



Are we guilty of errors of omission on the potential role of electronic nicotine delivery systems as less harmful substitutes for combusted tobacco use?

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ABSTRACT

Two of the more controversial tobacco control and regulatory strategies in recent years are the nicotine reduction and tobacco harm reduction (THR) strategies. They have become inextricably intertwined as a successful nicotine reduction policy might only be possible in an environment in which alternative, noncombusted forms of nicotine like electronic nicotine delivery systems (ENDS) are available to address the needs of those who were unable or unwilling to completely give up nicotine. Unfortunately, ENDS have emerged as particularly controversial, in part, because they are the first product to carry reduced risk potential while being broadly appealing to cigarette smokers across demographic groups and subpopulations, and to a much smaller extent nonsmokers including, and most controversial, adolescents. In an effort to better understand some of the reasons that make this a controversial topic, we review some of the relevant history and discuss a broader dilemma that faces practitioners and policy developers of medical and public health interventions, namely, weighing the potential consequences of errors of commission versus omission. Commission errors involve a salient, direct link between an action and associated adverse or unintended consequences while omission errors are typically less salient with a more indirect link between inaction and associated adverse consequences. Decision-making research demonstrates that humans have a bias towards avoidance of commission errors and insensitivity to omission errors. This bias may be contributing to some of the aforementioned difficulties in finding common ground regarding the potential contribution of ENDS to reducing the harm of combusted tobacco use.

1. Introduction

The 2014 Surgeon General's Report made clear that the overwhelming cause of tobacco-related disease and premature mortality is smoke from combusted tobacco products, and cigarettes in particular (National Center for Chronic Disease et al., 2014). It concluded that more had to be done and done more rapidly to reduce exposure to smoke, suggesting the reduction of nicotine in cigarettes to levels that cannot support addiction (Benowitz and Henningfield, 1994, 2013, 2018; National Center for Chronic Disease et al., 2014) and substituting non-combusted forms of nicotine for combusted (Henningfield and Slade, 1998; National Center for Chronic Disease et al., 2014; Zeller and Hatsukami, 2009). In fact, nicotine reduction might only be possible in an environment in which alternative, noncombusted forms of nicotine were sufficiently accessible and appealing to address the needs of those who were unable or unwilling to completely give up nicotine (NRT)

(Benowitz et al., 2017; Henningfield et al., 1998). Recent population-level data highlight that smokers are indeed turning to more accessible and appealing nicotine products (e.g., e-cigarettes) to aid smoking cessation rather than conventional smoking cessation treatments (Beard et al., 2016; Benmarhnia et al., 2018; Caraballo et al., 2017), as an apparent tobacco harm reduction (THR) strategy.

THR has been discussed in various forms for decades, although never without controversy perhaps due in part to what is widely regarded as the public health disaster of efforts to encourage reduced tar and nicotine yield cigarettes (also known as “light” cigarettes) as a THR product for continuing cigarette smokers (Gray, 2010; Koop, 2010; Kozlowski and Abrams, 2016; National Cancer Institute (U.S.), 2001; Stratton et al., 2001; Zeller and Hatsukami, 2009). Despite the failure of light cigarettes, Kozlowski and others continued to make an evidence-based case for THR by underscoring that substituting noncombusted forms of nicotine should reduce the risk of disease as compared to

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continued cigarette smoking and proposed the “risk/use equilibrium” which came to be known as “the continuum of risk” across tobacco products (Kozlowski et al., 2001). According to this increasingly widely accepted hypothesis, the risk of nicotine use was expected to be lowest for medicinal forms of nicotine and highest for cigarettes and other combustion products (Zeller and Hatsukami, 2009).

Smokeless tobacco (ST) substitution for cigarettes provided a population level proof of concept for THR. As promoted by Michael Russell and colleagues (Russell et al., 1980), and in Sweden in the 1980s, harm reduction involved increased acceptance of oral ST product use as an alternative to cigarettes for those who could not give up nicotine (Foulds et al., 2003; Henningfield and Fagerstrom, 2001). The Swedish data suggest that the cessation of smoking, whether enabled by substitution of cigarettes with low nitrosamine Swedish snus or otherwise, is associated with at least a 90–95% reduction in the risk of tobacco-related mortality (Gartner et al., 2007; Lee, 2013; Levy et al., 2004; World Health Organization, 2008; Ramstrom et al., 2016). Subsequently, the Strategic Dialog on THR concluded that a variety of noncombustible forms of tobacco including Electronic Nicotine Delivery Systems (ENDS) held promise for cigarette smokers who are unable or unwilling to give up tobacco and nicotine completely to migrate to less harmful forms (Zeller and Hatsukami, 2009). More recently this THR concept has been embraced by the FDA in 2017 and 2018 as part of a comprehensive plan that reduces the addictiveness of cigarettes by lowering nicotine content while underscoring the potential of less harmful tobacco products to have a role in improving public health (Gottlieb and Zeller, 2017; U.S. Food and Drug Administration, 2018).

2. ENDS emerge as a controversial potential THR strategy

Until the introduction of ENDS to the US in about 2007 (Consumer Advocates for Smoke Free Alternatives Association, 2018), little progress was made in the proliferation of diverse and widely appealing NRT or noncombustible tobacco (Henningfield and Slade, 1998; Warner et al., 1998). Although NRT and other smoking cessation products are important components of tobacco control, their potential for harm reduction and population impact are limited as many smokers find them ineffective or unappealing forms of nicotine delivery, thus supporting suggestions that more people could be reached with more diverse noncombustible products (Abrams et al., 2018a, b; Kozlowski et al., 2001; Shiffman et al., 2007; Slade and Henningfield, 1998; US DHHS, 2014; Warner et al., 1996) (Table 1).

ENDS were early on viewed with both promise and peril for THR and with particular concerns about how they should be regulated (Henningfield and Zaatari, 2010; WHO Study Group on Tobacco Product Regulation, 2009). Despite many uncertainties about ENDS risks, their rapidly increasing uptake during the first few years of mass marketing in the US (Loomis et al., 2016; Wahba, 2014) fueled thinking that with appropriate regulation and promotion they could substantially benefit public health by substituting for conventional tobacco cigarettes (Abrams, 2014; Green et al., 2016b; Henningfield, 2014; National Center for Chronic Disease et al., 2014; The National Academies of Sciences, Engineering, and Medicine, 2018; Niaura et al., 2014; Walton et al., 2015). Moreover, there was concern that failure to support such innovations could be harmful to public health by slowing their uptake and thereby missing an opportunity to find an effective substitute for smokers unwilling or unable to quit nicotine use (Abrams et al., 2018b; Kozlowski and Sweanor, 2016; Warner, 2018). Some organizations argued that ENDS may be as dangerous as cigarettes, and that ENDS use by youth was as great a concern as cigarette smoking by youth (Green et al., 2016a, b; Kozlowski and Warner, 2017; McKee, 2016; Myers, 2016; Nocera, 2015). Not surprisingly, perceptions of ENDS risks in the U.S. shifted in adult smokers from over 70% believing that ENDS were less harmful than cigarettes in 2010 (Pearson et al., 2012; Tan and Bigman, 2014) to the present in which the majority of

people polled in the U.S. believe that ENDS are as or more harmful than cigarettes (Huerta et al., 2017; Majeed et al., 2017). Nonetheless, the US ENDS market has steadily increased from approximately 1.5 billion dollars in 2014 to a projected 3.6 billion dollars in 2018 (Statista, 2018).

3. ENDS are integrated into THR and treatment in the United Kingdom

In recent years, messaging in the U.K. highlighted the lower relative harm of e-cigarettes compared to conventional cigarettes and the promise of their utility in facilitating smoking cessation (Britton and Bogdanovica, 2014; McNeill et al., 2015, 2018). Governmental reports were accompanied by calls for health professionals to advise patients on the use of e-cigarettes for smoking cessation (Public Health England, 2015). In addition to the U.K.'s communications efforts there was the first approval of an ENDS product for smoking cessation by the U.K.'s Medicines and Healthcare Products Regulatory Agency, the equivalent to the U.S.'s FDA. That approval formally recognized an ENDS brand as an approved smoking-cessation product and made it available for use through the U.K.'s National Health Service (Barrett, 2016). Importantly, the UK approach included regulations to minimize their harms. For example, the 2016 Tobacco Products Directive highlights quality and safety standards required of e-cigarette products on the U.K. consumer market, including: being child-resistant and protected against breakage and leakage; regulating the content of constituents in e-liquid; requiring a large (30%) text-based health warning regarding the addictiveness of nicotine on e-cigarette packaging; and other restrictions.

4. FDA regulatory policy shifts towards facilitation of ENDS integration into tobacco control along with a nicotine reduction strategy

As mentioned above, in 2017 the U.S. Food and Drug Administration (FDA) announced that there was a need for less harmful alternatives to cigarettes “delivering satisfying levels of nicotine for adults who still need or want it.” (Gottlieb and Zeller, 2017). Subsequent announcements from FDA included increased flexibility in timelines for sponsors to submit applications to FDA for approval of ENDS (Gottlieb, 2018; U.S. Food and Drug Administration, 2017a) suggesting that FDA is embracing the concept that ready access to diverse and more satisfying ENDS is vital to migrate cigarette smokers away from combustible products as has been discussed by several leading tobacco control experts (Abrams et al., 2018b; Benowitz et al., 2017; Meier et al., 2016; Warner, 2018).

FDA's shift in its ENDS regulatory approach was not in response to a major new study supporting ENDS safety and benefits. Rather, it appeared to be an increased willingness to accept the risks of ENDS with a realignment of policy that was more consistent with tobacco control experts who were more accepting of ENDS' promise than those who emphasized their peril (Craver, 2017; Maloney, 2017) and their potential to play an important role in the comprehensive regulatory plan mentioned above. However, it may be useful to consider FDA's shift in the context of the broader question of what has been driving the differences of opinion among experts and organizations as to whether ENDS should be communicated from the perspective of promise or peril?

Often such differences reflect different interpretations and conclusions following rational evaluation of the same data. This is reflected in evidence reviews on the use of ENDS for smoking cessation (Villanti et al., 2018) and in contrasting results from simulation models on the population risks and benefits of ENDS (Levy et al., 2017, 2018; Soneji et al., 2018; Warner and Mendez, 2018). However, there may also be influence from differences in the types of risks that people are willing to accept. At the level of the product, there is increasing understanding of a continuum of nicotine-related risks that vary widely from the very low

Table 1
ENDS background and timeline.

2003	ENDS were invented and marketed in China by pharmacist, Hon Lik of Golden Dragon Holdings, which was renamed Ruyan (translation: “like smoke”) as safer substitute for cigarettes (Consumer Advocates for Smoke Free Alternatives Association, 2018).
2007	Marketing and consumer uptake began to rapidly increase in the US and many countries by internet and shopping mall kiosks (Consumer Advocates for Smoke Free Alternatives Association, 2018).
2009	The World Health Organization Tobacco Regulation Study Group (TobReg) concluded that since the products did not burn tobacco and tobacco was not necessary for their operation, they should be termed electronic nicotine delivery systems (ENDS), and recommended their regulation as drugs and/or combination drug/device products (Henningfield and Zaatari, 2010 ; World Health Organization, 2009).
2009	The Strategic Dialog on THR concluded that noncombustible substitutes for cigarettes (e.g., low nitrosamine oral smokeless tobacco) posed less risk than combusted tobacco for tobacco users (Zeller and Hatsukami, 2009).
2009	Family Smoking Prevention and Tobacco Control gave FDA regulatory authority over cigarettes and smokeless tobacco signed into law. ENDS were not included but the law provided the basis for adding other tobacco products to the regulatory framework.
2009	FDA acted to ban the import of ENDS on the premise that they were “unapproved drug-device combination products”. Two ENDS companies sued FDA to block its order. A federal judge sided with the companies and declared ENDS “tobacco products” arguing, in part, that insofar as their nicotine was derived from tobacco they should be considered tobacco products (Public Health Law Center, 2018 ; U.S. Food and Drug Administration, 2017b).
2010	A rapidly emerging disagreement among tobacco control experts and organizations emerged with some focused on the potential for ENDS to undermine progress in tobacco control by perpetuating smoking and serving as a “gateway” to smoking by young people, whereas others viewed ENDS as a potential path away from combustible tobacco use by people unable or unwilling to completely give up tobacco and nicotine.
2014	Surgeon general's report discussed both nicotine reduction as an approach to accelerate the reduction of exposure to combusted tobacco smoke with ENDS as a potential strategy to facilitate this transition (National Center for Chronic Disease et al., 2014).
2015	Evidence reviews suggested ENDS were likely substantially less harmful than cigarettes (Public Health England, 2015 ; Truth Initiative, 2015).
2016	FDA Tobacco Deeming Rule, finalized May 10, provided two years for ENDS marketers to submit applications for approval, was supported by ENDS opponents but questioned by ENDS supporters because it could greatly shrink the ENDS market and potentially put many small ENDS innovators and vape shops out of business (Sullum, 2016a, b ; U.S. Food and Drug Administration, 2016a, b ; Warner et al., 2016).
2017	FDA Commissioner Scott Gottlieb and FDA Center for Tobacco Products Director Mitch Zeller endorsed nicotine reduction as a strategy that would be pursued by FDA through its formal rule making process and that this would be facilitated by access to “potentially less harmful tobacco products [that] could reduce risk while delivering satisfying levels of nicotine for adults who still need or want it.” (Gottlieb and Zeller, 2017), and announced significant extension of deadlines for compliance with 2016 Tobacco Deeming Rule until 2022 allowing marketing to continue during the review process (U.S. Food and Drug Administration, 2017a).
2018	FDA issued an advance notice of proposed rulemaking (ANPRM) to develop a nicotine reduction regulation and described its intent to incentivize alternative nicotine delivery systems including NRT products and ENDS to “make it possible for current adult smokers who still seek nicotine to get it from alternative and less harmful sources” (U.S. Food and Drug Administration, 2018).

risks of nicotine replacement products such as nicotine gum and patches, to the extraordinarily high risks of the modern cigarette ([Abrams et al., 2018a, b](#)). Risks of ENDS include their potential uptake in some young people unlikely to use any nicotine product but for ENDS. Additionally, ENDS may delay or reduce smoking cessation by “dual use”, whereby some people use ENDS when they cannot smoke to manage nonsmoking environments thereby subverting the smoking cessation impact of environmental smoking bans. We share this concern but also recognize that some period of dual use among cigarette smokers may be one path to smoking reduction and eventual complete or near complete smoking cessation ([Buu et al., 2018](#); [Etter and Bullen, 2014](#); [Russell et al., 2018](#)).

5. ENDS policy in the context of errors of omission versus errors of commission

From an intervention and policy perspective, whether to promote or discourage THR might be viewed as a struggle between the potential errors of commission (allowing for or promoting ENDS despite potential risks), omission (failure to allow for or promote ENDS despite potential benefits in facilitating smoking cessation or as a safer source of nicotine), or complacency (lack of attention to ENDS resulting in maintaining the status quo) ([Hayward et al., 2005](#); [Holtgrave, 2010](#)).

In public health policy, medical practice, and other areas of policy, practice, and services, there has been increasing focus on errors and harms resulting from what is referred to as an ‘omission bias’ in human decision-making—a bias towards avoidance of commission errors and insensitivity to or an undervaluing of omission errors ([Baron and Ritov, 2004](#); [Ritov and Baron, 1990](#)). As illustrated by [Hayward et al. \(2005\)](#), the general tendency in industry to be more greatly concerned about errors of commission is often evident in product warnings which tend to focus on what should not be done.

As in most areas of public health, virtually all potential policies carry some sort of risks to various populations and since ENDS are still relatively new devices with unknown long-term health consequences, it is not surprising that such uncertainties contribute to policy disagreements among experts and the public in general. Underscoring the

potential health benefits of ENDS only to be contradicted by later evidence of longer-term adverse impacts (error of commission) could greatly tarnish the critically important credibility of the agency or individual scientists who promoted policies encouraging migration from smoking to ENDS. This fear is often voiced by agencies and individuals by statements that appropriately emphasize potential risks, but often with little or no mention of potential benefits relative to smoking. For example, from the American Academy of Pediatrics (AAP): “ENDS pose health risks to both users and nonusers. Nicotine, the major psychoactive ingredient in ENDS solutions, is both highly addictive and toxic. In addition to nicotine, other toxicants, carcinogens, and metal particles have been detected in solutions and aerosols of ENDS.” ([American Academy of Pediatrics, 2015](#)). From the Centers for Disease Control and Prevention (CDC) “We want parents to know that nicotine is dangerous for kids at any age, whether it's an e-cigarette, hookah, cigarette or cigar,” ([Centers for Disease Control and Prevention, 2015](#)). From the U.S. Surgeon General: “E-cigarette use among U.S. youth and young adults is now a major public health concern.” ([U.S. Department of Health and Human Services, 2016](#)). These and other reports also highlight concerns including theoretical risks (e.g., formaldehyde produced in extreme ENDS test conditions) and unintended consequences that appear to be rare (e.g., exploding ENDS) (see discussion in [Abrams et al., 2018a, b](#); [Kozlowski and Warner, 2017](#)).

Such concerns may reflect in part the omission error bias by underscoring the potential risks of promoting migration from combustible products to ENDS while ignoring the potential harms of inaction that allows cigarette smoking to continue at levels greater than necessary ([Kozlowski and Warner, 2017](#); [Warner, 2018](#)). As suggested by [Abrams et al. \(2018a, b, p. 12\)](#): Staying the course now risks perpetuation of smoked tobacco, prolongs unnecessary excessive deaths and slows adoption of much less harmful NNPs [noncombustible nicotine products]. It might take a decade or more to determine if the failure to more broadly support THR was a substantial error of omission that perpetuated the tobacco epidemic. Thus, in the near term, any public ramifications of the omission error are almost certainly going to be less salient than those resulting from a commission error. Moreover, even if the error of omission is eventually identified and publicized, people

generally judge errors of omission less harshly than those of commission (Baron, 1996); hence, there is a lower risk of adverse professional repercussions.

6. Conclusion

Complex policy decisions such as those being made around ENDS are surely multiply determined and by no means are we trying to argue that the omission bias is playing a pivotal role. However, we think there is good reason to be mindful of this bias in human decision-making and the possibility that it may be a factor that is slowing efforts to adopt the type of multipronged comprehensive approach that FDA is advocating. Namely, a tobacco control policy that includes efforts to decrease the addictiveness of cigarettes by reducing their nicotine content in combination with an explicit role for substitution of ENDS and other less harmful non-combusted sources of nicotine for adults who are unable or unwilling to discontinue nicotine use. We hope that the concept of omission bias may be one tool to facilitate critical thinking and dialog by helping understand that differences of opinion concerning the implications of the same facts around ENDS, may reflect, in part differing perspectives or decision-making biases on the management of risk more generally.

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In the past three years, through Pinney Associates, Dr. Henningfield has provided consulting services on smoking cessation and tobacco harm minimization (including nicotine replacement therapy and electronic vapor products) to Nicotivum USA, Inc., R.J. Reynolds Vapor Company, and RAI Services Company, all subsidiaries of Reynolds American Inc. RAI was acquired by British American Tobacco (BAT) in July 2017. RAI had no input into any facet of this manuscript. JEH co-holds a patent for a novel nicotine medication that has not been developed or commercialized. He also advises pharmaceutical developers on the evaluation and regulation of medications with respect to their potential for abuse and addiction.

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References

Abrams, D.B., 2014. Promise and peril of e-cigarettes: can disruptive technology make cigarettes obsolete? *JAMA* 311, 135–136.

Abrams, D.B., Glasser, A.M., Pearson, J.L., Villanti, A.C., Collins, L.K., Niaura, R.S., 2018a. Harm minimization and tobacco control: reframing societal views of nicotine use to rapidly save lives. *Annu. Rev. Public Health* 39, 193–213.

Abrams, D.B., Glasser, A.M., Villanti, A.C., Pearson, J.L., Rose, S., Niaura, R., 2018b. Managing nicotine without smoke to save lives now: evidence for harm minimization. *Prev. Med.* <https://doi.org/10.1016/j.ypmed.2018.06.010>.

American Academy of Pediatrics, 2015. Electronic nicotine delivery systems. *Pediatrics* 136, 1018–1026.

Baron, J., 1996. Do no harm. In: Messick, D., Tenbrunsel, A. (Eds.), *Codes of Conduct: Behavioral Research Into Business Ethics*. Russell Sage, New York, pp. 197–213.

Baron, J., Ritov, I., 2004. Omission bias, individual differences, and normality. *Organ. Behav. Hum. Decis. Process.* 94, 74–85.

Barrett, D., 2016. E-cigarettes Win First Approval as a ‘Medicine’ Opening Way for Prescription by the NHS. *The Telegraph*. <https://www.telegraph.co.uk/news/health/news/12079130/E-cigarettes-win-first-approval-as-a-medicine-opening-way-for-prescription-by-the-nhs.html>, Accessed date: 24 April 2018.

Beard, E., West, R., Michie, S., Brown, J., 2016. Association between electronic cigarette use and changes in quit attempts, success of quit attempts, use of smoking cessation

pharmacotherapy, and use of stop smoking services in England: time series analysis of population trends. *BMJ* 354, i4645.

Benmarhnia, T., Pierce, J.P., Leas, E., White, M.M., Strong, D.R., Noble, M.L., Trinidad, D.R., 2018. Can e-cigarettes and pharmaceutical aids increase smoking cessation and reduce cigarette consumption? Findings from a Nationally Representative Cohort of American Smokers. *Am. J. Epidemiol.* <https://doi.org/10.1093/aje/kwy129>.

Benowitz, N.L., Henningfield, J.E., 1994. Establishing a nicotine threshold for addiction. The implications for tobacco regulation. *N. Engl. J. Med.* 331, 123–125.

Benowitz, N.L., Henningfield, J.E., 2013. Reducing the nicotine content to make cigarettes less addictive. *Tob. Control.* 22 (Suppl. 1), i14–i17.

Benowitz, N.L., Henningfield, J.E., 2018. Nicotine reduction strategy: state of the science and challenges to tobacco control policy and FDA tobacco product regulation. *Prev. Med.* <https://doi.org/10.1016/j.ypmed.2018.06.012>.

Benowitz, N.L., Donny, E.C., Hatsukami, D.K., 2017. Reduced nicotine content cigarettes, e-cigarettes and the cigarette end game. *Addiction* 112, 6–7.

Britton, J., Bogdanovska, I., 2014. Electronic Cigarettes: A Report Commissioned by Public Health England. University of Nottingham.

Buu, A., Hu, Y.H., Piper, M.E., Lin, H.C., 2018. The association between e-cigarette use characteristics and combustible cigarette consumption and dependence symptoms: results from a national longitudinal study. *Addict. Behav.* 84, 69–74.

Caraballo, R.S., Shafer, P.R., Patel, D., Davis, K.C., McAfee, T.A., 2017. Quit methods used by US adult cigarette smokers, 2014–2016. *Prev. Chronic Dis.* 14, E32.

Centers for Disease Control and Prevention, 2015. E-cigarette Use Triples Among Middle and High School Students in Just One Year. <https://www.cdc.gov/media/releases/2015/p0416-e-cigarette-use.html>, Accessed date: 28 July 2018.

Consumer Advocates for Smoke Free Alternatives Association, 2018. Historical Timeline of Electronic Cigarettes. <http://www.casaa.org/historical-timeline-of-electronic-cigarettes/>, Accessed date: 24 April 2018.

Craver, R., 2017. FDA unveils plan for major changes to tobacco product regulations. Winston-Salem J. http://www.journalnow.com/business/business_news/local/fda-unveils-plan-for-major-changes-to-tobacco-product-regulations/article_ca4ebc67-73d9-5962-b370-7846b7d764fb.html.

Etter, J.F., Bullen, C., 2014. A longitudinal study of electronic cigarette users. *Addict. Behav.* 39, 491–494.

Foulds, J., Ramstrom, L., Burke, M., Fagerstrom, K., 2003. Effect of smokeless tobacco (snus) on smoking and public health in Sweden. *Tob. Control.* 12, 349–359.

Gartner, C.E., Hall, W.D., Vos, T., Bertram, M.Y., Wallace, A.L., Lim, S.S., 2007. Assessment of Swedish snus for tobacco harm reduction: an epidemiological modelling study. *Lancet* 369, 2010–2014.

Gottlieb, S., 2018. Policy Theme Lecture. Society for Research on Nicotine and Tobacco, Baltimore. <https://www.youtube.com/watch?v=SOySnYh3mI>.

Gottlieb, S., Zeller, M., 2017. A nicotine-focused framework for public health. *N. Engl. J. Med.* 377, 1111–1114.

Gray, N., 2010. Global tobacco control policy. In: Boyle, P., Gray, N., Henningfield, J.E., Seffrin, J., Zatonski, W.A. (Eds.), *Tobacco: Science, Policy, and Public Health*, Second ed. Oxford University Press, New York, pp. 643–651.

Green, S.H., Bayer, R., Fairchild, A.L., 2016a. Evidence, policy, and e-cigarettes. *N. Engl. J. Med.* 375, e6.

Green, S.H., Bayer, R., Fairchild, A.L., 2016b. Evidence, policy, and e-cigarettes—will England reform the debate? *N. Engl. J. Med.* 374, 1301–1303.

Hayward, R.A., Asch, S.M., Hogan, M.M., Hofer, T.P., Kerr, E.A., 2005. Sins of omission: getting too little medical care may be the greatest threat to patient safety. *J. Gen. Intern. Med.* 20, 686–691.

Henningfield, J.E., 2014. The tobacco endgame: it's all about behavior. *Prev. Med.* 68, 11–16.

Henningfield, J.E., Fagerstrom, K.O., 2001. Swedish match company, Swedish snus and public health: a harm reduction experiment in progress? *Tob. Control.* 10, 253–257.

Henningfield, J.E., Slade, J., 1998. Tobacco-dependence medications: public health and regulatory issues. *Food Drug Law J.* (53 suppl), 75–114.

Henningfield, J.E., Zaatari, G.S., 2010. Electronic nicotine delivery systems: emerging science foundation for policy. *Tob. Control.* 19, 89–90.

Henningfield, J.E., Benowitz, N.L., Slade, J., Houston, T.P., Davis, R.M., Deitchman, S.D., 1998. Reducing the addictiveness of cigarettes. Council on Scientific Affairs, American Medical Association. *Tob. Control.* 7, 281–293.

Holtgrave, D.R., 2010. Public health errors: costing lives, millions at a time. *J. Public Health Manag. Pract.* 16, 211–215.

Huerta, T.R., Walker, D.M., Mullen, D., Johnson, T.J., Ford, E.W., 2017. Trends in e-cigarette awareness and perceived harmfulness in the U.S. *Am. J. Prev. Med.* 52, 339–346.

Koop, C.E., 2010. Preface. In: Boyle, P., Gray, N., Henningfield, J.E., Seffrin, J., Zatonski, W.A. (Eds.), *Tobacco: Science, Policy, and Public Health*, Second ed. Oxford University Press, New York, pp. v–xvii.

Kozlowski, L.T., Abrams, D.B., 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.

Kozlowski, L.T., Swenor, 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.

Kozlowski, L.T., Warner, K.E., 2017. Adolescents and e-cigarettes: objects of concern may appear larger than they are. *Drug Alcohol Depend.* 174, 209–214.

Kozlowski, L.T., Strasser, A.A., Giovino, G.A., Erickson, P.A., Terza, J.V., 2001. Applying the risk/use equilibrium: use medicinal nicotine now for harm reduction. *Tob. Control.* 10, 201–203.

Lee, P.N., 2013. Epidemiological evidence relating snus to health—an updated review based on recent publications. *Harm Reduct J.* 10, 36.

Levy, D.T., Mumford, E.A., Cummings, K.M., Gilpin, E.A., Giovino, G., Hyland, A.,

- Sweanor, D., Warner, K.E., 2004. The relative risks of a low-nitrosamine smokeless tobacco product compared with smoking cigarettes: estimates of a panel of experts. *Cancer Epidemiol. Biomark. Prev.* 13, 2035–2042.
- Levy, D.T., Borland, R., Villanti, A.C., Niaura, R., Yuan, Z., Zhang, Y., Meza, R., Holford, T.R., Fong, G.T., Cummings, K.M., Abrams, D.B., 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, 149–159.
- Levy, D.T., Borland, R., Lindblom, E.N., Goniewicz, M.L., Meza, R., Holford, T.R., Yuan, Z., Luo, Y., O'Connor, R.J., Niaura, R., Abrams, D.B., 2018. Potential deaths averted in USA by replacing cigarettes with e-cigarettes. *Tob. Control.* 27, 18–25.
- Loomis, B.R., Rogers, T., King, B.A., Dench, D.L., Gammon, D.G., Fulmer, E.B., Agaku, I.T., 2016. National and state-specific sales and prices for electronic cigarettes-U.S., 2012–2015. *Am. J. Prev. Med.* 50, 18–29.
- Majeed, B.A., Weaver, S.R., Gregory, K.R., Whitney, C.F., Slovic, P., Pechacek, T.F., Eriksen, M.P., 2017. Changing perceptions of harm of e-cigarettes among U.S. adults, 2012–2015. *Am. J. Prev. Med.* 52, 331–338.
- Maloney, J., 2017. FDA wants nicotine in cigarettes to be cut to nonaddictive levels. *Wall Street J.* <https://www.wsj.com/articles/fda-seeks-to-reduce-nicotine-levels-in-cigarettes-to-nonaddictive-levels-1501253894>.
- McKee, M., 2016. Evidence, policy, and e-cigarettes. *N. Engl. J. Med.* 375, e6.
- McNeill, A., Brose, L., Calder, R., Hitchman, S., Hajek, P., McRobbie, H., 2015. E-cigarettes: An Evidence Update. Public Health England, London.
- McNeill, A., Brose, L., Calder, R., Bauld, L., Robson, D., 2018. Evidence Review of E-cigarettes and Heated Tobacco Products 2018: A Report Commissioned by Public Health England. Public Health England, London.
- Meier, E., Isaksson Vogel, R., O'Connor, R.J., Severson, H.H., Shields, P.G., Hatsukami, D.K., 2016. Preference for flavored noncombustible nicotine products among smokers motivated to switch from cigarettes. *Nicotine Tob. Res.* 18, 892–893.
- Myers, M.L., 2016. Evidence, policy, and e-cigarettes. *N. Engl. J. Med.* 375, e6.
- National Cancer Institute (U.S.), 2001. Risks Associated With Smoking Cigarettes With Low Machine-measured Yields of Tar and Nicotine. xi The Institute, Bethesda, MD (236 p).
- National Center for Chronic Disease, P., Health Promotion Office on, S., Health, 2014. Reports of the Surgeon General. The Health Consequences of Smoking-50 Years of Progress: A Report of the Surgeon General. Centers for Disease Control and Prevention (US), Atlanta (GA).
- Niaura, R.S., Glynn, T.J., Abrams, D.B., 2014. Youth experimentation with e-cigarettes: another interpretation of the data. *JAMA* 312, 641–642.
- Nocera, J., 2015. Peering through the haze. *New York Times* A19. <https://www.nytimes.com/2015/04/18/opinion/joe-nocera-peering-through-the-haze.html>, Accessed date: 25 April 2018.
- Pearson, J.L., Richardson, A., Niaura, R.S., Vallone, D.M., Abrams, D.B., 2012. E-cigarette awareness, use, and harm perceptions in US adults. *Am. J. Public Health* 102, 1758–1766.
- Public Health England, 2015. E-cigarettes: A New Foundation for Evidence-based Policy and Practice. London.
- Public Health Law Center, 2018. Sottera Inc. v. U.S. Food and Drug Administration. <http://www.publichealthlawcenter.org/content/sottera-inc-v-us-food-and-drug-administration>, Accessed date: 24 April 2018.
- Ramstrom, L., Borland, R., Wikmans, T., 2016. Patterns of smoking and snus use in Sweden: implications for public health. *Int. J. Environ. Res. Public Health* 13.
- Ritov, I., Baron, J., 1990. Reluctance to vaccinate: omission bias and ambiguity. *J. Behav. Decis. Mak.* 3, 263–277.
- Russell, M.A., Jarvis, M.J., Feyerabend, C., 1980. A new age for snuff? *Lancet* 1, 474–475.
- Russell, C., Dickson, T., McKeganey, N., 2018. Advice from former-smoking e-cigarette users to current smokers on how to use e-cigarettes as part of an attempt to quit smoking. *Nicotine Tob. Res.* 20, 977–984.
- Shiffman, S., Hughes, J.R., Ferguson, S.G., Pillitteri, J.L., Gitchell, J.G., Burton, S.L., 2007. Smoker's interest in using nicotine replacement to aid smoking reduction. *Nicotine Tob. Res.* 9, 1177–1182.
- Slade, J., Henningfield, J.E., 1998. Tobacco product regulation: context and issues. *Food Drug Law J.* (53 suppl), 43–74.
- Soneji, S.S., Sung, H.Y., Primack, B.A., Pierce, J.P., Sargent, J.D., 2018. Quantifying population-level health benefits and harms of e-cigarette use in the United States. *PLoS One* 13, e0193328.
- Statista, 2018. Electronic Cigarettes (E-cigarettes) Dollar Sales in the United States From 2014 to 2018 (in Billion U.S. Dollars). <https://www.statista.com/statistics/285143/us-e-cigarettes-dollar-sales/>, Accessed date: 15 July 2018.
- Stratton, K.R., Shetty, P., Wallace, R., Bondurant, S. (Eds.), 2001. Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction. Institute of Medicine. National Academy Press, Washington, D.C.
- Sullum, J., 2016a. The FDA's Deadly E-cigarette Regulations. Reason. <http://reason.com/archives/2016/05/11/the-fdas-deadly-e-cigarette-regulations>, Accessed date: 3 May 2018.
- Sullum, J., 2016b. The FDA's incomprehensible answer to a crucial question about its e-cigarette regulations. *Forbes*. <https://www.forbes.com/sites/jacobsullum/2016/07/25/the-fdas-incomprehensible-answer-to-a-crucial-question-about-its-e-cigarette-regulations/#13f3a16870cc>, Accessed date: 3 May 2018.
- Tan, A.S., Bigman, C.A., 2014. E-cigarette awareness and perceived harmfulness: prevalence and associations with smoking-cessation outcomes. *Am. J. Prev. Med.* 47, 141–149.
- The National Academies of Sciences, Engineering, and Medicine, 2018. New Report One of the Most Comprehensive Studies on Health Effects of E-cigarettes; Finds That Using E-cigarettes May Lead Youth to Start Smoking, Adults to Stop Smoking. <http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=24952>.
- Truth Initiative, 2015. The Truth About: Electronic Nicotine Delivery Systems. https://truthinitiative.org/sites/default/files/The_Truth_About_Electronic_Nicotine_Delivery_Systems.pdf, Accessed date: 25 April 2018.
- US Department of Health and Human Services, 2014. National Center for Chronic Disease, P., Health Promotion Office on, S., Health. In: Reports of the Surgeon General. The Health Consequences of Smoking-50 Years of Progress: A Report of the Surgeon General. Centers for Disease Control and Prevention (US), Atlanta (GA).
- U.S. Department of Health and Human Services, 2016. E-cigarette Use Among Youth and Young Adults: A Report of the Surgeon General. National Center for Chronic Disease Prevention and Health Promotion Office on Smoking and Health, Atlanta, GA.
- U.S. Food and Drug Administration, 2016a. Deeming tobacco products to be subject to the federal food, drug, and cosmetic act, as amended by the family smoking prevention and tobacco control act; restrictions on the sale and distribution of tobacco products and required warning statements for tobacco products. Final rule. *Fed. Regist.* 81, 28973–29106.
- U.S. Food and Drug Administration, 2016b. The Facts on the FDA's New Tobacco Rule. <https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm506676.htm>, Accessed date: 3 May 2018.
- U.S. Food and Drug Administration, 2017a. FDA Announces Comprehensive Regulatory plan to Shift Trajectory of Tobacco-related Disease, Death. <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm568923.htm>.
- U.S. Food and Drug Administration, 2017b. Tobacco Product Regulation: Sottera Court Decision. <https://www.fda.gov/tobaccoproducts/guidancecomplianceregulatoryinformation/manufacturing/ucm335294.htm>, Accessed date: 24 April 2018.
- U.S. Food and Drug Administration, 2018. Statement from FDA commissioner Scott Gottlieb, M.D. In: On Pivotal Public Health Step to Dramatically Reduce Smoking Rates by Lowering Nicotine in Combustible Cigarettes to Minimally or Non-addictive Levels, . <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm601039.htm>.
- Villanti, A.C., Feirman, S.P., Niaura, R.S., Pearson, J.L., Glasser, A.M., Collins, L.K., Abrams, D.B., 2018. 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* 113, 391–404.
- Wahba, P., 2014. U.S. E-cigarette Sales Seen Rising 24.2% per Year Through 2018. *Fortune*. <http://fortune.com/2014/06/10/e-cigarette-sales-rising/>, Accessed date: 15 July 2018.
- Walton, K.M., Abrams, D.B., Bailey, W.C., Clark, D., Connolly, G.N., Djordjevic, M.V., Eissenberg, T.E., Fiore, M.C., Goniewicz, M.L., Haverkos, L., Hecht, S.S., Henningfield, J.E., Hughes, J.R., Oncken, C.A., Postow, L., Rose, J.E., Wanke, K.L., Yang, L., Hatsukami, D.K., 2015. NIH electronic cigarette workshop: developing a research agenda. *Nicotine Tob. Res.* 17, 259–269.
- Warner, K.E., 2018. How to Think, Not Feel, About Tobacco Harm Reduction. *N Engl J Med* In Press.
- Warner, K.E., Mendez, D., 2018. E-cigarettes: comparing the possible risks of increasing smoking initiation with the potential benefits of increasing smoking cessation. *Nicotine Tob. Res.*, nty062. <https://doi.org/10.1093/ntn/nty062>.
- Warner, K.E., Slade, J., Sweanor, D.T., 1996. The emerging market for long-term nicotine maintenance. *JAMA* 278, 1087–1092.
- Warner, K.E., Peck, C.C., Woosley, R.L., Henningfield, J.E., Slade, J., 1998. Treatment of tobacco dependence: innovative regulatory approaches to reduce death and disease: preface. *Food Drug Law J.* (53 suppl), 1–8.
- Warner, K.E., Wimmer, H.P., Fairchild, A.L., Jefferson, D., 2016. Will regulating e-cigarettes mean fewer will quit smoking? *New York Times*. <https://www.nytimes.com/roomfordebate/2016/05/10/will-regulating-e-cigarettes-mean-fewer-will-quit-smoking>.
- WHO Study Group on Tobacco Product Regulation, 2009. Report on the Scientific Basis of Tobacco Product Regulation: Third Report of a WHO Study Group. WHO Technical Report Series. World Health Organization.
- World Health Organization, 2008. Advisory Note on Smokeless Tobacco Products: Health Effects, Implications for Harm Reduction and Research. The Scientific Basis of Tobacco Product Regulation: Second Report of a WHO Study Group. World Health Organization, Geneva, pp. 1–15.
- World Health Organization, 2009. TobReg Scientific Recommendation: Devices Designed for the Purpose of Nicotine Delivery to the Respiratory System in Which Tobacco Is Not Necessary for Their Operation. WHO Study Group on Tobacco Product Regulation: Report on the Scientific Basis of Tobacco Product Regulation: Third Report of a WHO Study Group. World Health Organization, Geneva, Switzerland, pp. 3–21.
- Zeller, M., Hatsukami, D., 2009. The strategic dialogue on tobacco harm reduction: a vision and blueprint for action in the US. *Tob. Control.* 18, 324–332.