important role in improving the overall appeal of less harmful ANDS on a large-scale basis (32, 33). Smokers who have completely switched to e-cigarettes report that flavors other than tobacco helped them to sustain exclusive e-cigarette use (33, 104).

NRT products, while minimally harmful and dependence inducing, lack widespread appeal among smokers. NRT has demonstrated a weak ability to displace cigarettes, despite its evidence-based CDER approval as a cessation therapy and its strong support in tobacco control policy for more than 20 years (112). In contrast with NRT, some new innovations in e-cigarettes do begin to occupy the sweet spot in this three-dimensional space because some smokers have found an e-cigarette with sufficient appeal for them to sustain use and quit smoking (11, 15, 32, 33, 41, 51, 75). As evidence of their appeal, e-cigarettes are used by smokers more often than NRT in quit attempts in both the United States and the United Kingdom (19, 103).

The three-dimensional space provides a road map to help inform a harm minimization framework and to guide research, policy, and practice. Different products can be ordered in this space and be compared with one another. Classes of nicotine-containing products (e.g., combustible versus noncombustible; high versus low nitrosamine; fast versus slow nicotine delivery; flavored versus nonflavored) can be evaluated for comparative safety, appeal, and impact on smoking prevalence. One challenge is to identify products that move the largest proportion of nicotine users to a place along these three dimensions that minimizes net harm and maximizes net benefits.

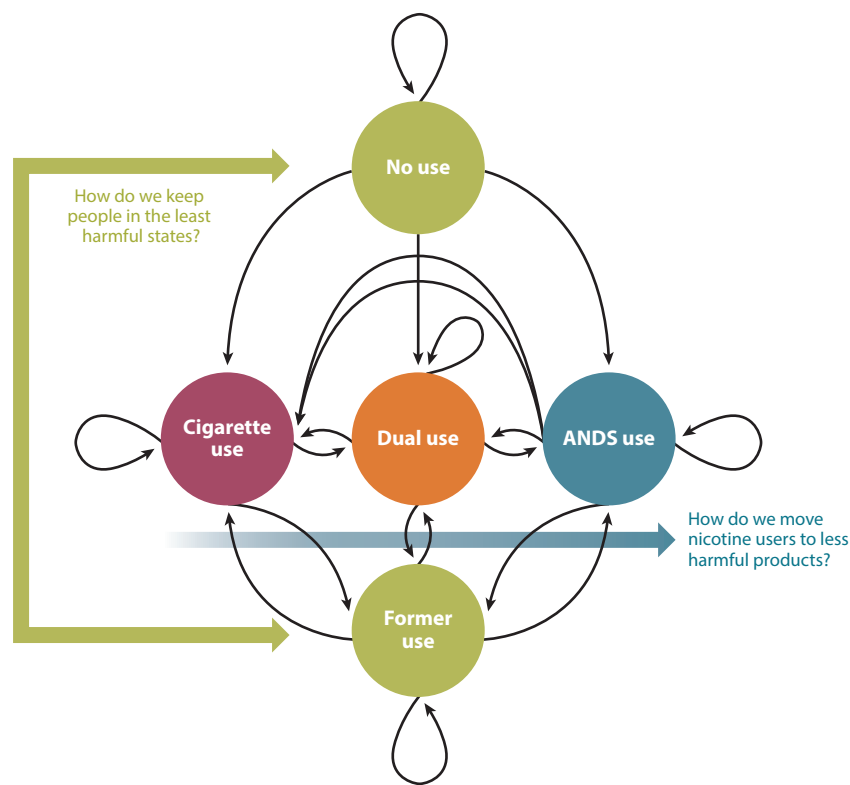


Figure 3

Markov state transition model of cigarette and e-cigarette use. This figure presents a state transition model using the example of cigarettes and ANDS to illustrate the possible states and pathways that must be considered to optimize a harm minimization strategy in tobacco control. Directed arrows represent transitions, whereas looped arrows at each state represent maintenance of that state. Youth prevention and smoking cessation strategies reinforce the states of noncurrent and former use depicted by green circles, and harm minimization strategies facilitate movement away from smoking to less harmful alternatives (*blue arrow*). Adapted with permission from Cobb et al. 2015 (23). Abbreviation: ANDS, alternative nicotine delivery systems.

Tobacco control strategy should be aligned so that less harmful ANDS are able to compete with, and ultimately completely replace, smoking for adults who want to use nicotine.

2.4. Systems Integration: Optimizing Population Benefits Over Harms

Population net exposure to harmful toxicants depends on the actual patterns and prevalence of product use, which vary along the continuum of harm (Figures 1 and 2). Figure 3 presents a state transition model using the example of cigarettes and ANDS to illustrate the possible states and pathways that must be considered to optimize the benefits of a harm minimization strategy for smoking control (23, 57).

Individuals begin in the noncurrent use state (a variant of never use) and can either remain in that state or transition to current exclusive use of cigarettes or ANDS or to dual use. Once in a current use state, individuals can maintain use, transition to one of two alternative states, or cease use of both products. Former users may also maintain no use or relapse to current exclusive or dual

use. The CTP's public health standard implies an integrated consideration of product harms and benefits at the individual and population levels (including likelihoods of initiation and cessation). Population health could be improved by changes in nicotine-containing product use that result in transitions to less harmful use states (23). These changes include limiting movement from noncurrent use (i.e., preventing initiation of any nicotine product use by nonusers) and increasing movement away from cigarette use (perhaps via dual use) to exclusive use of less harmful ANDS and/or increased transition to former use and reduced relapse to smoking.

Each tobacco control strategy (e.g., taxes, media campaigns, treatment availability, accurate consumer knowledge of relative harms, regulations) will influence the flows from one state to another. Prevention of youth initiation and support for cessation will keep noncurrent and former users from starting or relapsing (depicted by green arrows and circles in [Figure 3](#)). Harm minimization strategies facilitate movement away from smoking (depicted by the blue arrow in [Figure 3](#)) by regulating and managing products according to their relative harms. Outcomes are determined empirically by estimating the prevalence rates within states and the transition rates between states based on population surveillance. Simulation modeling of the effects of policies and regulations on transition rates can indicate where harms might exceed benefits, given different scenarios of product use (70).

Three examples of these approaches could be (a) imposing a differential tax on nicotine-containing products that is proportional to their degree of harm, with less harmful products being minimally taxed and all combusted products being very highly taxed (22); (b) reducing the addiction liability of combusted tobacco via nicotine reduction while ensuring adequate and satisfying nicotine delivery in ANDS (9, 27); and (c) reducing the appeal of smoking by banning menthol and other flavors in smoked products (32, 33, 111, 124) but not in ANDS. Making combusted tobacco more expensive and less appealing while making ANDS more appealing, less harmful, and less costly are consistent with fully embracing harm minimization to speed users away from smoking as the primary end goal.

3. TWO MAJOR CHALLENGES TO ANDS AS A HARM MINIMIZATION STRATEGY

The concerns about a harm minimization strategy that relies on ANDS derive from two concerns about unintended harmful consequences and the fact that abstinence from all tobacco and nicotine products is safest. The concerns are that the availability of e-cigarettes or any other ANDS might lure some youth who would otherwise not smoke into smoking and that smokers who adopt e-cigarettes/ANDS, and who otherwise would have quit smoking altogether, might be led to continue smoking.

3.1. Do E-Cigarettes Attract Youth and Lead Them to Smoking and Lifelong Addiction?

Consistent with harm minimization, tobacco control should strive to prevent all youth initiation of nicotine, (e.g., prohibiting the sale of nicotine-containing products to those under legal purchase age, preventing predatory marketing to youth). This aspiration must be understood in the context of adolescent behavior. Risk-taking in adolescence is normative and results from competition between the strong socioemotional network in the brain and the immature cognitive-control network (108). Early risk-taking with any tobacco or nicotine product, such as an e-cigarette, may result from social or emotional rewards from trying a product, including peer approval or mood

Precautionary principle: resisting a new product with little known effects

enhancement. Thus, eliminating all experimentation may not be a realistic goal, just as it has not been for cigarettes.

Existing studies show that current e-cigarette use by youth consists largely of experimentation, not long-term adoption (25, 127). As many as 70% of youth using e-cigarettes report only using flavors without nicotine (80). Poly-product use is common (25, 127). Findings are consistent with adolescent risk-taking (108) and shared vulnerabilities (25, 86, 123, 127). In the United States, whereas rates of past 30-day e-cigarette use in youth have risen between 2011 and 2014, these leveled off or dropped in 2015–2016 (25, 55, 81, 127, 133); contemporaneously, the prevalence of past 30-day cigarette smoking declined rapidly in youth to the lowest levels in history (41, 131). These patterns are consistent with data from the United Kingdom (8).

Longitudinal studies of youth never-cigarette users show that some ever-e-cigarette users try cigarettes during a follow-up period (6, 53, 67, 68, 79, 99, 107, 140–142), which raises some concern about so-called gateway effects (i.e., e-cigarette use leading directly to smoking) (63). But few studies examine the opposite transition: from cigarette use to e-cigarette use, a move toward less harm (blue arrow in Figure 3). Recent data show that 87% of past 30-day e-cigarette users have previously used a tobacco product, and 63% used a tobacco product in the past 30 days (127). Kozlowski & Warner (63) concluded that although society must be vigilant in tracking youth use trends, fears of harms (118) due to gateway effects seem to be exaggerated and are unlikely to undermine the much larger potential benefits of discouraging smoking behavior in the whole population.

Jurisdictions have adopted bans on e-cigarette sales to youth. Studies comparing the rates of youth cigarette use in US states with and without bans on sales to minors found that the prevalence of smoking was higher when youth access to e-cigarettes was restricted (37, 94, 95). These data illustrate the potential for some well-intentioned precautionary policies to have harmful effects.

Simulation modeling with sensitivity analyses that examine all the state and transition pathways in the state transition model (Figure 3) shows that the gateway effect would have to be implausibly large to increase the net public health harm (23, 70). Overall, the strongest science to date does not support the concerns that e-cigarettes are such a dire threat as to undermine 50 years of tobacco control success, to renormalize smoking, and to set off the addiction cycle for another generation of youth.

3.2. Do E-Cigarettes Help Smokers Quit or Do They Inhibit Cessation?

The public health benefits of e-cigarettes are enhanced if they promote complete cessation of smoking. Four randomized controlled trials (RCTs) and well-designed observational studies show that e-cigarettes are effective in helping some adult smokers successfully quit smoking (4, 16, 18, 31, 39, 41, 72, 78, 91, 93, 114, 126, 144). Rates of cessation using e-cigarettes are similar to or higher than rates of cessation from previous clinical trials of NRT (103, 112, 126). Although some studies with loosely defined measures of use (e.g., ever use, not necessarily for cessation), inadequate or no appropriate comparison groups, or inability to rule out plausible confounders or selection bias have reported that e-cigarette use may be associated with no change or negative correlations with cessation (41, 126), those studies with more robust measures of how e-cigarettes were used (e.g., duration of use, type of device, use specifically for cessation) suggest that daily vaping can facilitate quit attempts and cessation (11, 15, 51, 75, 126). Weak observational studies that did not meet the minimum criteria for scientific rigor [see details in Villanti et al. (126)] were also excluded from two reviews (47, 78) that employed the Cochrane criteria for inclusion in systematic reviews and meta-analyses (50). One other meta-analysis did not employ Cochrane standards, included most of the weak studies (56), and reported a negative association among

e-cigarette use and smoking cessation, concluding that e-cigarettes inhibit cessation. The Cochrane Handbook warns: “Meta-analysis of studies that are at risk of bias may be seriously misleading. If bias is present in each (or some) of the individual studies, meta-analysis will simply compound the errors, and produce a ‘wrong’ result that may be interpreted as having more credibility” (50, p. 247). New innovations in e-cigarette models (e.g., tank, mod and pod systems) provide more effective nicotine delivery, so studies on earlier devices may not be as strong as recent evaluations of e-cigarettes’ positive public health effect (92, 126). Four recently published studies using large national US data sets add to the science that e-cigarettes are associated with smoking cessation (39, 72, 93, 144).

Smokers’ complete displacement of cigarettes can take time. For many, a period of dual use is expected and can be acceptable along the path to smoking cessation. A transitional period of dual use with e-cigarettes and cigarettes is consistent with CDER-approved dual use of NRT (38). We are not aware of any evidence indicating that vaping has contributed to reduced interest in quitting smoking, has slowed the rate of cessation, or has promoted relapse in large numbers of long-term former smokers who had been quit for 5 years or longer (41). Surveys of e-cigarette users consistently indicate that, for most smokers, quitting cigarettes is one major reason for ANDS use (41), even among youth (125). In the years when e-cigarette use increased the most, studies revealed a rise in quit attempts (5, 40), along with either a steady or faster drop in cigarette use among both youth and adults rather than a slowing of prevalence reduction (21, 82). Studies suggest that daily users of e-cigarettes for a month or more are six times more likely to have quit smoking cigarettes two years later (11); former smokers who quit less than one year prior are four times more likely to be daily e-cigarette users compared with current smokers (26); and studies from the United Kingdom suggest that e-cigarettes have increased quitting rates and therefore reduced smoking prevalence above what would have otherwise been expected (135). In 2014, more than six million smokers in the European Union quit smoking with e-cigarettes (31).

Available scientific evidence does not support the contention that e-cigarettes when used daily specifically to quit smoking either inhibit cessation or are undermining historical tobacco control cessation efforts (31, 41, 63, 70, 77, 103, 126). Much less harmful ANDS products such as e-cigarettes could help displace cigarettes on a larger scale than NRT has because of differential appeal such as the use of flavors while eliminating flavors from smoked products, lower cost due to differential taxation, and differential ease of access relative to smoked tobacco (22–24).

4. POLICY IMPLICATIONS

The harm minimization approach yields clear implications for tobacco control policies, which demands a reorientation of these policies starting with a return to their harm minimization roots (see the sidebar titled *Saving Smokers’ Lives Now While Simultaneously Protecting Youth*). A core harm minimization principle is that policy, regulation, and advocacy be science based and proportional to the degree of product harm, with the most restrictive strategies applying to the most harmful products (2, 7, 13, 57, 77, 103).

4.1. Reaffirming Harm Minimization in Tobacco Control

Harm minimization was an accepted strategy at the beginning of tobacco control efforts in the 1960s (57). It was and still is implicit in tobacco control support for CDER-approved over-the-counter use of NRT as a safe nicotine product (38). Public health advocates are now often skeptical of reduced harm products because of mistrust of the tobacco industry and commercial entities more generally, given the experience of the highly misleading promotion of low-tar “light” cigarettes

SAVING SMOKERS' LIVES NOW WHILE SIMULTANEOUSLY PROTECTING YOUTH

The key challenge is to implement policies that maximize the net flow away from smoking and toward the use of safer products or to no use. A balance can and must be found to protect youth without discouraging cleaner nicotine use by smokers unable or not wishing to stop their nicotine use (1, 2, 7, 13, 77, 103). Considerations include (a) devising a regulatory and policy framework that focuses on reducing smoking; (b) enabling the public to have accurate information about and incentives to adopt less harmful options of nicotine delivery; and (c) allowing product innovation and market forces, as well as regulation proportionate to product harms, to contribute to the speedy demise of smoking. Delays in harm minimization may impede the end of smoking rather than encourage smokers to switch to safer nicotine delivery products. Emergence and uptake of low-risk tobacco and nicotine products, including ANDS such as e-cigarettes, as alternatives to smoking create the possibility of deep and rapid public health gains through the substitution of high-risk products by low-risk products.

(57, 59) that were not, in fact, reduced-harm products (84). This skepticism has generalized, negating all harm minimization strategies and data, including the well-documented successful Swedish experience with snus. Smokeless tobacco is still viewed by the World Health Organization and most countries as “not a safe alternative to smoking” even if it is much less harmful (57, 58, 60, 76), and e-cigarettes are also being banned in many countries (13).

Harm minimization approaches have often been resisted in many areas of risky behavior because of fears of unintended harmful consequences. But when carefully implemented, these approaches have dramatically reduced harm at the individual and population levels [e.g., condom use (115) and needle-exchange programs for HIV prevention (17, 85, 116, 129, 138)].

4.2. Industry Considerations

In tobacco control, there is understandable trepidation in supporting alternatives that may risk undermining 50 years of tobacco control efforts, given past tobacco industry behavior [for details, see Royal College of Physicians (103, pp. 135–45)]. While holding the traditional tobacco industry and the newer ANDS industries strictly accountable, if, out of an abundance of caution, tobacco control strategies fail to fully embrace movement to less harmful products (or actively discourage such movement), the result could be detrimental for smokers who are unable to quit or who do not wish to quit nicotine use completely (143). A key question is whether the combination of technological advances (i.e., ANDS) and regulation can align makers of safer nicotine-containing products with public health advocates to eliminate combusted tobacco as a defective and unacceptable product for human use (12, 31, 77, 87, 88, 100, 101, 143).

4.3. Public Education and Communication

Accurate public information is a crucial part of tobacco control policy (28). The positive impact of e-cigarettes may have been slowed by exaggerated claims of their harms (62, 63) and the harms of nicotine in general (28). Only 5.3% of Americans correctly believe that e-cigarettes are “much less harmful” than cigarettes, 37% believe they are the same or worse than smoking, and 34% don’t know (74, 83). Misperceptions of the harms of nicotine and e-cigarettes have recently increased, undermining their full potential to displace smoking (14, 52, 62, 74). A misinformed public lacks the information required to take health-protective action (28, 60, 62). Accurate public education is needed to counteract misperceptions of harm from nicotine and ANDS, to communicate the

continuum of risk related to the use of different tobacco and ANDS products (**Figure 1**), and to emphasize the importance of smoking cessation. ANDS should always be compared with smoked tobacco products (relative harms), and the mistaken public beliefs that nicotine is the cause of disease risk and cancer, rather than the smoke from combustion, must be dispelled (44). Fears that nicotine causes cancer discourages use of FDA-approved NRTs as well as e-cigarettes and other ANDS as viable ways to stop smoking cigarettes (28).

5. CONCLUSIONS

Harm minimization is a pragmatic approach that can complement proven current tobacco control efforts of prevention and cessation (1, 2, 7, 13, 41, 57, 63, 77, 85, 103). Its primary goal is to move the whole population of smokers of toxic combusted tobacco products to exclusive use of much safer products as quickly and as early as possible in their individual smoking careers. If prudently regulated (2, 103), e-cigarettes and Swedish snus (64–66) provide a great opportunity to disrupt the US and global smoking-related disease pandemic and offer a proof-of-principle for the potential role of further innovations in ANDS in improving public health (7, 13, 28, 70, 71, 143, 144). This opportunity depends on encouraging increased technological innovation and finding the appropriate balance between product safety, consumer appeal, and regulations targeted specifically to decrease the use of conventional, combusted tobacco products.

Regulation, policy, practice, and advocacy for harm minimization approaches have the potential to realign market forces and economic incentives for those willing to responsibly manufacture and market much less harmful ANDS products to adult consumers (2, 22, 24, 28, 66, 143). Even if the risk of harm to some youth who otherwise would not have smoked is marginally increased, such risks must be weighed against the substantial and immediate benefits of displacing smoking with safer nicotine products among both youth and adults (2, 13, 22, 24, 57, 63, 77, 103). Under all but the most implausible scenarios, population simulation modeling estimates millions of life years saved by employing the principles of harm minimization and switching smokers to safer ANDS products (70, 71, 126). Replacement of most cigarette use by e-cigarette use over a 10-year period yields up to 6.6 million fewer premature deaths with 86.7 million fewer life years lost (69). America and the world need a candid smoking control champion—a figure like C. Everett Koop, Surgeon General during the first eight years of the AIDS epidemic—to get out the latest accurate information about reduced harm ANDS products that could save millions of smokers' lives (28). Ethics and integrity in responsibly interpreting the scientific evidence with rigor (3, 7, 13, 28, 41, 57, 62, 63, 77, 78, 103, 127, 126), and with common sense, demand it.

SUMMARY POINTS

1. Inhaled tobacco smoke remains the single biggest threat to public health; it is widely used, highly appealing, addictive, and extremely toxic.
2. There is a continuum of harm of nicotine-containing products, from the high harm of combusted tobacco to much lower harms of noncombustible nicotine delivery with or without tobacco, including NRT.
3. In considering how to maximize population benefit and minimize population harm, one must fully consider all three dimensions of nicotine products and locate the sweet spot (see **Figures 2** and **3**), which defines the characteristics of products most likely to displace smoking: (a) lower harm, (b) sufficient appeal, and (c) sufficiently satisfying nicotine delivery.

4. Tobacco control strategies should adopt the concept of harm minimization in developing coordinated regulations, policies, and interventions to rapidly move smokers toward less harmful nicotine delivery products, while preventing the adoption of regular nicotine-containing or tobacco product use among youth.
5. The public must be accurately educated about the relative harms of nicotine-containing products relative to smoking.
6. A harm minimization approach implies proportionality of harm based on each product class. Policies and regulations must be aligned on the basis of proportionate harm.
7. Harm minimization is an evidence-based approach to tobacco control, which, when complemented by other, proven tobacco control interventions, can simultaneously prevent youth from starting to smoke and help current smokers stop, saving many lives more quickly than would otherwise be possible.

FUTURE ISSUES

1. Research is needed on the pathways by which ANDS can lead to the displacement of smoking. Traditional smoking cessation treatment designs may not be optimal because they focus on near-term outcomes of focused quit efforts, whereas the adoption of ANDS as an alternative to smoking may involve more of a gradual evolution in the smoker's goals and behaviors.
2. New and evolving ANDS products may raise new issues and data needs. For example, products that heat rather than burn tobacco, but still mimic smoking, may raise issues different from those raised by e-cigarettes.
3. Because not all effects of policies or products can be anticipated, frameworks for robust and responsive postmarket population surveillance and for modeling of likely outcomes of ANDS use need to be established.
4. A regulatory framework that aligns business goals with public health goals will need to be developed. Absent regulation, ANDS have evolved very quickly toward more effective nicotine delivery. Although regulation is necessary to ensure that product innovations are consistent with public health goals, it also has the potential to stifle innovation and thus undermine the potential of ANDS as a public health success.
5. A harm minimization strategy acknowledges that nicotine use and even dependence may be acceptable in the interest of reducing tobacco-caused death and disease. This approach will require a focused, objective, evidence-based dialogue that separates concerns about nicotine use and dependence from concerns about medical harm and implies a substantial shift in public, professional, and regulatory attitudes in the interest of eventually ending combusted tobacco use.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

14.14 Abrams et al.



Review in Advance first posted on
January 11, 2018. (Changes may
still occur before final publication.)

ACKNOWLEDGMENTS

All authors were supported by Truth Initiative. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health, the US Food and Drug Administration, or the Truth Initiative.

LITERATURE CITED

1. Abrams DB. 2014. Potential and pitfalls of e-cigarettes—reply. *JAMA* 311:1922–23
2. Abrams DB. 2014. Promise and peril of e-cigarettes: Can disruptive technology make cigarettes obsolete? *JAMA* 311:135–36
3. Abrams DB, Niaura R. 2015. The importance of science-informed policy and what the data really tell us about e-cigarettes. *Isr. J. Health Policy Res* 4:22
4. Adriaens K, Van Gucht D, Declerck P, Baeyens F. 2014. Effectiveness of the electronic cigarette: an eight-week Flemish study with six-month follow-up on smoking reduction, craving and experienced benefits and complaints. *Int. J. Environ. Res. Public Health* 11:11220–48
5. Babb S, Malarcher A, Schauer G, Asman K, Jamal A. 2017. Quitting smoking among adults—United States, 2000–2015. *MMWR* 65:1457–64
6. Barrington-Trimis JL, Urman R, Berhane K, Unger JB, Cruz TB, et al. 2016. E-cigarettes and future cigarette use. *Pediatrics* 138:e20160379
7. Bates C. 2017. *Rethinking nicotine: implications for U.S. federal tobacco policy*. Discuss. Pap., Counterfactual, London. <https://www.clivebates.com/documents/FDAReformJune2017.pdf>
8. Bauld L, MacKintosh AM, Ford A, McNeill A. 2016. E-cigarette uptake amongst UK youth: experimentation, but little or no regular use in nonsmokers. *Nicotine Tob. Res.* 18:102–3
9. Benowitz NL, Donny EC, Hatsukami DK. 2017. Reduced nicotine content cigarettes, e-cigarettes and the cigarette end game. *Addiction* 112:6–7
10. Benowitz NL, Fraiman JB. 2017. Cardiovascular effects of electronic cigarettes. *Nat. Rev. Cardiol.* 14:447–56
11. Biener L, Hargraves JL. 2015. A longitudinal study of electronic cigarette use among a population-based sample of adult smokers: association with smoking cessation and motivation to quit. *Nicotine Tob. Res.* 17:127–33
12. Brandt AM. 2007. *The Cigarette Century: The Rise, Fall, and Deadly Persistence of the Product That Defined America*. New York: Basic Books
13. Britton J, Bogdanovica I, McNeill A, Bauld L. 2016. *Commentary on WHO Report on electronic nicotine delivery systems and electronic non-nicotine delivery systems*. UK Cent. Tob. Alcohol Stud., Nottingham, UK. <http://ukctas.net/pdfs/UKCTAS-response-to-WHO-ENDS-report-26.10.2016.pdf>
14. Brose LS, Brown J, Hitchman SC, McNeill A. 2015. Perceived relative harm of electronic cigarettes over time and impact on subsequent use. A survey with 1-year and 2-year follow-ups. *Drug Alcohol. Depend.* 157:106–11
15. Brose LS, Hitchman SC, Brown J, West R, McNeill A. 2015. Is the use of electronic cigarettes while smoking associated with smoking cessation attempts, cessation and reduced cigarette consumption? A survey with a 1-year follow-up. *Addiction* 110:1160–68
16. Bullen C, Howe C, Laugesen M, McRobbie H, Parag V, et al. 2013. Electronic cigarettes for smoking cessation: a randomised controlled trial. *Lancet* 382:1629–37
17. Can. Paediatr. Soc. 2008. Harm reduction: an approach to reducing risky health behaviours in adolescents. *Paediatr. Child Health* 13:53–56
18. Caponnetto P, Campagna D, Cibella F, Morjaria JB, Caruso M, et al. 2013. Efficiency and Safety of an eElectronic cigAreTte (ECLAT) as tobacco cigarettes substitute: a prospective 12-month randomized control design study. *PLOS ONE* 8:e66317
19. Caraballo RS, Shafer PR, Patel D, Davis KC, McAfee TA. 2017. Quit methods used by US adult cigarette smokers, 2014–2016. *Prev. Chronic Dis.* 14:E32



20. CDC (Cent. Dis. Control Prev.). 2014. *Best Practices for Comprehensive Tobacco Control Programs—2014*. Atlanta: US Dep. Health Hum. Serv., Cent. Dis. Control Prev., Natl. Cent. Chronic Dis. Prev. Health Promot., Off. Smok. Health
21. CDC (Cent. Dis. Control Prev.). 2016. *Early Release of Selected Estimates Based on Data from the National Health Interview Survey, January–March 2016*. Atlanta: US Dep. Health Hum. Serv., Cent. Dis. Control Prev., Natl. Cent. Health Stat.
22. Chaloupka FJ, Sweanor D, Warner KE. 2015. Differential taxes for differential risks—toward reduced harm from nicotine-yielding products. *N. Engl. J. Med.* 373:594–97
23. Cobb CO, Villanti AC, Graham AL, Pearson JL, Glasser AM, et al. 2015. Markov modeling to estimate the population impact of emerging tobacco products: a proof-of-concept study. *Tobacco Reg. Sci.* 1(2):121–41
24. Cobb NK, Abrams DB. 2014. The FDA, e-cigarettes, and the demise of combusted tobacco. *N. Engl. J. Med.* 371:1469–71
25. Collins LK, Villanti AC, Pearson JL, Glasser AM, Johnson AL, et al. 2017. Frequency of youth e-cigarette, tobacco, and poly-use in the United States, 2015: Update to Villanti et al., “Frequency of Youth E-Cigarette and Tobacco Use Patterns in the United States: Measurement Precision Is Critical to Inform Public Health.” *Nicotine Tob. Res.* 19:1253–54
26. Delnevo CD, Giovenco DP, Steinberg MB, Villanti AC, Pearson JL, et al. 2016. Patterns of electronic cigarette use among adults in the United States. *Nicotine Tob. Res.* 18:715–19
27. Donny EC, Denlinger RL, Tidey JW, Koopmeiners JS, Benowitz NL, et al. 2015. Randomized trial of reduced-nicotine standards for cigarettes. *N. Engl. J. Med.* 373:1340–49
28. Fairchild A, Niaura R, Abrams D. 2017. America needs a candid smoking control champion. *The Hill*, Nov. 13. <http://thehill.com/opinion/healthcare/360111-america-needs-a-candid-smoking-control-champion>
29. Fagerstrom K, Etter JF, Unger JB. 2015. E-cigarettes: a disruptive technology that revolutionizes our field? *Nicotine Tob. Res.* 17:125–26
30. Fagerstrom KO, Bridgman K. 2014. Tobacco harm reduction: the need for new products that can compete with cigarettes. *Addict. Behav.* 39:507–11
31. Farsalinos KE, Poulas K, Voudris V, Le Houezec J. 2016. Electronic cigarette use in the European Union: analysis of a representative sample of 27,460 Europeans from 28 countries *Addiction* 111(11):2032–40
32. Farsalinos KE, Poulas K, Voudris V, Le Houezec J. 2017. Prevalence and correlates of current daily use of electronic cigarettes in the European Union: analysis of the 2014 Eurobarometer survey. *Intern. Emerg. Med.* 12:757–63
33. Farsalinos KE, Romagna G, Tsiapras D, Kyrzopoulos S, Spyrou A, Voudris V. 2013. Impact of flavour variability on electronic cigarette use experience: an Internet survey. *Int. J. Environ. Res. Public Health* 10:7272–82
34. Farsalinos KE, Voudris V, Poulas K. 2015. E-cigarettes generate high levels of aldehydes only in ‘dry puff’ conditions. *Addiction* 110:1352–56
35. Feirman SP, Glasser AM, Rose S, Niaura R, Abrams DB, et al. 2017. Computational models used to assess US tobacco control policies. *Nicotine Tob. Res.* 19:1257–67
36. Fiore MC, Schroeder SA, Baker TB. 2014. Smoke, the chief killer—strategies for targeting combustible tobacco use. *N. Engl. J. Med.* 370:297–99
37. Friedman AS. 2015. How does electronic cigarette access affect adolescent smoking? *J. Health Econ.* 44:300–8
38. Fucito LM, Bars MP, Forray A, Rojewski AM, Shiffman S, et al. 2014. Addressing the evidence for FDA nicotine replacement therapy label changes: a policy statement of the Association for the Treatment of Tobacco use and Dependence and the Society for Research on Nicotine and Tobacco. *Nicotine Tob. Res.* 16:909–14
39. Giovenco DP, Delnevo CD. 2018. Prevalence of smoking cessation by electronic cigarette use status in a national sample of recent smokers. *Addict Behav.* 76:129–34
40. Gitchell JG, Shiffman S, Sembower MA. 2017. Trends in serious quit attempts in the United States, 2009–14. *Addiction* 112:897–900



41. Glasser AM, Collins L, Pearson JL, Abudayyeh H, Niaura RS, et al. 2017. Overview of electronic nicotine delivery systems: a systematic review. *Am. J. Prev. Med.* 52:e33–66
42. Goniewicz ML, Gawron M, Smith DM, Peng M, Jacob P 3rd, Benowitz NL. 2017. Exposure to nicotine and selected toxicants in cigarette smokers who switched to electronic cigarettes: a longitudinal within-subjects observational study. *Nicotine Tob. Res.* 19:160–67
43. Goniewicz ML, Knysak J, Gawron M, Kosmider L, Sobczak A, et al. 2014. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tob. Control* 23:133–39
44. Gottlieb S, Zeller M. 2017. A nicotine-focused framework for public health. *N Engl. J. Med.* 377(12):1111–14
45. Hammond D, McDonald PW, Fong GT, Borland R. 2004. Do smokers know how to quit? Knowledge and perceived effectiveness of cessation assistance as predictors of cessation behaviour. *Addiction* 99:1042–48
46. Harm Reduct. Int. 2017. *What is harm reduction?* Harm Reduct. Int., London. <https://www.hri.global/what-is-harm-reduction>
47. Hartmann-Boyce J, McRobbie H, Bullen C, Begh R, Stead LF, Hajek P. 2016. Electronic cigarettes for smoking cessation. *Cochrane Database Syst. Rev* (9):CD010216
48. Hecht SS, Carmella SG, Kotandeniya D, Pillsbury ME, Chen M, et al. 2015. Evaluation of toxicant and carcinogen metabolites in the urine of e-cigarette users versus cigarette smokers. *Nicotine Tob. Res.* 17:704–9
49. Heishman SJ, Kleykamp BA, Singleton EG. 2010. Meta-analysis of the acute effects of nicotine and smoking on human performance. *Psychopharmacology* 210:453–69
50. Higgins JPT, Green S. 2008. *Cochrane Handbook for Systematic Reviews of Interventions*, *Cochrane Book Series*. West Sussex, UK: Wiley-Blackwell
51. Hitchman SC, Brose LS, Brown J, Robson D, McNeill A. 2015. Associations between e-cigarette type, frequency of use, and quitting smoking: findings from a longitudinal online panel survey in Great Britain. *Nicotine Tob. Res.* 17:1187–94
52. Huerta TR, Walker DM, Mullen D, Johnson TJ, Ford EW. 2017. Trends in e-cigarette awareness and perceived harmfulness in the U.S. *Am. J. Prev. Med.* 52:339–46
53. Huh J, Leventhal AM. 2016. Progression of poly-tobacco product use patterns in adolescents. *Am. J. Prev. Med.* 51:513–17
54. IOM (Inst. Med.). 2007. *Ending the Tobacco Problem: A Blueprint for the Nation*. Washington, DC: Natl. Acad. Press
55. Jamal A, Gentzke A, Hu SS, Cullen KA, Apelberg BJ, et al. 2017. Tobacco use among middle and high school students—United States, 2011–2016. *MMWR* 66:597–603
56. Kalkhoran S, Glantz SA. 2016. E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and meta-analysis. *Lancet Respir. Med.* 4:116–28
57. Kozłowski LT, Abrams DB. 2016. Obsolete tobacco control themes can be hazardous to public health: the need for updating views on absolute product risks and harm reduction. *BMC Public Health* 16:432
58. Kozłowski LT, Edwards BQ. 2005. “Not safe” is not enough: Smokers have a right to know more than there is no safe tobacco product. *Tob. Control.* 14(Suppl. 2):ii3–7
59. Kozłowski LT, Goldberg ME, Yost BA, White EL, Sweeney CT, Pillitteri JL. 1998. Smokers’ misperceptions of light and ultra-light cigarettes may keep them smoking. *Am. J. Prev. Med.* 15:9–16
60. Kozłowski LT, O’Connor RJ. 2003. Apply federal research rules on deception to misleading health information: an example on smokeless tobacco and cigarettes. *Public Health Rep.* 118:187–92
61. Kozłowski LT, Strasser AA, Giovino GA, Erickson PA, Terza JV. 2001. Applying the risk/use equilibrium: use medicinal nicotine now for harm reduction. *Tob. Control.* 10:201–3
62. Kozłowski LT, Sweanor D. 2016. Withholding differential risk information on legal consumer nicotine/tobacco products: the public health ethics of health information quarantines. *Int. J. Drug Policy* 32:17–23
63. Kozłowski LT, Warner KE. 2017. Adolescents and e-cigarettes: Objects of concern may appear larger than they are. *Drug Alcohol. Depend.* 174:209–14
64. Lee PN. 2011. Summary of the epidemiological evidence relating snus to health. *Regul. Toxicol. Pharmacol.* 59:197–214



65. Lee PN. 2013. Epidemiological evidence relating snus to health—an updated review based on recent publications. *Harm. Reduct. J.* 10:36
66. Lee PN, Hamling J. 2009. Systematic review of the relation between smokeless tobacco and cancer in Europe and North America. *BMC Med.* 7:36
67. Leventhal AM, Stone MD, Andrabi N, Barrington-Trimis J, Strong DR, et al. 2016. Association of e-cigarette vaping and progression to heavier patterns of cigarette smoking. *JAMA* 316:1918–20
68. Leventhal AM, Strong DR, Kirkpatrick MG, Unger JB, Sussman S, et al. 2015. Association of electronic cigarette use with initiation of combustible tobacco product smoking in early adolescence. *JAMA* 314:700–7
69. Levy DT, Borland R, Lindblom EN, Goniewicz ML, Meza R, et al. 2017. Potential deaths averted in USA by replacing cigarettes with e-cigarettes. *Tob Control* <https://doi.org/10.1136/tobaccocontrol-2017-053759>
70. Levy DT, Borland R, Villanti AC, Niaura R, Yuan Z, et al. 2017. The application of a decision-theoretic model to estimate the public health impact of vaporized nicotine product initiation in the United States. *Nicotine Tob. Res.* 19:149–59
71. Levy DT, Cummings KM, Villanti AC, Niaura R, Abrams DB, et al. 2017. A framework for evaluating the public health impact of e-cigarettes and other vaporized nicotine products. *Addiction* 112(1):8–17
72. Levy DT, Yuan Z, Luo Y, Abrams DB. 2017. The relationship of e-cigarette use to cigarette quit attempts and cessation: insights from a large, nationally representative U.S. survey. *Nicotine Tob. Res.* <https://doi.org/10.1093/ntr/ntx166>
73. Liu G, Wasserman E, Kong L, Foulds J. 2017. A comparison of nicotine dependence among exclusive E-cigarette and cigarette users in the PATH study. *Prev. Med.* <https://doi.org/10.1016/j.ypmed.2017.04.001>
74. Majeed BA, Weaver SR, Gregory KR, Whitney CF, Slovic P, et al. 2017. Changing perceptions of harm of e-cigarettes among U.S. adults, 2012–2015. *Am. J. Prev. Med.* 52:331–38
75. Manzoli L, Flacco ME, Fiore M, La Vecchia C, Marzuillo C, et al. 2015. Electronic cigarettes efficacy and safety at 12 months: cohort study. *PLOS ONE* 10:e0129443
76. Marlatt GA, Witkiewitz K. 2010. Update on harm-reduction policy and intervention research. *Annu. Rev. Clin. Psychol.* 6:591–606
77. McNeill A, Brose LS, Calder R, Hitchman S, Hajek P, McRobbie H. 2015. *E-Cigarettes: An Evidence Update—A Report Commissioned by Public Health England*. London: Public Health England
78. McRobbie H, Bullen C, Hartmann-Boyce J, Hajek P. 2014. Electronic cigarettes for smoking cessation and reduction. *Cochrane Database Syst. Rev.* 12:CD010216
79. Miech R, Patrick ME, O'Malley PM, Johnston LD. 2017. E-cigarette use as a predictor of cigarette smoking: results from a 1-year follow-up of a national sample of 12th grade students. *Tob. Control* <https://doi.org/10.1136/tobaccocontrol-2016-053291>
80. Miech R, Patrick ME, O'Malley PM, Johnston LD. 2017. What are kids vaping? Results from a national survey of US adolescents. *Tob. Control.* 26:386–91
81. Monit. Future—Univ. Mich. 2017. *Table 1: Trends in annual and 30-day prevalence of use of other tobacco products for grades 8, 10, and 12*. Univ. Mich., Ann Arbor. <http://www.monitoringthefuture.org/data/16data/16cigtbl1.pdf>
82. Monit. Future—Univ. Mich. 2017. *Table 2: Trends in prevalence of use of cigarettes in grades, 8, 10, and 12*. Univ. Mich., Ann Arbor. <http://www.monitoringthefuture.org/data/16data/16cigtbl2.pdf>
83. NCI (Natl. Cancer Inst.). 2015. *Compared to smoking cigarettes, would you say that electronic cigarettes are...* Health Inf. Natl. Trends Survey (HINTS) Response, NCI, Natl. Inst. Health, Bethesda, MD. https://hints.cancer.gov/question-details.aspx?PK_Cycle=8&qid=1282
84. NCI (Natl. Cancer Inst.). 2017. *Dispelling myths about nicotine replacement therapy*. Fact Sheet, NCI, Natl. Inst. Health, Bethesda, MD. <http://smokefree.gov/sites/default/files/pdf/mythsaboutNRTfactsheet.pdf>
85. Niaura R. 2016. *Re-thinking nicotine and its effects*. Schroeder Inst. Tob. Res. Policy Stud., Truth Initiat., Washington, DC. <https://truthinitiative.org/sites/default/files/ReThinking-Nicotine.pdf>
86. Niaura RS, Glynn TJ, Abrams DB. 2014. Youth experimentation with e-cigarettes: another interpretation of the data. *JAMA Pediatr.* 312:641–42



87. Nocera J. 2015. Can e-cigarettes save lives? *New York Times*, Oct. 16. https://www.nytimes.com/2015/10/17/opinion/can-e-cigarettes-save-lives.html?_r=0
88. Nocera J. 2017. When public health and Big Tobacco align. *Bloomberg View*, March 9. <https://www.bloomberg.com/view/articles/2017-03-09/when-public-health-and-big-tobacco-align>
89. Nutt DJ, Phillips LD, Balfour D, Curran HV, Dockrell M, et al. 2014. Estimating the harms of nicotine-containing products using the MCDA approach. *Eur. Addict. Res.* 20:218–25
90. Nutt DJ, Phillips LD, Balfour D, Curran HV, Dockrell M, et al. 2016. E-cigarettes are less harmful than smoking. *Lancet* 387:1160–62
91. O'Brien B, Knight-West O, Walker N, Parag V, Bullen C. 2015. E-cigarettes versus NRT for smoking reduction or cessation in people with mental illness: secondary analysis of data from the ASCEND trial. *Tob. Induc. Dis.* 13:5
92. O'Leary R, MacDonald M, Stockwell T, Reist D. 2017. *Clearing the Air: A Systematic Review on the Harms and Benefits of E-Cigarettes and Vapour Devices*. Victoria, BC, Can.: Univ. Vic. Cent. Addict. Res. BC
93. Parks SH, Duncan DT, Shahawy OE, Lee L, Shearston JA, et al. 2017. Characteristics of adults who switched from cigarette smoking to e-cigarettes. *Am. J. Prev. Med.* 53(5):652–60
94. Pesko MF, Currie JM. 2016. *The effect of e-cigarette minimum legal sale age laws on traditional cigarette use and birth outcomes among pregnant teenagers*. NBER Work. Pap. 22792
95. Pesko MF, Hughes JM, Faisal FS. 2016. The influence of electronic cigarette age purchasing restrictions on adolescent tobacco and marijuana use. *Prev. Med.* 87:207–12
96. Polosa R, Campagna D, Sands MF. 2016. Counseling patients with asthma and allergy about electronic cigarettes: an evidence-based approach. *Ann. Allergy Asthma Immunol.* 116:106–11
97. Polosa R, Morjaria J, Caponnetto P, Caruso M, Strano S, et al. 2014. Effect of smoking abstinence and reduction in asthmatic smokers switching to electronic cigarettes: evidence for harm reversal. *Int. J. Environ. Res. Public Health* 11:4965–77
98. Polosa R, Morjaria JB, Caponnetto P, Caruso M, Campagna D, et al. 2016. Persisting long term benefits of smoking abstinence and reduction in asthmatic smokers who have switched to electronic cigarettes. *Discov. Med.* 21:99–108
99. Primack BA, Soneji S, Stoolmiller M, Fine MJ, Sargent JD. 2015. Progression to traditional cigarette smoking after electronic cigarette use among US adolescents and young adults. *JAMA Pediatr.* 169:1018–23
100. Proctor RN. 2011. *Golden Holocaust: Origins of the Cigarette Catastrophe and the Case for Abolition*. Oakland: Univ. Calif. Press
101. Reuters. 2016. Philip Morris CEO sketches a future where the company doesn't sell cigarettes. *Fortune*, Nov. 30. <http://fortune.com/2016/11/30/philip-morris-ceo-future-without-cigarettes/>
102. Rose JE, Turner JE, Murugesan T, Behm FM, Laugesen M. 2010. Pulmonary delivery of nicotine pyruvate: sensory and pharmacokinetic characteristics. *Exp. Clin. Psychopharmacol.* 18:385–94
103. RPC (R. Coll. Phys.). 2016. *Nicotine Without Smoke: Tobacco Harm Reduction*. London: RPC. <https://www.rcplondon.ac.uk/projects/outputs/nicotine-without-smoke-tobacco-harm-reduction-0>
104. Russell C, McKeganey N. 2017. *Patterns of cigarette smoking and e-cigarette use among 20,676 adult frequent e-cigarette users in the United States*. Cent. Subst. Use Res., Glasgow, UK. <http://substanceuseresearch.org/usvaperssurvey>
105. Russell MA. 1976. Low-tar medium-nicotine cigarettes: a new approach to safer smoking. *BMJ* 1:1430–33
106. Smiley SL, DeAtley T, Rubin LF, Harvey E, Kierstead EC, et al. 2017. Early subjective sensory experiences with “cigalike” e-cigarettes among African American menthol smokers: a qualitative study. *Nicotine Tob. Res.* <https://doi.org/10.1093/ntr/ntx102>
107. Spindle TR, Hiler MM, Cooke ME, Eissenberg T, Kendler KS, Dick DM. 2017. Electronic cigarette use and uptake of cigarette smoking: a longitudinal examination of U.S. college students. *Addict. Behav.* 67:66–72
108. Steinberg L. 2007. Risk taking in adolescence: new perspectives from brain and behavioral science. *Curr. Dir. Psychol. Sci.* 16:55–59



109. Strong DR, Pearson J, Ehlke S, Kirchner TR, Abrams D, et al. 2017. Indicators of dependence for different types of tobacco product users: descriptive findings from wave 1 (2013–2014) of the Population Assessment of Tobacco and Health (PATH) study. *Drug Alcohol Depend.* 178:257–66
110. Talati A, Keyes KM, Hasin DS. 2016. Changing relationships between smoking and psychiatric disorders across twentieth century birth cohorts: clinical and research implications. *Mol. Psychiatry* 21:464–71
111. Tob. Prod. Sci. Advis. Comm. 2011. *Menthol Cigarettes and Public Health: Review of the Scientific Evidence and Recommendations*. Rockville, MD: US Food Drug Adm., Cent. Tob. Prod.
112. Tob. Use Depend. Guidel. Panel. 2008. *Treating Tobacco Use and Dependence: 2008 Update*. Rockville, MD: US Dep. Health Hum. Serv.
113. Trefis Team. 2016. FDA approval for iQOS to be a game changer for Altria. *Forbes*, Dec. 30. <https://www.forbes.com/sites/greatspeculations/2016/12/30/fda-approval-for-iqos-to-be-a-game-changer-for-altria/#385ca26b1a36>
114. Tseng TY, Ostroff JS, Campo A, Gerard M, Kirchner T, et al. 2016. A randomized trial comparing the effect of nicotine versus placebo electronic cigarettes on smoking reduction among young adult smokers. *Nicotine Tob. Res.* 18:1937–43
115. US Dep. Health Hum. Serv. 2001. *Workshop summary: scientific evidence on condom effectiveness for sexually transmitted disease (STD) prevention*. Workshop Summ., July 20, Natl. Inst. Allergy Infect. Dis., Natl. Inst. Health, Dep. Health Hum. Serv., Herndon, VA. <https://chastityproject.com/wp/wp-content/uploads/2013/05/NIH-Condom-Report.pdf>
116. US Dep. Health Hum. Serv. 2010. *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General*. Atlanta: US Dep. Health Hum. Serv., Cent. Dis. Control Prev., Natl. Cent. Chronic Dis. Prev. Health Promot., Off. Smok. Health. <https://www.ncbi.nlm.nih.gov/books/NBK53017/>
117. US Dep. Health Hum. Serv. 2014. *The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General*. Atlanta: US Dep. Health Hum. Serv., Cent. Dis. Control Prev., Natl. Cent. Chronic Dis. Prev. Health Promot., Off. Smok. Health. <https://www.surgeongeneral.gov/library/reports/50-years-of-progress/full-report.pdf>
118. US Dep. Health Hum. Serv. 2016. *E-Cigarette Use Among Youth and Young Adults: A Report of the Surgeon General*. Atlanta: US Dep. Health Hum. Serv., Cent. Dis. Control Prev., Natl. Cent. Chronic Dis. Prev. Health Promot., Off. Smok. Health. https://e-cigarettes.surgeongeneral.gov/documents/2016_sgr_full_report_non-508.pdf
119. US Dep. Health Hum. Serv. 2017. *FDA announces comprehensive regulatory plan to shift trajectory of tobacco-related disease, death*. News Release, July 28. <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm568923.htm>
120. US FDA (Food Drug Adm.). 2009. *Division A—Family Smoking Prevention and Tobacco Control Act*. Public Law 111–31, Jun 22. <https://www.gpo.gov/fdsys/pkg/PLAW-111publ31/pdf/PLAW-111publ31.pdf>
121. US FDA (Food Drug Adm.). 2012. Harmful and potentially harmful constituents in tobacco products and tobacco smoke; established list. *Fed. Regist.* 77:20034–37. <https://www.federalregister.gov/documents/2012/04/03/2012-7727/harmful-and-potentially-harmful-constituents-in-tobacco-products-and-tobacco-smoke-established-list>
122. US FDA (Food Drug Adm.). 2013. *Nicotine replacement therapy labels may change*. April 1, US FDA, Silver Spring, MD. <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm345087.htm>
123. Vanyukov MM, Tarter RE, Kirillova GP, Kirisci L, Reynolds MD, et al. 2012. Common liability to addiction and “gateway hypothesis”: theoretical, empirical and evolutionary perspective. *Drug Alcohol Depend.* 123(Suppl. 1):S3–17
124. Villanti AC, Giovino GA, Burns DM, Abrams DB. 2013. Menthol cigarettes and mortality: keeping focus on the public health standard. *Nicotine Tob. Res.* 15:617–18
125. Villanti AC, Johnson AL, Ambrose BK, Cummings KM, Stanton CA, et al. 2017. Flavored tobacco product use in youth and adults: findings from the first wave of the PATH study (2013–2014). *Am. J. Prev. Med.* 53:139–51



126. Villanti AC, Feirman SP, Niaura RS, Pearson JL, Glasser AM, et al. 2017. How do we determine the impact of e-cigarettes on cigarette smoking cessation or reduction? Review and recommendations for answering the research question with scientific rigor. *Addiction* <https://doi.org/10.1111/add.14020>
127. Villanti AC, Pearson JL, Glasser AM, Johnson AL, Collins LK, et al. 2017. Frequency of youth e-cigarette and tobacco use patterns in the U.S.: measurement precision is critical to inform public health. *Nicotine Tob. Res.* 19:1345–50
128. Villanti AC, Vargyas EJ, Niaura RS, Beck SE, Pearson JL, Abrams DB. 2011. Food and Drug Administration regulation of tobacco: integrating science, law, policy, and advocacy. *Am. J. Public Health* 101:1160–62
129. Vlahov D, Robertson AM, Strathdee SA. 2010. Prevention of HIV infection among injection drug users in resource-limited settings. *Clin. Infect. Dis.* 50(Suppl. 3):S114–21
130. Walton KM, Abrams DB, Bailey WC, Clark D, Connolly GN, et al. 2015. NIH electronic cigarette workshop: developing a research agenda. *Nicotine Tob. Res.* 17:259–69
131. Warner K. 2015. The remarkable decrease in cigarette smoking by American youth: further evidence. *Prev. Med. Rep.* 2:259–61
132. Warner KE. 2013. An endgame for tobacco? *Tob. Control* 22(Suppl. 1):i3–5
133. Warner KE. 2016. Frequency of e-cigarette use and cigarette smoking by American students in 2014. *Am. J. Prev. Med.* 51:179–84
134. West R, Hajek P, Foulds J, Nilsson F, May S, Meadows A. 2000. A comparison of the abuse liability and dependence potential of nicotine patch, gum, spray and inhaler. *Psychopharmacology* 149:198–202
135. West R, Shahab L, Brown J. 2016. Estimating the population impact of e-cigarettes on smoking cessation in England. *Addiction* 111:1118–19
136. WHO (World Health Organ.). 2008. *WHO Report on the Global Tobacco Epidemic, 2008: The MPOWER Package*. Geneva: WHO
137. WHO (World Health Organ.). 2011. *WHO Report on the Global Tobacco Epidemic, 2011: Warning About the Dangers of Tobacco*. Geneva: WHO
138. WHO (World Health Organ.). 2016. *HIV/AIDS: people who inject drugs*. WHO, Geneva. <http://www.who.int/hiv/topics/idu/en/>
139. WHO (World Health Organ.). 2017. *Tobacco*. Updated May, Fact Sheet, WHO, Geneva. <http://www.who.int/mediacentre/factsheets/fs339/en/>
140. Wills TA, Gibbons FX, Sargent JD, Schweitzer RJ. 2016. How is the effect of adolescent e-cigarette use on smoking onset mediated: a longitudinal analysis. *Psychol. Addict. Behav.* 30:876–86
141. Wills TA, Knight R, Sargent JD, Gibbons FX, Pagano I, Williams RJ. 2017. Longitudinal study of e-cigarette use and onset of cigarette smoking among high school students in Hawaii. *Tob. Control* 26:34–39
142. Wills TA, Sargent JD, Gibbons FX, Pagano I, Schweitzer R. 2017. E-cigarette use is differentially related to smoking onset among lower risk adolescents. *Tob. Control* 26:534–39
143. Yach D. 2017. Foundation for a smoke-free world. *Lancet* 390:1807–10
144. Zhu S-H, Zhuang Y-L, Wong S, Cummins SE, Tedeschi GJ. 2017. E-cigarette use and associated changes in population smoking cessation: evidence from US current population surveys. *BMJ* 358:j3262

