HHS Public Access

Author manuscript

Prev Med. Author manuscript; available in PMC 2019 December 01.

Published in final edited form as:

Prev Med. 2018 December ; 117: 8–14. doi:10.1016/j.ypmed.2018.03.021.

Whether to push or pull? Nicotine reduction and non-combusted alternatives - two strategies for reducing smoking and improving public health

Tracy T. Smith[1], **Dorothy K. Hatsukami**[2], **Neal L. Benowitz**[3], **Suzanne M. Colby**[4], **F. Joseph McClernon**[5], **Andrew A. Strasser**[6], **Jennifer W. Tidey**[4], **Cassidy M. White**[7], and **Eric C. Donny**[7]

[1]Psychiatry and Behavioral Sciences, Medical University of South Carolina

[2]Masonic Cancer Center, University of Minnesota

[3]Departments of Medicine and Bioengineering & Therapeutic Sciences, University of California San Francisco

[4]Center for Alcohol & Addiction Studies, Brown University

[5]Department of Psychiatry and Behavioral Sciences, Duke University

[6]Department of Psychiatry, University of Pennsylvania Perelman School of Medicine

[7]Department of Physiology and Pharmacology, Wake Forest University School of Medicine

Abstract

Combustible cigarettes remain the most harmful and addictive tobacco product, and reducing the prevalence of smoking continues to be a critical public health goal. While nicotine is the constituent primarily responsible for addiction to cigarettes, most of the harm associated with smoking comes from byproducts of tobacco combustion. Recently, two different approaches for reducing the harms of smoking have emerged, both of which focus on breaking the link between the addiction to nicotine and the harms caused by smoking. First, the addictive potential of cigarettes could be minimized by requiring a large reduction in the nicotine content of cigarettes. Evidence for a nicotine reduction policy thus far shows that the use of very low nicotine content cigarettes results in a reduction in the number of cigarettes people smoke per day and a reduction in cigarette dependence. Second, emerging alternative nicotine delivery systems (ANDS) like electronic cigarettes may provide sufficient nicotine to act as substitutes for cigarettes while delivering much lower levels of toxicants. Evidence suggests that the emergence of ANDS has increased the percentage of smokers who are able to quit. The present paper will briefly review the

Corresponding author: Tracy T. Smith, PhD, Postdoctoral Fellow, Addiction Sciences Division, Psychiatry and Behavioral Sciences, Medical University of South Carolina, (843) 792-5164, smithtra@musc.edu.

Conflicts of Interest: Dr. Benowitz is a consultant to pharmaceutical companies that market smoking cessation medications and has been an expert witness in litigation against tobacco companies.

evidence for each of these approaches, and consider what contemporary reinforcement and addiction theories can tell us about their likely success. We argue that the most effective endgame approach is one that pursues both nicotine reduction and alternative nicotine delivery systems as complementary.

Keywords

Nicotine reduction; Alternative nicotine delivery systems; e-cigarettes; endgame

I. Harms associated with burned tobacco

Tobacco use continues to devastate public health, causing an estimated 6 million deaths worldwide annually [1]. The vast majority of the harm from tobacco use is caused by cigarettes and can be traced to the byproducts of combustion and specific constituents in tobacco [2]. Combustion is not necessary for nicotine delivery, although it does facilitate the rapidity with which nicotine is delivered by enabling pulmonary absorption [2]. Nicotine itself, when delivered in cigarette-like doses, is not benign [2], but is far less toxic than other constituents of tobacco smoke and hence would likely be less harmful if it was delivered in a non- combusted vehicle [3]. Indeed, the harms associated with nicotine and tobacco products may be best viewed as a continuum in which abstinence from all tobacco products would be the least harmful, the use of combusted tobacco products would be the most harmful, and non-combusted tobacco products are somewhere in the middle [3–8]. The goal of policies and interventions should be to effectively move the population down that continuum of harm in order to improve public health [5].

Unfortunately, cigarettes are highly addictive, engineered over decades to maximize the development and maintenance of chronic, dependent smoking [2, 9, 10]. In the US, only 7.4% of adult smokers are able to quit smoking each year, despite the fact that 68.0% are interested in quitting and 55.4% make a quit attempt [11]. Since at least 1988 and arguably much longer [10, 12], the addictive properties of cigarettes have been attributed almost exclusively to nicotine. This perspective, that nicotine is the cause of cigarette addiction, has driven smoking cessation medication development and innovation of Alternative Nicotine Delivery Systems (ANDS)—noncombustible nicotine or tobacco products designed to deliver fewer toxicants than cigarettes [13, 14]. ANDS include products like snus, nicotine replacement therapy products, and, in recent years, e- cigarettes. Understanding nicotine as the driving force in cigarette addiction has also provided a rationale for potential tobacco policies such as reducing the nicotine content of combusted tobacco products to render the product less addictive [15].

Of course, smoking is about more than nicotine. Other factors such as the sensory stimuli associated with smoking and the act of smoking itself, become potent drivers of use [16, 17]. Indeed, smoking is interwoven throughout much of smokers' lives, and smokers have strong expectations and feelings about smoking, both positive and negative [18]. Smoking also remains embedded in culture. Many tobacco control policies have effectively shifted the cultural norms, although implementation and impact of those policies is quite heterogeneous

and smoking remains normative in many parts of the world [19]. Traditional tobacco control efforts have and should continue to address these issues, particularly reshaping cultural norms. Nevertheless, managing how people use nicotine - the constituent that is widely considered to be the central determinant of long-term use - has the potential to greatly improve public health. Currently, some 40 million Americans and over one billion smokers worldwide are using a product developed and aggressively marketed over decades, deeply embedded into the environments in which smoker's live, and integrated into their personal histories, making behavioral change extremely difficult [19, 20].

II. Two approaches to breaking the link between nicotine and harm

Two approaches to reducing combusted product use have recently received considerable attention. One approach is to encourage smokers to switch to ANDS rather than continue to smoke cigarettes [21, 22], and thus to reduce the harms of nicotine delivery among those who are unable or unwilling to quit using nicotine. The other approach focuses on reducing the nicotine content of combusted tobacco products to render them less addictive [23–26]. The intent is to reduce the harms associated with smoking, not by altering the toxicity of the product, but by reducing the likelihood that someone will start smoking or continue to smoke. Both represent approaches directed at breaking the link between nicotine consumption and the harms associated with inhalation of smoke from combusted tobacco. At the core, both are harm reduction approaches in that neither is particularly concerned with nicotine use per se, but instead focus on reducing exposure to smoke as a delivery vehicle for nicotine. Indeed, when the Food and Drug Administration (FDA) recently announced a new strategy for regulating tobacco products, these two approaches were considered essential and complementary components of a comprehensive FDA strategy [7].

Despite the shared focus on reducing use of combusted products and the two-pronged approach announced by FDA, some have argued that these two approaches are fundamentally and philosophically opposed. ANDS have been conceptualized as a bottom-up or pull approach, emphasizing that market-driven, consumer-driven approaches will persuade smokers to switch products while still protecting individual rights. ANDS, and policies that favor use of ANDS over cigarettes (e.g., light-touch regulation, differential taxation), might be conceptualized as a "nudging" approach to public health or what Loewenstein has called "asymmetric paternalism" [27]. Conversely, nicotine reduction has been described as a top-down or push technique, emphasizing the forced nature of product standards that some smokers may not want [28]. Kozlowski and Bates have described nicotine reduction as cigarette prohibition [28, 29] - more of a shove than a nudge. It is true that reducing nicotine would likely result in a reduction in cigarette sales, but it is important not to confound a reduction in the appeal and addictiveness of cigarettes with the prohibition of nicotine itself. Regardless, nicotine reduction is undeniably a more invasive tobacco control policy, and thus it is important to justify its necessity [30].

III. Promises, pitfalls, and prognosis of alternative nicotine delivery systems (ANDS)

Proponents of ANDS point to the number of smokers who have quit or reduced their smoking using ANDS [31]. Evidence of the potential utility for reducing smoking is most clearly observed in surveys focusing on the number of ANDS users who were smokers and have subsequently switched partly or entirely to e- cigarettes. For example, Farsalinos and colleagues estimated that as of 2014, 6.1 and 9.2 million European Union citizens have quit or reduced their smoking with the help of ANDS, respectively [31]. The evidence seems clear that for some smokers, ANDS may provide a path towards cessation [32]. Smokers who use e- cigarettes frequently, particularly those using systems that more effectively deliver nicotine, may be more likely to quit smoking [33–38]. Furthermore, some data have shown that in 2014 and 2015, when the prevalence of ANDS use rose drastically among adolescents, use of cigarettes in the same population decreased [39], which might suggest that the availability of ANDS reduces the use combustible cigarettes in youth. In Japan, a class of ANDS known as heat-not-burn products are increasing in prevalence. These products may provide a superior sensory experience to e-cigarettes because they involve heated tobacco rather than nicotine isolated from tobacco and reduced harm in comparison to cigarettes because the tobacco is not combusted [40, 41]. As these products have taken off in Japan, cigarette sales have declined, again suggesting that their availability reduces cigarette use [42]. Proponents of ANDS argue that these encouraging findings are only the tip of the iceberg because the nicotine delivery and positive subjective effects associated with ANDS products should continue to improve if innovation in this area is encouraged [28].

However, several observations warrant caution with regard to the impact of ANDS on current smokers. First, the vast majority of smokers either have not tried e-cigarettes, have tried them but abandoned them after a short trial period, or continue to use both products (i.e., dual use). In the EU, only an estimated 31.1% of current smokers have ever tried e-cigarettes, with just 4.2% reporting current use [31]. In the UK, an estimated 45% of e-cigarette users continue to smoke cigarettes, suggesting a sizeable portion of users do not switch completely in the timeframe assessed [43]. Likewise, although population data in England and the U.S. have concluded that e-cigarettes are increasing the rate of smoking cessation [45, 46], most smokers have not benefitted. For example, in England, an estimated 16,000–28,000 additional long-term quitters were generated by e-cigarettes in 2014 [44], an important contribution, but a relatively small fraction of England’s 8.46 million adult smokers. Furthermore, 891,000 smokers tried to quit and used an e-cigarettes over the same time period [44]. Thus, it appears that while e-cigarettes are a popular product for current smokers to try, a minority of smokers are able to switch completely from cigarettes to ANDS. Second, many smokers report that e- cigarettes are an unacceptable alternative to smoking. The most common reason for stopping use of e- cigarettes among current smokers in the UK is that they did not feel enough like smoking a cigarette, and the second most common reason is that they did not help deal with cravings to smoke cigarettes [43]. Third, many smokers appear to harbor misperceptions about the harm of e-cigarettes relative to cigarettes, and these misperceptions are growing. In 2017, an estimated 22% of smokers in

the UK reported that they believed e- cigarettes were as or more harmful than cigarettes, up from 9% in 2013 [43]. These beliefs were strongest among smokers who have never tried e-cigarettes, which may mean that these beliefs are a barrier to even trying e-cigarettes [43]. Combined, these limitations may mean that while ANDS are likely to offer a good alternative to smoking for those who find them appealing or are less dependent on traditional cigarettes, they may not be a satisfactory alternative to cigarettes for the masses of smokers who try to stop smoking each year. For ANDS to truly displace smoking, an intervention that can reduce the addictiveness of conventional cigarettes may be required.

In addition, several other concerns have been raised about the ultimate impact of ANDS on public health. First, while the health implications of nicotine replacement therapy [47] and products like snus are well understood [48, 49], we still know relatively little about the health risks of more novel ANDS like e-cigarettes [50]. It seems clear that ANDS deliver substantially lower levels of many of the toxicants present in cigarette smoke [51–54] and thus, they likely represent reduced health risks for smokers who switch completely [50]. However, nicotine is not harmless [55], and ANDS such as e-cigarettes and heat-not-burn products may present health risks that are not yet fully understood [51, 55, 56]. These risks are important given that the prevalence of smoking has been decreasing for a long time in much of the developed world, and the rise in use of these products may mean maintaining some health risks for tobacco use that may have dissipated on its own given enough time and increased use of established tobacco control policies. Second, recent evidence suggests that youth who use e-cigarettes are more likely to go on to initiate cigarette use [50, 57–64]. Proponents of ANDS argue that these data are limited because e-cigarette use among nonsmokers is rare [65] and e-cigarette and cigarette use may both be a product of a shared vulnerability for tobacco use, rather than evidence of a causal gateway effect. Indeed, national surveys show a rapid decline in adolescent smoking since the emergence of e-cigarettes [39, 66]. Nonetheless, the possibility is difficult to dismiss. Finally, a rise in the prevalence of ANDS use could slow the decline in combustible product use by renormalizing tobacco products [67]. Any of these concerns has the potential to limit the beneficial impact of ANDS on public health.

IV. Promises, pitfalls, and prognosis for nicotine reduction

The Tobacco Control Act in the U.S. and World Health Organization Framework Convention on Tobacco Control provide a regulatory framework for product standards and have reignited debate as to whether nicotine reduction would improve public health. The policy approach envisioned by most would involve large reductions in the nicotine content of combusted tobacco, including roll-your-own, cigarillos, little cigars, and potentially large cigars, but not non-combusted products, which are assumed to be less harmful. Hence, it is, by definition, an approach aimed at reducing the harm associated with nicotine use. Clinical trials investigating the impact of nicotine reduction have had promising results. Sizeable reductions in nicotine content [68, 69] reduce the rate of smoking, decrease nicotine dependence, and increase quit attempts [68, 70–73]. Reducing nicotine in cigarettes is technologically feasible. In fact, several very low nicotine content (VLNC) cigarettes have been manufactured and sold in the past (e.g., Next, Quest), suggesting that large scale production is feasible. The magnitude of nicotine reduction is important. A reduction from

about 15.8 mg nicotine / g tobacco to at least 2.4 mg/g appears to be required to observe any reduction in smoking rate, and a reduction to 0.4 mg/g was required to observe significant changes in nicotine dependence across multiple measures [68].

A primary concern of critics has been the potential for compensatory smoking. Some have even boldly stated that VLNC cigarettes are a “more toxic product” because nicotine reduction would increase the ratio of toxicants to nicotine within a cigarette [28]. The assumption is that in an attempt to maintain nicotine exposure, people will smoke more and will therefore be exposed to higher toxicant levels. This assumption, which is based on a loose analogy to “light” and “mild” cigarettes, runs counter to the data [25]. Light cigarettes have similar levels of nicotine to conventional cigarettes, but a reduced nicotine yield (i.e., when a machine smokes the product) because the design of the cigarette dilutes the smoke with ambient air and/or alters cigarette papers to accelerate burn times [74–77]. Smokers can easily adjust how they smoke light cigarettes to maintain a similar level of nicotine [74, 78]. Similarly, when smokers switch to cigarettes with small to moderate reductions in nicotine content, there is some evidence that they may compensate by increasing the number of cigarettes they smoke per day [70, 79] (but see [80]). However, when nicotine is reduced to very low levels (0.4 mg/g), changes in smoking behavior cannot maintain nicotine exposure [68, 70]. Indeed, studies have consistently shown that smokers who are switched to VLNC cigarettes for at least 6 weeks do not engage in compensatory smoking [80]. In this case, smokers are more likely to compensate for the reduction of nicotine in cigarettes by titrating their nicotine intake through a much more effective means - use of alternative products.

Some concerns center around how the public might respond to a mandated reduction in the appeal of such a popular product. Interestingly, surveys suggest that the majority of both non-smokers and smokers support reducing nicotine as a means to reducing addictiveness of cigarettes [81–84]. Even in studies in which participants have experience with VLNC cigarettes, the majority of participants report they are supportive of such a policy [85]. However, there is strong evidence that smokers find these cigarettes unappealing. Although VLNC cigarettes have been available commercially before, they were commercial failures, suggesting that given the choice, smokers will continue to use the normal nicotine content cigarettes to which they are addicted rather than choose a novel brand with very low nicotine content [86]. When participants try VLNC cigarettes, they rate them as less satisfying than research cigarettes with a normal nicotine content [24]. Furthermore, in clinical trials where participants are asked to smoke only the VLNC cigarettes provided to them, most participants smoke non-study normal nicotine content cigarettes anyway [68], even though the VLNC cigarettes are provided for free. We also know that attrition is higher in clinical trials when smokers are asked to switch directly from their usual brand to a VLNC cigarette rather than transitioning to an intermediate nicotine content before ultimately switching to VLNC cigarettes, suggesting that smokers find VLNC cigarettes especially unappealing when contrasted directly with their usual brand [87]. Collectively, these data suggest that if a nicotine reduction policy were implemented, many would likely find VLNC cigarettes to be unsatisfying and may seek out alternative sources of nicotine.

In an environment where smokers can no longer purchase their normal nicotine content cigarettes, consumers may respond by hoarding normal-nicotine content cigarettes, product

tampering, and/or turning to an illicit market. Hoarding of normal nicotine content cigarettes would seem to be a minor concern since the effective delay in nicotine reduction through hoarding is likely small. Smokers could try to add nicotine to their cigarettes, possibly by adding e-liquids or other nicotine-containing fluids. The effectiveness of this practice and the extent of its use (relative to just using ANDS, for which the fluids are designed) are difficult to predict, but would need to be monitored. Finally, regulation would almost certainly contribute to an increased demand for illicit cigarettes. Like other unintended consequences, the critical question is not whether this would occur, but rather how much harm would likely result and whether regulators could effectively mitigate both the supply of and demand for illicit cigarettes. The size of an illicit market is likely to depend on factors such as the speed at which nicotine in cigarettes is reduced (immediate vs. a stepped or gradual approach), effective enforcement of manufacturers and retailers, and the availability of alternative products [88]. If consumers can easily access a satisfying and legal alternative to VLNC cigarettes such as ANDS, hoarding, tampering, and participation in an illicit market may be much less appealing.

Some of the impact of nicotine reduction will depend on choices that regulatory agencies make when designing the policy. We do not know the exact nicotine target that would be required for reduction, but lower nicotine contents produce greater benefits [68, 89]. A gradual reduction in nicotine content has the potential to produce compensatory smoking at intermediate levels [79], but may be tolerated better by consumers than an immediate reduction [87]. Any policy will need to be accompanied by well-researched public health messages because smokers harbor misperceptions about the harms associated with nicotine and perceive VLNC cigarettes to be safer than conventional cigarettes [90]. Thus, it is important that agencies clearly communicate the relative risks of available products.

V. A theoretical perspective on approaches to reducing combusted product use

The central premise of both strategies is that the harm caused by tobacco products will be reduced because current and potential smokers will be less likely to smoke and more likely to opt for a less harmful product or abstinence. In this section, we review what contemporary theories on reinforcement, choice behavior, and addiction tell us about the likely impact of each approach. This review is not meant to be exhaustive, but instead to provide a starting framework for understanding both the challenges and opportunities related to the choice to use cigarettes, use ANDS, or be abstinent. We set aside issues related to the health consequence of use, except to the degree to which it may impact choice.

Reinforcement and choice.

We have known for decades that the primary reinforcer for using tobacco is nicotine [10, 12]. We also know that non-nicotine stimuli (such as the taste, smell, and sights associated with smoking) become conditioned reinforcers through their pairing with nicotine [16, 17], and contribute to the reinforcement value of smoking. Ultimately, the choices people make about which tobacco products to use, if any, will depend on the overall reinforcement value of cigarettes relative to ANDS.

Contemporary learning theory emphasizes that behavior is allocated in a manner that is proportional to the reward value of one behavior relative to other possible behaviors (i.e., matching, [91–94]) and that some behaviors may be even more likely to occur than predicted because of bias (i.e., because of a preference for one environment or mode of responding [95]). In the case of cigarettes and ANDS, use behavior might be shifted from smoking to alternative ways to use nicotine by decreasing the reward derived from smoking or by increasing the reward derived from alternative ways to use nicotine. Relying on ANDS as an endgame strategy alone requires the belief that emerging products will ultimately provide enough reinforcement through improved sensorimotor cues and nicotine delivery to compete with combustible products [96], and that smokers would give up a product they are already using, that is ubiquitous in their environment, and maintains an extremely high value both related to its rapid nicotine delivery and conditioned reinforcement value. Alternatively, relying on a nicotine reduction strategy alone as an endgame strategy requires the belief that the reinforcement value of cigarettes following nicotine reduction will be low enough that smokers will choose to abstain, that the motivation to smoke doesn't drive harmful alternative smoking behaviors such as product tampering or use of illicit cigarettes, and that the bias to persist in smoking even VLNC cigarettes doesn't maintain use.

The belief that most people will choose to switch to ANDS instead of continuing to smoke conventional cigarettes assumes that people will make a rationale choice to use ANDS because of their reduced negative health consequences. However, people often do not make rationale choices about their individual health [97]. First, when people are choosing between two or more options, there is a bias for the default option [97], regardless of which option is the most beneficial. For example, when choosing home, car, or health insurance, one can shift the most popular insurance plans just by changing the default plan [98]. Applied to the choice of ANDS and cigarettes, this bias suggests that while people might choose ANDS if they had never used either product and they were presented with an array of tobacco products and their health consequences at the same time, current smokers will have a bias for the option they are currently using. Second, when people are choosing between two or more options, they discount the value of reinforcers that are delayed in time [99, 100], like any perceived health benefits of switching from cigarettes to e-cigarettes. Thus, in order for people to choose ANDS, the discounted value of long-term health has to be larger than the value of the immediate reward of their preferred product.

Addiction Theory.

Rational choice between ANDS and cigarettes is even more complicated because a sizeable portion of daily smokers are addicted [101–103]. Addiction processes may make this choice different from the choices that people make between products in other categories. This addiction is not just to nicotine, but to cigarettes [104, 105]. Adult smokers typically have used cigarettes for decades, taking tens of thousands of puffs associating the taste, smell, and feel of their cigarette with nicotine delivery. The product is deeply embedded in their daily lives. When a smoker runs out of cigarettes, they do not substitute smokeless tobacco - they seek out, sometimes with great effort, their preferred product and often their preferred brand.

Some theories of addiction focus on the importance of smoking cues and smoking-associated contexts, which are relevant for understanding why smokers may be unable or unwilling to switch to ANDS. The incentive salience theory posits that, as a consequence of the pharmacological actions of nicotine and other drugs of abuse, the neural systems mediating the relationship between stimuli and behavior become hypersensitive, rendering drug-associated cues "attractive" to smokers and robust triggers for drug use [106]. The importance of smoking cues in nicotine addiction is one reason that some ANDS products, like e- cigarettes and heat-not-burn products, are likely to be better substitutes for cigarettes than NRT—because the sensory cues associated with using these products are more similar to smoking. However, because the cues associated with using ANDS are not the *same* as cigarettes, smokers are likely to continue to be attracted to and biased by the cues associated with smoking. One advantage of nicotine reduction is that the power of smoking cues will be reduced through extinction over time as they are no longer paired with a reinforcing dose of nicotine. However, cigarette use can also become automated (i.e., habitual) in the presence of stimuli and contexts where cigarette use has occurred before, and changes in reinforcement value (such as those associated with reducing nicotine in cigarettes) sometimes do not alter these habit-driven tendencies [107– 109]. These automated memory sequences, called drug use action schemas, make it difficult for a smoker to refrain from smoking; in the presence of stimuli that trigger automatic smoking behaviors, abstaining requires that smokers exert a great deal of cognitive effort to deviate from this otherwise automated process. Any mental state that reduces cognitive processing availability, such as stress or nicotine withdrawal, will make it more difficult for smokers to successfully stop smoking or switch to another product [110]. Nonetheless, automated processes are not immutable; their influence is impacted by one's goals and underlying motivation [111]. For smoking, the availability of ANDS that act as highly satisfying alternatives to smoking may activate goal-driven systems allowing smokers to abstain from using reduced nicotine cigarettes.

Another important concept in addiction theory is related to the perceived probability of and expected effects of use. First, the perceived availability of tobacco products is a potent contextual determinant of dependence (craving, mood, use behavior) [112, 113]. Indeed, smokers who view visual smoking cues have greater activation of brain areas involved in reward value if they are expecting to smoke in the near future [114, 115], suggesting that cigarettes may actually hold greater incentive value when smokers perceive them to be available. In smokers who are currently trying to switch to ANDS, the wide availability of normal nicotine cigarettes may maintain craving for cigarettes, whereas if normal-nicotine cigarettes were unavailable, cigarette craving may be less intense. Second, the expectancies that users have about each class of tobacco products impacts their reinforcement value. Real or imagined, smokers generally believe that cigarettes are more likely to reduce stress, reduce negative affect, control weight, and provide more stimulation than e- cigarettes [116]. ANDS may have other advantages such as reduced belief they will be addictive, cause craving, and negatively impact health [116, 117]. However, the latter expectancies about ANDS are related to outcomes that are more delayed than immediate and could consequently have less impact on choice.

VI. Complementary approaches to ending combusted tobacco

The concurrent emergence of the nicotine reduction strategy and ANDS has triggered a contentious debate within the public health community. At times, this debate seems to have fueled a division between those who support vs. oppose nicotine reduction. Some advocates for ANDS have argued that nicotine reduction is unnecessary or a costly distraction with the advent of ANDS. We want to be clear - we consider ANDS an important technological advance that could help reduce the prevalence of smoking and reduce the harms associated with nicotine use. However, as discussed above, there is reason to be skeptical about whether ANDS can function as an endgame for smoking on their own. Likewise, nicotine reduction clearly holds promise in its ability to reduce reinforcement and dependence from cigarettes. However, in nicotine reduction clinical trials, most participants continue to smoke at some level [68, 70] and to supplement their study cigarettes with non-study normal nicotine cigarettes, highlighting a persistent demand for nicotine. The endgame should be to end combustible cigarette use. Tobacco regulators and public health experts should set clear goals for reaching this objective, and then ask whether either approach is likely to reach these goals on its own. If not, they should consider how much more likely we are to shift product use away from combusted products in favor of alternatives if we consider the two approaches as complementary. Indeed, these two approaches may ultimately need each other to have the greatest public health impact [7, 13].

Some have emphasized that much larger and potentially very long trials would need to be conducted or that evidence from a single country or locality is needed before any other country should entertain mandated reductions in the nicotine content of combusted products [29, 118]. The empirical basis for policy is never complete and clinical trials cannot fully predict real-world experience [119]; nevertheless, past and current studies [26, 68, 70, 72, 73, 120] are likely to provide a strong foundation well within the likely timeframe for regulatory change. A nicotine reduction policy will take years to enact. Given that most smokers intend/want to quit smoking, it is likely that these pending changes will increase quit attempts and/or use of alternative products. Indeed, when new cigarette taxes are announced, there is a spike in online searches for non-cigarette tobacco products, including ANDS [121]. Consequently, any locality considering reducing nicotine should have a strong infrastructure for providing smoking cessation services and be prepared for a potential increase in the use of alternative products.

Some critics of nicotine reduction are worried about the heavy-handed role of government in a potential nicotine reduction policy. One has likened nicotine reduction to a stick and ANDS to a carrot [122]. Critics have asked *If nicotine is reduced, what's next? What precedent does it set?* Regulators and society broadly have to struggle with where to draw lines that infringe on personal freedom for the public good. The issue is not new nor is it unique to tobacco [30]. However, we must not lose sight of the unique nature of cigarettes in society. They are the only legal product that kills a third to half its users and maintains its use through addiction. Most users want to stop [123]. For smokers, continuing to use cigarettes as they are currently designed in a marketplace dominated by these products is not a free choice [13]. One might reasonably ask… *What precedent does it set when agencies with the regulatory authority to limit the addiction to and devastation from cigarettes fail to*

act? Indeed, when the stakes are high enough, a stick may be needed when a carrot will not do [30, 124]. Addiction is not rationale. We may have to loosen its grip to enable change.

Acknowledgments

Funding: Research reported in this publication was supported by the National Institute on Drug Abuse and FDA Center for Tobacco Products (CTP) (U54 DA031659). Support for JWT was also provided by P50DA036114 and for DKH by U19CA157345). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or the Food and Drug Administration.

REFERENCES

1. World Health Organization, WHO global report on trends in prevalence of tobacco smoking 2015. WHO Library Cataloguing, 2015.
2. The Surgeon General., in The Health Consequences of Smoking-50 Years of Progress: A Report of the Surgeon General. 2014: Atlanta (GA).
3. Nutt DJ, et al., Estimating the harms of nicotine-containing products using the MCDA approach. Eur Addict Res, 2014 20(5): p. 218–25. [PubMed: 24714502]
4. Sweanor D, Alcabes P, and Drucker E, Tobacco harm reduction: how rational public policy could transform a pandemic. Int J Drug Policy, 2007 18(2): p. 70–4. [PubMed: 17689347]
5. Zeller M, Hatsukami D, and Strategic G Dialogue on Tobacco Harm Reduction, *The Strategic Dialogue on Tobacco Harm Reduction: a vision and blueprint for action in the US*. Tob Control, 2009 18(4): p. 324–32. [PubMed: 19240228]
6. Saitta D, et al., A Risk Assessment Matrix for Public Health Principles: The Case for E-Cigarettes. Int J Environ Res Public Health, 2017 14(4).
7. Food and Drug Administration., FDA accounces comprehensive regulatory place to shift trajectory of tobacco-related disease, death. 2017.
8. Kozlowski LT, et al., Applying the risk/use equilibrium: use medicinal nicotine now for harm reduction. Tob Control, 2001 10(3): p. 201–3. [PubMed: 11544374]
9. Proctor RN, Golden holocaust: Origins of the cigarette catastrophe and the case for abolition. 2011, Berkeley, Los Angeles, London: University of California Press.
10. US Department of Health and Human Services. How tobacco smoke causes disease: the biology and behavioral basis for smoking-attributable disease: A report of the Sugeon General. 2010, Dept. of Health and Human Services: Rockville, MD.
11. Babb S, et al., Quitting Smoking Among Adults - United States, 2000–2015. MMWR Morb Mortal Wkly Rep, 2017 65(52): p. 1457–1464. [PubMed: 28056007]
12. US Departmenf of Health and Human Services., The health consequences of smoking: Nicotine addiction: A report of the Surgeon General. 1988.
13. Warner KE and Pollack HA, *The Nicotine Fix,* in *The Atlantic*. 2014: United States.
14. Kunze U, et al., Alternative nicotine delivery systems (ANDS)--public health-aspects. Wien Klin Wochenschr, 1998 110(23): p. 811–6. [PubMed: 10025033]
15. Benowitz NL and Henningfield JE, Establishing a nicotine threshold for addiction. The implications for tobacco regulation. N Engl J Med, 1994 331(2): p. 123–5. [PubMed: 7818638]
16. Rupprecht LE, et al., Behavioral mechanisms underlying nicotine reinforcement. Curr Top Behav Neurosci, 2015 24: p. 19–53. [PubMed: 25638333]
17. Caggiula AR, et al., The role of nicotine in smoking: a dual-reinforcement model. Nebr Symp Motiv, 2009 55: p. 91–109. [PubMed: 19013940]
18. Brandon TH, Wetter DW, and Baker TB, Affect, expectancies, urges, and smoking: Do they conform to models of drug motivation and relapse? Exp Clin Psychopharmacol, 1996 4(1): p. 29–36.
19. Eriksen M, et al., The Tobacco Atlas, Fifth Edition 2015: American Cancer Society and World Lung Foundation.
20. World Health Organization., WHO report on the global tobacco epidemic, 2015 2015.

21. Abrams DB, Promise and peril of e-cigarettes: can disruptive technology make cigarettes obsolete? JAMA, 2014 311(2): p. 135–6. [PubMed: 24399548]
22. Henningfield JE, The tobacco endgame: it's all about behavior. Prev Med, 2014 68: p. 11–6. [PubMed: 25236479]
23. Hatsukami DK, et al., Nicotine reduction: strategic research plan. Nicotine Tob Res, 2013 15(6): p. 1003–13. [PubMed: 23100460]
24. Hatsukami DK, et al., Dose-response effects of spectrum research cigarettes. Nicotine Tob Res, 2013 15(6): p. 1113–21. [PubMed: 23178320]
25. Donny EC, et al., Reduced nicotine product standards for combustible tobacco: building an empirical basis for effective regulation. Prev Med, 2014 68: p. 17–22. [PubMed: 24967958]
26. Donny EC, et al., Reducing the nicotine content of combusted tobacco products sold in New Zealand. Tob Control, 2017 26(e1): p.e37–e42. [PubMed: 27672126]
27. Loewenstein G, Brennan T, and Volpp KG, Asymmetric paternalism to improve health behaviors. Jama-Journal of the American Medical Association, 2007 298(20): p. 2415–2417.
28. Bates C, The Tobacco Endgame: A critique of policy proposals aimed at ending tobacco ue. Tobacco Endgame supplement of the journal Tobacco Control, 2015.
29. Kozlowski LT, Cigarette prohibition and the need for more prior testing of the WHO TobReg's global nicotine-reduction strategy. Tob Control, 2016.
30. Nuffield Council on Bioethics., Public Health: ethical issues. 2007, London: Cambridge Publishers Ltd.
31. Farsalinos KE, et al., Electronic cigarette use in the European Union: analysis of a representative sample of 27 460 Europeans from 28 countries. Addiction, 2016 111(11): p. 2032–2040. [PubMed: 27338716]
32. Brown J, et al., Real-world effectiveness of e-cigarettes when used to aid smoking cessation: a cross-sectional population study. Addiction, 2014 109(9): p. 1531–40. [PubMed: 24846453]
33. McRobbie H, et al., Electronic cigarettes for smoking cessation and reduction. Cochrane Database Syst Rev, 2014 12: p. CD010216.
34. Hitchman SC, et al., Associations Between E-Cigarette Type, Frequency of Use, and Quitting Smoking: Findings From a Longitudinal Online Panel Survey in Great Britain. Nicotine Tob Res, 2015.
35. Blank MD and Eissenberg T, Commentary on Brose et al. (2015): Protecting individual and public health by regulating electronic cigarette nicotine delivery. Addiction, 2015 110(7): p. 1169–70. [PubMed: 26094498]
36. Bullen C, et al., Electronic cigarettes for smoking cessation: a randomised controlled trial. Lancet, 2013 382(9905): p. 1629–37. [PubMed: 24029165]
37. Adkison SE, et al., Electronic nicotine delivery systems: international tobacco control four-country survey. Am J Prev Med, 2013 44(3): p. 207–15. [PubMed: 23415116]
38. Carpenter M, et al., A Naturalistic, Randomized Pilot Trial of E-Cigarettes: Uptake, Exposure, and Behavioral Effects. Cancer Epidemiol Biomarkers Prev, 2017.
39. Jamal A, et al., Tobacco Use Among Middle and High School Students - United States, 2011–2016. MMWR Morb Mortal Wkly Rep, 2017 66(23): p. 597–603. [PubMed: 28617771]
40. FDA. Philip Morris Products S.A. Modified Risk Tobacco Product (MRTP) Applications. 2017 12 26, 2017]; Available from: https://www.fda.gov/TobaccoProducts/Labeling/MarketingandAdvertising/ucm546281.htm.
41. Tobacco Meets Technology. 12 26, 2017]; Available from: https://www.pmi.com/smoke-free-products/iqos-our-tobacco-heating-system.
42. Fojtik BUS, FDA can learn from Japan how to reduce smoking. 2017 12, 26, 2017]; Available from: https://www.huffingtonpost.com/entry/us-fda-can-learn-from-japan-how-to-reduce-smoking_us_5a395a92e4b0c12e6337b182?ncid=engmodushpmg00000006.
43. Action on Smoking and Health., ASH Factsheet: Use of e-cigarettes (vapourisers) among adults in Great Britain. 2017.
44. West R, Shahab L, and Brown J, Estimating the population impact of e-cigarettes on smoking cessation in England. Addiction, 2016 111(6): p. 1118–9. [PubMed: 26920514]

45. Beard E, et al., 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, 2016 354: p. i4645. [PubMed: 27624188]
46. Zhu SH, et al., E-cigarette use and associated changes in population smoking cessation: evidence from US current population surveys. BMJ, 2017 358: p. j3262. [PubMed: 28747333]
47. Shields PG, Long-term nicotine replacement therapy: cancer risk in context. Cancer Prev Res (Phila), 2011 4(11): p. 1719–23. [PubMed: 22052338]
48. Lee PN, The effect on health of switching from cigarettes to snus - a review. Regul Toxicol Pharmacol, 2013 66(1): p. 1–5. [PubMed: 23454227]
49. Lee PN, Summary of the epidemiological evidence relating snus to health. Regul Toxicol Pharmacol, 2011 59(2): p. 197–214. [PubMed: 21163315]
50. National Academy of Sciences, Engineering, and Medicine, Public Health Consequences of E-cigarettes. 2018, Washington, DC: The National Academicis Press.
51. Hajek P, et al., Electronic cigarettes: review of use, content, safety, effects on smokers and potential for harm and benefit. Addiction, 2014 109(11): p. 1801–10. [PubMed: 25078252]
52. Hecht SS, et al., Evaluation of toxicant and carcinogen metabolites in the urine of e-cigarette users versus cigarette smokers. Nicotine Tob Res, 2015 17(6): p. 704–9. [PubMed: 25335945]
53. Goniewicz ML, et al., Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. Tob Control, 2014 23(2): p. 133–9. [PubMed: 23467656]
54. Czogala J, et al., Secondhand exposure to vapors from electronic cigarettes. Nicotine Tob Res, 2014 16(6): p. 655–62. [PubMed: 24336346]
55. Glantz S Accumulating evidence suggests e-cigs 1/3 to 1/2 as bad as cigs (maybe higher). . Glantz blog 2016 December 14, 2017].
56. Bean ST and Smith MJ, Victimless vapour? Health care organizations should restrict the use of e-cigarettes. Can J Public Health, 2016 106(8): p. e467–9. [PubMed: 26986904]
57. Primack BA, et al., Progression to Traditional Cigarette Smoking After Electronic Cigarette Use Among US Adolescents and Young Adults. JAMA Pediatr, 2015 169(11): p. 1018–23. [PubMed: 26348249]
58. Leventhal AM, et al., Association of e-Cigarette Vaping and Progression to Heavier Patterns of Cigarette Smoking. JAMA, 2016 316(18): p. 1918–1920. [PubMed: 27825000]
59. Lanza ST, Russell MA, and Braymiller JL, Emergence of electronic cigarette use in US adolescents and the link to traditional cigarette use. Addict Behav, 2017 67: p. 38–43. [PubMed: 27988415]
60. Soneji S, et al., Association Between Initial Use of e-Cigarettes and Subsequent Cigarette Smoking Among Adolescents and Young Adults: A Systematic Review and Meta-analysis. JAMA Pediatr, 2017 171(8): p. 788–797. [PubMed: 28654986]
61. Goldenson NI, et al., Associations of Electronic Cigarette Nicotine Concentration With Subsequent Cigarette Smoking and Vaping Levels in Adolescents. JAMA Pediatr, 2017.
62. Etter JF, Gateway effects and electronic cigarettes. Addiction, 2017.
63. Bold KW, et al., Trajectories of E-Cigarette and Conventional Cigarette Use Among Youth. Pediatrics, 2017.
64. Primack BA, et al., Initiation of Traditional Cigarette Smoking after Electronic Cigarette Use among Tobacco-Naive U.S. Young Adults. Am J Med, 2017.
65. McNeill A, et al., E-cigarettes: an evidence uptake A report commissioned by Public Health England. 2015, London: Public Health England.
66. Kozlowski LT and Warner KE, Adolescents and e-cigarettes: Objects of concern may appear larger than they are. Drug Alcohol Depend, 2017 174: p. 209–214. [PubMed: 29350617]
67. Stanwick R, E-cigarettes: Are we renormalizing public smoking? Reversing five decades of tobacco control and revitalizing nicotine dependency in children and youth in Canada. Paediatr Child Health, 2015 20(2): p. 101–5. [PubMed: 25838785]
68. Donny EC, et al., Randomized Trial of Reduced-Nicotine Standards for Cigarettes. N Engl J Med, 2015 373(14): p. 1340–9. [PubMed: 26422724]

69. World Health Organization., WHO Study Group on Tobacco Product Regulation : report on the scientific basis of tobacco product regulation : fifth report of a WHO study group WHO technical report series,. 2015, Geneva: World Health Organization.
70. Hatsukami DK, et al., Reduced nicotine content cigarettes: effects on toxicant exposure, dependence and cessation. Addiction, 2010 105(2): p. 343–55. [PubMed: 20078491]
71. Smith TT, et al., Impact of smoking reduced nicotine content cigarettes on sensitivity to cigarette price: further results from a multi-site clinical trial. Addiction, 2017 112(2): p. 349–359. [PubMed: 27741367]
72. Hatsukami DK, et al., Reduced nicotine content cigarettes and nicotine patch. Cancer Epidemiol Biomarkers Prev, 2013 22(6): p. 1015–24. [PubMed: 23603206]
73. Donny EC, Houtsmuller E, and Stitzer ML, Smoking in the absence of nicotine: behavioral, subjective and physiological effects over 11 days. Addiction, 2007 102(2): p. 324–34. [PubMed: 17222288]
74. Benowitz NL, et al., Smokers of low-yield cigarettes do not consume less nicotine. N Engl J Med, 1983 309(3): p. 139–42. [PubMed: 6866013]
75. Zacny JP and Stitzer ML, Cigarette brand-switching: effects on smoke exposure and smoking behavior. J Pharmacol Exp Ther, 1988 246(2): p. 619–27. [PubMed: 3404450]
76. Kozlowski LT and O'Connor RJ, Cigarette filter ventilation is a defective design because of misleading taste, bigger puffs, and blocked vents. Tob Control, 2002 11 Suppl 1: p. I40–50. [PubMed: 11893814]
77. Scherer G, Smoking behaviour and compensation: a review of the literature. Psychopharmacology (Berl), 1999 145(1): p. 1–20. [PubMed: 10445368]
78. Blackford AL, et al., Cotinine concentration in smokers from different countries: relationship with amount smoked and cigarette type. Cancer Epidemiol Biomarkers Prev, 2006 15(10): p. 1799–804. [PubMed: 17021350]
79. Mercincavage M, et al., A Randomized Controlled Trial of Progressively Reduced Nicotine Content Cigarettes on Smoking Behaviors, Biomarkers of Exposure, and Subjective Ratings. Cancer Epidemiol Biomarkers Prev, 2016 25(7): p. 1125–33. [PubMed: 27197288]
80. Hatsukami DK, et al., Compensatory smoking from gradual and immediate reduction in cigarette nicotine content. Cancer Epidemiol Biomarkers Prev, 2015 24(2): p. 472–6. [PubMed: 25515551]
81. Fix BV, et al., Smokers' reactions to FDA regulation of tobacco products: findings from the 2009 ITC United States survey. BMC Public Health, 2011 11: p. 941. [PubMed: 22177316]
82. Connolly GN, et al., Public attitudes regarding banning of cigarettes and regulation of nicotine. Am J Public Health, 2012 102(4): p. e1–2.
83. Pearson JL, et al., Public support for mandated nicotine reduction in cigarettes. Am J Public Health, 2013 103(3): p. 562–7. [PubMed: 23327262]
84. Li J, Newcombe R, and Walton D, Responses towards additional tobacco control measures: data from a population-based survey of New Zealand adults. N Z Med J, 2016 129(1428): p. 87–92.
85. Denlinger-Apte R, et al., Acceptability of a reduced nicotine product standard for cigarettes among smokers provided with reduced nicotine cigarettes for six weeks. Society for Research on Nicotine and Tobacco Symposium Abstract, 2017.
86. Bates C and Wade C, Reducing nicotine in cigarettes: Challenges and opportunities. R Street, 2017.
87. Mercincavage M, et al., Attrition during a randomized controlled trial of reduced nicotine content cigarettes as a proxy for understanding acceptability of nicotine product standards. Addiction, 2017 112(6): p. 1095–1103. [PubMed: 28107596]
88. Reuter P, Can tobacco control endgame analysis learn anything from the US experience with illegal drugs? Tob Control, 2013 22 **Suppl** 1: p. i49–51. [PubMed: 23591511] **Suppl**
89. Higgins ST, et al., Addiction Potential of Cigarettes With Reduced Nicotine Content in Populations With Psychiatric Disorders and Other Vulnerabilities to Tobacco Addiction. JAMA Psychiatry, 2017 74(10): p. 1056–1064. [PubMed: 28832876]
90. Pacek LR, et al., Perceived nicotine content of reduced nicotine content cigarettes is a correlate of perceived health risks. Tob Control, 2017.

91. McDowell JJ, Matching theory in natural human environments. Behav Anal, 198811(2): p. 95–109. [PubMed: 22478003]
92. McDowell JJ, On the classic and modern theories of matching. J Exp Anal Behav,2005 84(1): p. 111–27. [PubMed: 16156140]
93. Herrnstein RJ, Relative and absolute strength of response as a function of frequency of reinforcement. J Exp Anal Behav, 1961 4: p. 267–72. [PubMed: 13713775]
94. Herrnstein RJ, On the law of effect. J Exp Anal Behav, 1970 13(2): p. 243–66. [PubMed: 16811440]
95. Baum WM, On two types of deviation from the matching law: bias and undermatching. J Exp Anal Behav, 1974 22(1): p. 231–42. [PubMed: 16811782]
96. Kozlowski LT and Abrams DB, 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, 2016 16: p. 432. [PubMed: 27221096]
97. Loewenstein G, Brennan T, and Volpp KG, Asymmetric paternalism to improve health behaviors. JAMA, 2007 298(20): p. 2415–7. [PubMed: 18042920]
98. Choi JJ, et al., Defined contribution pensions: plan rules, participant decisions, and the path of least resistance., in Tax policy and the economy, Poterba JM, Editor. 2002, MIT Press: Cambridge, MA p. 67–113.
99. Bickel WK and Marsch LA, Toward a behavioral economic understanding of drug dependence: delay discounting processes. Addiction, 2001 96(1): p. 73–86. [PubMed: 11177521]
100. O'Donoghue T and Rabin M, Doing it now or later. Am Econ Rev, 1999 89(1): p. 103–124.
101. Goodwin RD, Keyes KM, and Hasin DS, Changes in cigarette use and nicotine dependence in the United States: evidence from the 2001–2002 wave of the national epidemiologic survey of alcoholism and related conditions. Am J Public Health, 2009 99(8): p. 1471–7. [PubMed: 19008515]
102. Breslau N, et al., Nicotine dependence in the United States: prevalence, trends, and smoking persistence. Arch Gen Psychiatry, 2001 58(9): p. 810–6. [PubMed: 11545662]
103. Donny EC and Dierker LC, The absence ofDSM-IV nicotine dependence in moderate-to-heavy daily smokers. Drug Alcohol Depend, 2007 89(1): p. 93–6. [PubMed: 17276627]
104. Fagerstrom K and Eissenberg T, Dependence on tobacco and nicotine products: a case for product- specific assessment. Nicotine Tob Res, 2012 14(11): p. 1382–90. [PubMed: 22459798]
105. Cowie GA, et al., Cigarette brand loyalty in Australia: findings from the ITC Four Country Survey. Tob Control, 2014 23 Suppl 1: p. 173–9. [PubMed: 23152098]
106. Robinson TE and Berridge KC, Incentive-sensitization and addiction. Addiction, 2001 96(1): p. 103–14. [PubMed: 11177523]
107. Tiffany ST, A cognitive model of drug urges and drug-use behavior: role of automatic and nonautomatic processes. Psychol Rev, 1990 97(2): p. 147–68. [PubMed: 2186423]
108. Tiffany ST and Conklin CA, A cognitive processing model of alcohol craving and compulsive alcohol use. Addiction, 2000 95 Suppl 2: p. S145–53.
109. Hogarth L, et al., Associative learning mechanisms underpinning the transition from recreational drug use to addiction. Ann N Y Acad Sci, 2013 1282: p. 12–24. [PubMed: 23126270]
110. Dias-Ferreira E, et al., Chronic stress causes frontostriatal reorganization and affects decision-making. Science, 2009 325(5940): p. 621–5. [PubMed: 19644122]
111. Balleine BW and O'Doherty JP, Human and rodent homologies in action control: corticostriatal determinants of goal-directed and habitual action. Neuropsychopharmacology, 2010 35(1): p. 48–69. [PubMed: 19776734]
112. Carter BL and Tiffany ST, The cue-availability paradigm: the effects of cigarette availability on cue reactivity in smokers. Exp Clin Psychopharmacol, 2001 9(2): p. 183–90. [PubMed: 11518094]
113. Ross KC and Juliano LM, Perceived smoking availability differentially affects mood and reaction time. Addict Behav, 2015 45: p. 234–8. [PubMed: 25727393]

114. Wilson SJ, Sayette MA, and Fiez JA, Quitting-unmotivated and quitting-motivated cigarette smokers exhibit different patterns of cue-elicited brain activation when anticipating an opportunity to smoke. J Abnorm Psychol, 2012 121(1): p. 198–211. [PubMed: 21859165]
115. Wilson SJ, et al., Instructed smoking expectancy modulates cue-elicited neural activity: a preliminary study. Nicotine Tob Res, 2005 7(4): p. 637–45. [PubMed: 16085533]
116. Harrell PT, et al., Expectancies for cigarettes, e-cigarettes, and nicotine replacement therapies among e-cigarette users (aka vapers). Nicotine Tob Res, 2015 17(2): p. 193–200. [PubMed: 25168035]
117. Miller ME, et al., Electronic Cigarette Expectancies in Smokers with Psychological Distress. Tob Regul Sci, 2017 3(1): p. 108–114. [PubMed: 28653023]
118. Kozlowski LT, Let actual markets help assess the worth of optional very-low-nicotine cigarettes before deciding on mandatory regulations. Addiction, 2017 112(1): p. 3–5.
119. Baicker K and Chandra A, Evidence-Based Health Policy. N Engl J Med, 2017 377(25): p. 2413–2415. [PubMed: 29262287]
120. Benowitz NL, et al., Smoking behavior and exposure to tobacco toxicants during 6 months of smoking progressively reduced nicotine content cigarettes. Cancer Epidemiol Biomarkers Prev, 2012 21(5): p. 761–9. [PubMed: 22354905]
121. Jo CL, et al., US consumer interest in non-cigarette tobacco products spikes around the 2009 federal tobacco tax increase. Tob Control, 2015 24(4): p. 395–9. [PubMed: 24500270]
122. Kozlowski LT, Prospects for a nicotine-reduction strategy in the cigarette endgame: Alternative tobacco harm reduction scenarios. Int J Drug Policy, 2015 26(6): p. 543–7. [PubMed: 25795345]
123. Centers for Disease C and Prevention, Quitting smoking among adults--United States, 2001–2010. MMWR Morb Mortal Wkly Rep, 2011 60(44): p. 1513–9. [PubMed: 22071589]
124. Loewenstein G, et al., Can behavioural economics make us healthier? BMJ, 2012 344: p. e3482. [PubMed: 22623635]

Highlights:

- Cigarettes are the most harmful and addictive tobacco product available
- The nicotine content of cigarettes could be lowered to reduce their addictiveness
- New alternative nicotine delivery systems may be less harmful than cigarettes
- Both nicotine reduction and alternative products could reduce cigarette use
- The most effective strategy is to pursue both approaches simultaneously