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Reducing the relative value of cigarettes: Considerations for nicotine and non-nicotine factors

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Abstract

Despite notable progress in recent decades, cigarette smoke persists as a leading cause of premature death and preventable disease. To weaken the link between nicotine reinforcement and the toxicity associated with combusted tobacco, the United States Food and Drug Administration is considering a product standard targeting cigarette nicotine content. In this review, we summarize research assessing the potential impacts of reducing nicotine in cigarettes. Evidence to date suggests cigarette smoking, toxicant exposure and dependence would decline following substantial reductions in nicotine content. However, reduced nicotine content may not eliminate smoking entirely. Regulatory efforts that shape the nicotine and tobacco marketplace should consider that non-nicotine reinforcing factors and decision-making biases can contribute to the value of smoking. The impact of reducing nicotine in cigarettes will likely depend on the alternative nicotine products available to current smokers.

Keywords

low nicotine cigarettes; nicotine dependence; nicotine reduction; tobacco regulatory science

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1. Introduction

The proportion of smokers in the United States has steadily declined since the mid-1960s, reaching a record low of approximately 14% in 2018 (Creamer et al., 2019). Today, the public is well informed about cigarettes' negative health effects and smoking is more restricted, socially stigmatized and expensive than ever before (Cummings & Proctor, 2014). Yet, despite the observed declines and ongoing deterrents, an estimated 34.2 million Americans still smoke (Creamer et al., 2019). Most smokers attempt to quit each year, however less than 7% of quit attempts are sustained long term. Thus cigarette smoke persists as a leading cause of premature death and preventable disease (Creamer et al., 2019). Additionally, combusted tobacco use in the U.S. is increasingly concentrated among socially and economically disadvantaged populations, including racial and sexual/gender minorities and those coping with psychiatric illness (Creamer et al., 2019). Novel regulatory strategies are needed to further diminish the consequences of smoking and related health disparities.

The ability of nicotine to reinforce or strengthen behavior resulting in its delivery helps explain why many people continue to smoke. When inhaled, nicotine is rapidly transported to the brain where it triggers a variety of both positively and negatively reinforcing effects valuable to the smoker, such as inducing pleasurable sensations (DiFranza et al., 2004, Hu et al, 2006; Kandel et al, 2007), improving attention (Heishmann, Taylor, & Henningfield, 1994; Sherwood, 1993), modulating mood (Laje et al, 2001; Breslau et al., 1995; Picciotto et al., 2002), suppressing hunger (Voorhees et al., 2002; Fulkerson & French, 2003) and alleviating stress, anxiety and withdrawal symptoms (Pomerleau, 1987; Gilbert et al., 1979; Parrot et al, 1995; Benowitz, 2010; American Psychiatric Association, 2018). The acute effects of nicotine also dissipate quickly, prompting smokers to continue dosing to maintain positive effects and prevent withdrawal symptoms (Benowitz et al., 2003; Hughes, 2007; Benowitz, 2010). Theories of addiction suggest that anticipating the reliable, nearly immediate value of inhaling nicotine from a cigarette can outweigh or override other considerations (e.g. intentions to quit, concerns about long-term health consequences, financial burden) at the point of decision making, resulting in a bias to smoke (Bickel et al, 2018). While the resultant effects of rapid nicotine delivery to the nervous system facilitate dependence and continued use, nicotine is not directly responsible for the devastating health outcomes of smoking. Rather, the vast majority of the harm caused by cigarettes is derived from byproducts of burning tobacco, including carbon monoxide and tar (U.S. Department of Health and Human Services, 2014). While toxic combustion is inherent to cigarette use, theoretically, manipulating the nicotine level in cigarettes to minimize their reinforcing value could subsequently reduce smoking and therefore the harm caused by cigarettes.

Benowitz and Henningfield first proposed the idea of reducing nicotine in cigarettes in 1994 (Benowitz & Henningfield, 1994). A nicotine reduction strategy became more plausible with passage of the Family Smoking Prevention and Tobacco Control Act in 2009, wherein the U.S. Food and Drug Administration (FDA) was granted the authority to set a maximum-nicotine content in tobacco products at any level above zero (U.S. Government, 2009). In July 2017, FDA announced their intent to “render cigarettes minimally addictive” within a comprehensive framework for tobacco regulation (Gottlieb & Zeller, 2017). In March 2018, FDA then initiated the rulemaking process by releasing an advanced notice of a potential

product standard that would cap the amount of nicotine in cigarettes, and possibly other combusted tobacco products (U.S. Food and Drug Administration, 2018). In this review, we summarize evidence relevant to approximating the public health impact of reducing nicotine in combusted tobacco. Accumulating findings suggest substantial reductions in nicotine content do decrease the reinforcing value of cigarettes, lowering smoking rates as intended; however, we also discuss why reductions in nicotine content may not eliminate smoking. Anticipating how patterns of tobacco product use will change following a nicotine reduction product standard requires a thoughtful analysis of the choice processes that compare relative value of low nicotine cigarettes and other nicotine sources.

2. The promise of a product standard targeting nicotine in combusted tobacco

2.1 Low-nicotine research cigarettes

Though low-nicotine content cigarettes have been commercially available in the past (e.g. Quest®, Next®) and used in earlier research (Dunsby & Bero, 2004; Shadel et al., 2006; Strasser et al., 2007; Hatsukami et al., 2010; Hammond & O'Connor, 2014), the majority of studies explicitly assessing a hypothetical nicotine reduction policy use SPECTRUM research cigarettes manufactured by 22nd Century Group and administered by the National Institute on Drug Abuse. SPECTRUM cigarettes offer investigators menthol and non-menthol varieties with different nicotine-contents per weight of tobacco, achieved through genetic engineering techniques that disrupt the biosynthesis of nicotinic alkaloids in the tobacco plant (Richter et al, 2016). Low nicotine research cigarettes are therefore distinct from “light” cigarettes, which by contrast, manipulate ventilation to affect nicotine yield (as measured by a smoking machine) rather than the amount of nicotine available in the actual tobacco. SPECTRUM research cigarettes are otherwise similar to conventional cigarettes in design and in other-constituent levels (Richter et al., 2016; Ding et al., 2017), highlighting that reduced nicotine cigarettes would likely induce health effects comparable to conventional cigarettes when consumed in a similar manner and quantity.

2.2 Reduced use and smoke exposure

Toxicant exposure ultimately depends on the amount of smoke inhaled, which corresponds to the quantity of cigarettes consumed and puffing characteristics. Evidence generated from randomized clinical trials using low-nicotine research cigarettes suggest the relationship between nicotine content and quantity of cigarettes smoked is dose-dependent. In a large clinical trial directly assessing the effect of dose, daily smokers not interested in quitting were randomly assigned to use research cigarettes with one of six nicotine contents ranging from 0.4 to 15.8 milligrams nicotine per gram of tobacco (Donny et al., 2015). After six weeks, those assigned to cigarettes with 2.4mg nicotine per gram of tobacco or less, smoked fewer cigarettes per day (CPD) than a control group using normal-nicotine content cigarettes (15.8mg nicotine per gram of tobacco). The smoking rate of those assigned to cigarettes with 5.2mg nicotine per gram of tobacco did not differ from controls (Donny et al., 2015). In some studies, use of cigarettes with only moderate nicotine-content reductions (8.4mg per gram of tobacco) increased CPD and/or exhaled carbon monoxide levels, suggesting

possible compensatory smoking behavior (Hatsukami, 2010; Mercincavage et al., 2016). Yet consistent with the results of the aforementioned trial, several studies document that daily (Hatsukami et al., 2018) and nondaily (Shiffman et al., 2018a) smokers switching to cigarettes containing 2.4mg nicotine or less per gram smoke fewer CPD over time. Additionally, biomarker data indicate that decreases in smoking are accompanied by decreases in toxicant exposure (Benowitz et al., 2015; Hatsukami et al., 2017; Shiffman et al., 2018b; Hatsukami et al., 2018). Extended use of cigarettes with the lowest researched dose (0.4mg nicotine per gram of tobacco) also increases the likelihood of making and succeeding at a quit attempt, and of reporting smoke-free days (Donny et al., 2015, Hatsukami et al., 2018), although most smokers continue to use these products throughout the clinical trials (see Section 3.1 for more detail).

Further research has expanded our understanding of the relationship between nicotine-content and patterns of cigarette use. For instance, it has been demonstrated that smokers experiencing an immediate transition to very low nicotine content cigarettes have more rapid reductions in CPD and toxicant exposure compared to those experiencing gradual, stepped-down reductions in nicotine content (Hatsukami et al., 2018). Additionally, some evidence suggests the effects of nicotine dose on CPD may be moderated by menthol, such that decreases in CPD when using very low nicotine content cigarettes are smaller among menthol smokers than non-menthol smokers (Denlinger-Apte et al., 2019a). A recent review commenting on the effects low nicotine cigarette-use in smokers with mental health conditions and socioeconomic disadvantages concluded that these priority populations would likely reduce cigarette smoking without worsening psychiatric symptoms or sustained compensatory smoking in response to a reduced-nicotine product standard for cigarettes (Tidey et al, 2019). Several studies measuring puff topography characteristics, such as total puff volume, similarly demonstrate reductions in toxicant exposure as a function of CPD reduction and smoking less intensely on the cigarette (Donny et al., 2015; Tidey et al., 2016; Higgins et al., 2017a, Denlinger-Apte et al. 2019b). In sum, much of the available evidence suggests reducing nicotine content to very low levels would decrease smoking and toxicant exposure as intended.

2.3 Reduced dependence and dependence potential

To confirm and better understand the mechanisms through which low nicotine content cigarettes reduce smoking, some studies have assessed how manipulating nicotine content affects measures of dependence and dependence potential. These constructs can be measured using behavioral indices of the motivation to smoke. For example, using a classic paradigm for evaluating a substance's reinforcing value, researchers have shown that low nicotine cigarettes maintain self-administration similar to conventional cigarettes when they are the only option available (Shahan et al., 1999; Shahan et al., 2001). However, when presented with choices between concurrently available low and normal nicotine content cigarettes, participants demonstrate strong preferences for normal nicotine content, suggesting lower nicotine content reduces relative value (Shahan et al., 1999; Perkins et al., 2002; Perkins et al., 2016). Similarly, behavioral economic methods have been used to generate multiple indices of an individual's demand for cigarettes including how many cigarettes they would purchase if cigarettes were free, their sensitivity to price increases, their maximum

expenditure, the price at which their consumption becomes “elastic”, and the price at which they would no longer consume cigarettes; all of which are strongly associated with actual cigarette consumption (Cassidy et al., 2018; González-Roz et al., 2019). Studies manipulating cigarette nicotine content show that lower nicotine contents produce less economic demand (Davis et al., 2019; Higgins et al., 2017b). Comparing purchase task data within-subjects shows that relative to normal nicotine cigarettes, the projected use of low nicotine cigarettes is lower at given prices and more smokers anticipate abstaining across a wider range of prices (Smith et al., 2017). Together, this evidence suggests low nicotine cigarettes have reduced reinforcement value compared to conventional cigarettes.

Severity of cigarette dependence and dependence potential can also be evaluated using self-reported motivation to smoke and subjective positive and negative effects of smoking. Two widely used dependence assessments shown to correlate with withdrawal and cessation likelihood include the Brief Wisconsin Inventory of Smoking Dependence Motives (WISDM) and Fagerström Test for Cigarette Dependence, FTCD (Piper et al., 2008; Smith et al., 2010; Fagerström, 2012). Multiple clinical trials have found after at least six weeks, smokers using cigarettes with 0.4mg nicotine per gram of tobacco had lower WISDM and FTCD scores than smokers using normal nicotine-content cigarettes, suggestive of decreased dependence (Donny et al., 2015, Hatsukami et al., 2018). The modified Cigarette Evaluation Questionnaire (mCEQ) is commonly used to assess the subjective effects of cigarette smoking as a measure of dependence potential. The mCEQ includes subscales related to satisfaction, psychological reward, enjoyment of respiratory tract sensations, craving relief and aversion. Following brief sampling of low nicotine cigarettes or extended periods of use, smokers rate low nicotine cigarettes as less satisfying, less rewarding, less enjoyable, less able to reduce craving (Cassidy et al., 2019; Smith et al., 2019). Experiencing gradual reductions in dose to arrive at a very low nicotine content over time, relative to immediate dose reduction, however, may attenuate differences in subjective effect ratings between low nicotine and normal nicotine content cigarettes along these dimensions (Smith et al., 2019). In sum, these subjective measures, similar to the behavioral measures, suggest substantial reductions in nicotine content reduce cigarette reinforcement and decrease their dependence potential.

3. Very low nicotine content cigarettes remain reinforcing

3.1 Limited spontaneous cessation observed after extended use

As highlighted thus far, research suggests a nicotine reduction product standard would decrease the reinforcing value of cigarettes and reduce cigarette-related harm. However, there are caveats to bear in mind when interpreting these results. In particular, although extended use of low nicotine cigarettes appears to reduce CPD, it has not lead to complete cessation for most participants. On average, smokers assigned to very low nicotine cigarettes (0.4mg nicotine per gram of tobacco) for extended periods of time (6–20 weeks), experience reductions in CPD relative to controls but still smoke more than 10 CPD (Donny et al., 2015; Hatsukami et al., 2017; Hatsukami et al., 2018). Several study design factors could contribute to continued low nicotine cigarette use, including provision of free cigarettes, instructions to not use alternative nicotine products that would be available to smokers in a

real-world nicotine reduction scenario, enrollment of smokers not interested in quitting, and opportunities for non-adherence (smoking usual brand cigarettes) that could undermine the full effect of assigned nicotine dose. However, continued low nicotine cigarette smoking has also been observed when low nicotine cigarettes are “purchased” with points redeemable for money (Hatsukami et al., 2017; Smith et al., 2020), when alternative nicotine sources are available (Hastukami et al., 2017) and when adherence is assured in residential settings where only very low nicotine cigarettes are available (Donny et al., 2007; Smith et al., 2020).

As noted above, low nicotine cigarettes are self-administered at similar rates to conventional cigarettes during single- product operant self-administration procedures (Shahan et al., 1999; Shahan et al., 2001). Similarly, low nicotine cigarettes maintain higher breakpoints on progressive ratio schedules of reinforcement relative to not smoking (Rusted et al., 1998; Donny et al., 2007). Finally, when using purchase tasks to assess the economic demand of simultaneously available low and normal nicotine content cigarettes, escalating the price of regular nicotine content cigarettes increases the demand for low nicotine cigarettes presented at a fixed price (Johnson, Bickel, & Kirshenbaum, 2004; Higgins et al., 2017b; Branstetter et al., 2019). This cross-product elasticity suggests the relative value of low nicotine cigarettes is not zero and may increase as usual cigarettes become more difficult to acquire. Collectively, these outcomes convey that low nicotine cigarettes retain some value for most smokers.

3.2 Non-nicotine determinants of smoking

Nicotine delivery is not the sole determinant of cigarettes’ reinforcing value. For chronic smokers, the sensorimotor aspects of smoking, including the handling and lighting of a cigarette, the throat hit, and the sight, taste and smell of cigarettes are considered essential elements of cue-conditioning that maintain tobacco use (Carter & Tiffany, 1999; Rose, 2006). While some sensory effects are initially aversive, they can become reinforcing after repeated pairing with nicotine (Bevins & Palmatier, 2004). Smokers cite enjoyment from the sensorimotor effects as a motive for continued smoking and as an element of smoking they miss following cessation (Piper et al., 2008; Rose et al., 1990). Furthermore, smokers tend to associate cigarette smoking with certain situations, moods, or environmental factors (i.e. smoking after a meal, with alcohol, while driving, when anxious or depressed, when around friends who smoke, etc). These contexts can become strong cues to smoke, contributing to cravings that can arise long after nicotine withdrawal symptoms resolve (Conklin, 2006). Consistent with the notion that conditioned factors contribute to reinforcement, not all smokers can differentiate between cigarettes with variable nicotine content in a blinded context (Perkins, 2019) and smoking low nicotine content cigarettes effectively reduces craving and withdrawal for some smokers (Barrett, 2010; Higgins et al., 2017a). Beyond conditioned effects, smoking can also have important social and cultural value (Stewart et al., 2015; Boudreau et al., 2016). Acknowledging that non-nicotine factors reinforce smoking leads to questions about how the relative reinforcing value of low nicotine cigarettes compares to that of smokers’ other options, including abstaining and using other nicotine products.

4. Choice: Will smokers use low nicotine cigarettes when alternative sources of nicotine are available?

4.1 Marketplace of alternatives

Maximizing the potential public health net benefits of reducing nicotine in cigarettes will require understanding the effect of such a policy on not only cigarette use, but also on other forms of nicotine consumption. A nicotine-content product standard, announced by FDA in July 2017, was embedded in a broader regulatory vision aiming to reshape how Americans use nicotine. In addition to targeting the nicotine content of cigarettes, ensuring the availability of safer, non-combusted nicotine-delivery products for adults “who still need or want nicotine” was central to the stated plan (Gottlieb and Zeller, 2017; U.S. Food and Drug Administration, 2017). The intent of this regulatory strategy is reminiscent of Herrnstein’s matching law, which conceptualizes the allocation of behavior over time as a function of the relative reinforcement value of available options (Herrnstein, 1970). Minimizing the relative value of cigarettes by reducing nicotine content and maximizing the availability of nicotine reinforcement elsewhere could shift behavior away from smoking, “matching” behavior to differences in reinforcement magnitude. However, as noted above, nicotine is not the sole determinant of smoking reinforcement. Smokers may continue to use cigarettes for a multitude of factors in addition to nicotine content, including sensory and sensorimotor features, flavor, price, risk perceptions and social norms. Ultimately, use of low nicotine cigarettes will be determined by the reinforcing value of low nicotine cigarettes *relative to* alternatives available to the user. The choice of which product to use (if any) may depend on a number of factors that vary across individuals and the context in which the choice is made (Pacek, Wiley, & McClernon, 2019). A recent review of nicotine reduction research identified that much remains unknown about how low nicotine cigarettes will interact with other products in the evolving marketplace of alternative nicotine sources (Berman & Glasser, 2019).

The marketplace has substantially diversified in recent years, offering smokers a wide variety of cigarette alternatives that completely decouple nicotine-delivery from combustion; including pharmaceutical-grade nicotine replacement therapies, smokeless tobacco, and vaping and heat-not-burn devices (Prochaska & Benowitz, 2019). Despite the proliferation of non-combusted options, more than 80% of adults consuming nicotine in the U.S. still use combusted tobacco products (Creamer et al., 2019). A limited amount of complete switching suggests that under current conditions, the expected value of smoking is greater (some or all of the time) than that of abstaining or switching to a different nicotine source.

4.2 Decision making biases may promote smoking, even in the presence of safer alternatives

When confronted with opportunities to smoke or abstain, or to buy a pack of cigarettes or an alternative product, the underlying decision making process rarely involves deliberate, comprehensive weighting of pros and cons. Rather, like many choices, these decisions are made quickly with only partial information considered (Elrod et al., 2004; Shaw and Bagozzi, 2017). Cognitive factors may influence how partial information about each choice option is weighted when determining a relative value. More research in this area is needed,

but some evidence suggests default bias, ambiguity aversion and temporal-discounting are examples of decision making biases that could result in valuations of cigarette smoking that exceed valuations of alternative product use among regular smokers.

From a decision making perspective, choices are often framed as comparisons between a default, or familiar, option and alternative options. Neuroeconomic evidence suggests using a default option for reference allows for consistency and efficiency, but also induces a bias toward pre-selected or previously experienced options, sometimes producing suboptimal outcomes (Sharot et al, 2009). In particular, studies show that when two options are relatively similar in subjective value, the default option is reliably favored (Fleming, Thomas, & Dolan 2010; Kolling et al., 2012; Boorman, Rushman, & Behrens, 2013). The effects of default bias are consistent with the well-documented behavioral pattern of loss aversion, which describes a tendency to prefer avoiding a loss over acquiring an equivalent gain (Tversky & Kahneman, 1991). In other words, the disadvantages of changing options may be emphasized over the advantages when making decisions. Some neuroimaging research suggests selecting a default may therefore be encoded as particularly rewarding in and of itself (Yu et al, 2010). Someone who has smoked a pack per day for twenty-five years, has initiated the action and experienced the value of smoking a cigarette over 180,000 times. Thus applied to opportunities to smoke, try an alternative product, or abstain - smoking likely occupies a default-option position among smokers, potentially adding to a cigarette's relative value.

Relatedly, consumers also demonstrate ambiguity aversion, a systematic preference for known risks relative to unknown risks (Camerer & Weber, 1992). Preferring to avoid uncertain risk over guaranteed gain or loss has been demonstrated in a variety of health-related decision making contexts, suggesting ambiguous aspects of an option degrade its anticipated value (Han et al., 2006; Han et al., 2009; Berger et al., 2013; Attema et al., 2018). Novel products like vaping devices are often referenced with mention of their unknown, long term health effects (Wackowski et al., 2018). The public also receives conflicting information about the relative harms of vaping and smoking (Tan et al., 2017). Lacking clarity about the relative health risks of novel products could create an ambiguity bias that devalues non-combusted options relative to cigarettes.

Lastly, temporal discounting refers to the well-documented phenomenon of discounting the value of reinforcers that are delayed in time (Ainslie, 1992; Bickel & Marsch, 2000). Cigarette smokers discount future gains and losses significantly more than non-smokers, and discount-rates positively correlate with cigarette consumption and dependence among current smokers (Bickel et al., 1999; MacKillop et al., 2011; Ohmura et al., 2005). Thus, it's reasonable to expect the harms of smoking and the benefits of switching or quitting are minimized in smokers' valuations of their options.

Together, these effects demonstrate that the extent to which nicotine and non-nicotine product characteristics contribute to relative value may depend on cognitive biases. As these effects may inflate the value of cigarettes under current conditions, both decreasing the relative value of cigarettes through several avenues (nicotine content, flavor, price, relative harm perception, etc.) and increasing the relative value of non-combusted alternatives is

likely beneficial. Changing cigarette characteristics to alter the subjective experience of smoking, such as reducing nicotine content, could attenuate the impact of a default bias to smoke. Overcoming the biases that result from ambiguity aversion and delay discounting may require identifying and explicitly promoting alternatives' certain and immediate benefits. Overall, to construct a regulatory environment that minimizes combusted tobacco use, we must understand the dynamic processes involved in computing and comparing the value of cigarettes, alternative products, and abstinence.

5. Conclusions

Implementing a product standard that restricts the nicotine content of cigarettes to very low levels (0.4mg nicotine per gram of tobacco) could minimize the reinforcing value of smoking, subsequently reducing the health burden of tobacco use by decreasing smoking, toxicant exposure and dependence. The anticipated public health benefits of nicotine reduction are substantial, with one simulation model projecting that a product standard introduced in 2020 would prevent 8.5 million tobacco-related deaths by 2100 (Apelberg et al., 2018). However, nicotine reduction may not completely eliminate the reinforcing value of combusted tobacco use. As even low frequency smoking can carry significant health risks (Hackshaw, 2018), regulatory efforts that shape the nicotine and tobacco marketplace should consider that non-nicotine factors and decision making biases may also affect how consumers value and use tobacco products. There are public health trade-offs to examine when it comes to maximizing the reinforcing value of products like vaping devices (Fairchild et al., 2019). The availability of alternative non-combusted nicotine sources that exceed the relative value of low nicotine cigarettes in terms of both nicotine delivery and other potentially reinforcing characteristics is likely to facilitate reductions in tobacco-related harm.

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Highlights

- Limiting cigarette nicotine content reduces use, toxicant exposure and dependence.
- Yet limits do not eliminate smoking, as low nicotine cigarettes remain reinforcing.
- Non-nicotine factors and decision-making biases can also affect reinforcing value.
- The relative value of alternatives will affect the use of low nicotine cigarettes.