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Nicotine Standards in the United States

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Implications

This Special Issue on nicotine standards in the United States will address many of the questions raised in the Advance Notice of Proposed Rulemaking (ANPRM) through a series of policy commentaries and timely empirical studies across a variety of topic areas within the proposed comprehensive nicotine standards plan. The questions addressed in this issue include: (1) the threshold dose of nicotine (and other constituents) that would lead to minimally addictive cigarettes; (2) the effects of a nicotine product standard in smokers with co-morbidity, youth and young adult smokers, and menthol smokers; (3) a step-down or targeted data approach to reducing nicotine in cigarettes; (4) perceptions and communications about product standards; and (5) requirements associated with the implementation of a nicotine product standard.

In July 2017, the United States Food and Drug Administration (FDA) announced a "comprehensive plan for tobacco and nicotine regulation that will serve as a multi-year roadmap to better protect kids and significantly reduce tobacco-related disease and death."[1] This regulatory plan was based on the premise that nicotine containing products exist on a continuum of risk with combusted products being the most harmful and nicotine replacement therapy products being the least harmful. The key components of FDA's Comprehensive Plan included (1) reducing nicotine in the most toxic tobacco products, cigarettes and potentially other combusted tobacco products, to nonaddictive or minimally addictive levels; (2) using existing structures for rules and product standards encouraging the marketing and development of innovative tobacco products proven to be less dangerous than cigarettes and demonstrated to have public health benefit so that smokers who are unable to quit smoking can completely switch to these products; and (3) examining approaches to increasing innovation, access, and use of FDA-approved medicinal nicotine products. Subsequently in 2018, the FDA took the first formal step towards implementing this vision by releasing an Advance Notice of Proposed Rulemaking (ANPRM) related to limiting nicotine in cigarettes.[2] This Special Issue on nicotine standards in the United States will address many of the questions raised in the ANPRM through a series of policy commentaries and timely empirical studies across a variety of topic areas within the proposed comprehensive nicotine standards plan. The questions raised in the ANPRM that are addressed in this issue include: (1) the threshold dose of nicotine (and other constituents) that would lead to minimally addictive cigarettes; (2) the effects of a nicotine product standard in smokers with co-morbidity, youth and young adult smokers, and menthol smokers; (3) a step-down or targeted data approach to reducing nicotine in cigarettes; (4) perceptions and communications about product standards; and (5) requirements associated with the implementation of a nicotine product standard.

Maximum Level of Nicotine and Other Constituents: Effects on Behavior

To determine a threshold dose of nicotine associated with reduced abuse liability, in an original empirical paper report, Perkins[3] conducted a drug discrimination lab-based study in daily adult smokers to determine the threshold for discriminating different doses of nicotine in cigarettes compared with a 0.4 mg nicotine/g of tobacco (lowest dose in experimental cigarettes). He found that only 7% were able to discriminate between a 1.3 mg nicotine/g of tobacco and 0.4 mg nicotine/g of tobacco. This finding led Perkins to conclude that the nicotine content in cigarettes below the threshold for detecting nicotine's effects is likely lower than 1.0 mg nicotine/g of tobacco or ≤10% of that in typical commercial cigarettes. White and colleagues[4] summarized evidence to-date for a maximum nicotine level to minimize addictiveness. They stated that the available evidence supports reducing nicotine content in cigarettes (measured by weight in tobacco and including tobacco filler and wrapper) by at least 95% (≤0.4 mg/g of tobacco) relative to a typical commercially available cigarette would lead to the greatest public health benefit

across the population of smokers. This extent of nicotine reduction was associated with a decrease in smoking, exposure to toxicants, dependence, and an increase in quit attempts. These authors further stated that based on animal studies, there is no compelling evidence that non-nicotine constituents at levels that are currently present in tobacco smoke are enough to maintain abuse liability or sustain cigarette smoking; however, product standards for these constituents might be considered.

One major concern that is often raised is the occurrence of compensatory smoking with very low nicotine content cigarettes by smoking more frequently or intensely in order to maintain desired levels of nicotine intake, thereby leading to potential public health risk. Benowitz and colleagues[5] pointed out that there is minimal evidence of the occurrence of compensatory smoking, as assessed by cigarettes per day and exposure to tobacco combustion toxicants, when smokers switched to normal nicotine content cigarettes are compared with smokers switched to very low nicotine cigarettes (VLNC). Additionally, mathematical estimation showed that the amount of VLNC that would need to be smoked to simulate nicotine levels from smoking conventional nicotine cigarettes would be impossible to achieve.

One of the criteria to determine whether a product standard has public health benefit is its effect on increasing the likelihood of cessation. Piper and colleagues[6] summarized recent literature that suggests abrupt switching to, and extended use of, reduced nicotine cigarettes can reduce cigarettes per day, cigarette dependence, and increase the ability to quit smoking cigarettes. Additionally, they indicated that there is also credible evidence that reduced nicotine content when in conjunction with nicotine replacement therapy increases quit rates among smokers motivated to quit.

In a commentary, Koopmeiners and colleagues[7] reported that a major challenge in randomized clinical trials examining the effects of VLNC is noncompliance with only using the assigned product, which could obscure the actual effects of these cigarettes. They described a method of analysis that focuses on the estimation of causal effects (ie, the effect if all subjects were to adhere to randomized treatment assignment) using methods from the causal inference literature. This analysis projects the potential impact of nicotine standard in an environment that would not have access to normal nicotine content cigarettes. Using causal effect analysis, an even greater positive effect from VLNC had been observed.

Nicotine Standard and Smokers with Psychiatric Co-morbidity

An important evidence base is accumulating that examines how reduced nicotine in cigarettes might affect smokers who have heightened vulnerability to tobacco use and tobacco-related disease. Tidey and colleagues[8] reviewed results from laboratory studies and randomized clinical trials and concluded that a reduced-nicotine standard for cigarettes would likely reduce cigarette smoking among smokers with mental health conditions and socioeconomic disadvantages, without increasing psychiatric symptoms or compensatory smoking. Secondary analysis of a large multisite, randomized, clinical laboratory study[9] revealed that reducing nicotine dose reduced measures of cigarette addiction potential, with little evidence of moderation by either psychiatric diagnosis or symptom severity of anxiety and depression, thus providing evidence that those with co-morbid psychiatric disorders would respond to a nicotine reduction policy similarly to other smokers. Another original investigation[10] compared the effects of VLNC (0.4 mg/g tobacco) with normal nicotine cigarettes (NNC; 15.8 mg/g tobacco) cigarettes over a 6-week period in nontreatment-seeking smokers with schizophrenia, schizoaffective disorder, or bipolar disorder. Results suggest that a reduced-nicotine standard for cigarettes would reduce smoking among smokers with serious mental illness. However, nicotine exposure was not reduced across the two conditions, indicating noncompliance when using only VLNC cigarettes and suggesting that smokers with serious mental illness will likely seek alternative sources of nicotine.

Nicotine Standards and Youth and Young Adults

Less research attention has been paid to how youth will respond to nicotine standards. In a review, Colby and colleagues[11] observed that preclinical findings indicate that adolescent smokers and nonsmokers are likely to be less sensitive to reinforcement from VLNC compared with adults. In addition, human laboratory and clinical research suggest that reducing nicotine in cigarettes to 0.4 mg/g would reduce the abuse potential of cigarettes in adolescents and young adults. Finally, there was no evidence to indicate that nicotine reduction leads to compensatory smoking in young smokers. Similarly, in a secondary analysis of a double-blind, within-subject experiment with cigarette smokers with co-morbid psychiatric conditions or socioeconomic disadvantages, Davis and colleagues[12] found that reducing the nicotine content of cigarettes would decrease the addiction potential of cigarette smoking in young adult smokers as much or more than older adult smokers. Another analysis examined the effects of cigarette nicotine content and menthol preference/smoking on health risk perceptions, subjective ratings, and carbon monoxide (CO) boost in adolescent smokers in a laboratory-based study.[13] As observed in prior studies, VLNC were experienced as less satisfying and rewarding than NNC. Relevant to the section below, youth in general reported lower perception of health risk associated with VLNC compared with NNC with minimal moderating effects of menthol. Because the participants were blind to the nicotine dose, this finding reveals that the sensory aspects of smoking may affect perception of risk, which is similar to what has been observed with highly ventilated cigarettes (Lights and Ultralights).[14] Interestingly, there were no differences in perceived risk for addiction.

Nicotine Standard Among Menthol Smokers

Menthol cigarettes are smoked by 30% of the US population; therefore, understanding the impact of products standards on this population is warranted. In a secondary analysis of a large 20-week, double-blind clinical trial in which VLNC (0.4 mg/g tobacco) were compared with NNC (15.5 mg/g tobacco) in menthol versus nonmenthol smokers, Denlinger-Apte and colleagues[15] found that menthol smokers assigned to the VLNC cigarette condition experienced reduced cigarettes per day, toxicant exposures, and increase in quitting attempts, however, to a lesser degree than nonmenthol smokers.

Step-Down Versus Target Date for Nicotine Reduction

A prior study demonstrated that an immediate reduction to very low nicotine levels (0.4 mg/g tobacco) when compared with a gradual nicotine reduction is associated with a greater decrease in biomarkers of carcinogen and toxicant exposures, cigarettes per day, dependence, and more cigarette-free days.[16] In a secondary analysis of this 20-week, double-blind clinical trial data, Smith and colleagues[17] found that immediate nicotine reduction resulted in greater reductions in cigarette satisfaction than gradual nicotine reduction, even when matching for duration of VLNC cigarette use. Furthermore, reduced subjective response is related to changes in smoking behaviors

and cigarette dependence. Secondary data analyses from an exploratory clinical trial reveal that gradually reducing the frequency of smoking behavior increases quit attempts more than gradually reducing the nicotine content in cigarettes; however, there were no differences in quit attempts that were ≥24 h and 7-day point prevalence observed at the 1-month follow-up.[18]

Perceptions and Communications

An important set of papers in this special issue examines perceptions of very low nicotine tobacco products and communication with the public about potential standards. Villanti and colleagues[19] review current evidence in this area and point out that a significant portion of US adults incorrectly believe that nicotine causes cancer and adult smokers believe that smoking VLNC cigarettes is less likely to cause cancer than smoking their usual brand cigarettes. Furthermore, there is little public understanding of the basis for reducing nicotine in cigarettes. These authors recommend key elements of public education efforts to correct misperceptions of nicotine in order to maximize the potential benefits of a nicotine reduction standard. An empirical analysis[20] models latent classes of nicotine beliefs among US young adults and identifies four classes of beliefs, with the largest class believing that nicotine plays a major role in smoking risk. These beliefs are associated with perceived harm of nicotine and tobacco products and correlated with sociodemographic predictors of smoking.[20] These findings may help us to identify specific beliefs or groups to be targeted by public education efforts on nicotine.

Using evidence-based risk communication practices, Byron and colleagues[21] conducted an online experiment and examined how different descriptions of the nicotine level in VLNC affect the accuracy of the public's perceptions about nicotine content, addictiveness, and cancer risk. They found that simply stating that 95% of nicotine would be removed more accurately conveyed the nicotine content and addictiveness of VLNC; however, it misled people about cancer risk. They suggested a communication campaign that conveys that VLNC will be less addictive but equally toxic to smoke compared with NNC. Also examining public perceptions, Popova and colleagues[22] analyzed a nationally representative, online probability sample of US adult smokers to examine different ways of framing nicotine reduction in cigarettes and found that presenting nicotine reduction as making cigarettes unable to relieve cravings might be particularly effective at motivating cessation and was associated with the lowest percentage of participants believing that VLNC were less harmful than regular cigarettes.

Another online experiment[23] with young adult cigarette smokers examined how product marketing, packaging, and risk messaging on product marketing affects product appeal, perceptions, and use. Findings identified packaging (e.g., red pack color) and messaging (corrective statements about product risk) that are associated with greater recall of the advertisement content. These results demonstrated the importance of not only regulating the products but the need to regulate advertising and labeling.

Reactions to a Potential Nicotine Reduction Policy and Research Gaps

Public reactions to a nicotine reduction policy and subsequent changes in tobacco use are important to consider. Smith and colleagues[24] reported different possible behavioral outcomes of nicotine reduction among US adult smokers (e.g., continuing to smoke with VLNC but reduce consumption, switching partly or completely to noncigarette nicotine containing products, quitting smoking, smoking NNC from the illegal market). They recommended maximizing public health benefit of a nicotine product standard by: (1) including other noncombusted products; (2) considering a regulatory framework that favors less harmful products; and (3) providing information on the relative risk of nicotine containing products. Moreover, it is important to understand whether smokers' interest in illegally buying cigarettes with regular nicotine content would increase if a nicotine standard were adopted. An online experiment[25] with US adult smokers found that smokers who are informed about the reduced nicotine standard report increased interest in illegally purchasing regular cigarettes from a website, a street vendor, or a store on an Indian reservation. The authors indicated the importance of implementing different approaches to mitigating the illegal market such as a strong "track and trace" system, illicit trade penalties, or licensing requirements.

Finally, Berman and Glasser's[26] literature review summarized the state of the science and identified gaps, which include the need for more studies that better reflect the availability and use of a wide variety of tobacco and nicotine products (including cigarettes from illegal markets) and the potential for dual or multiproduct use, that model the impact of a nicotine standard in the context of other control measures, and that determine the impact of product standards on cessation, initiation *and* relapse.

Summary

Since the concept of reducing nicotine in cigarettes was introduced in 1994 by Benowitz and Henningfield,[27] there has been a growing body of scientific literature that supports the feasibility and potential public health benefit of this approach. In this special issue, some of the questions that were raised in the ANPRM for a nicotine product standard have been addressed. For example, there is growing evidence that supports an optimal threshold for a nicotine standard and that such a standard has potential to reduce addiction liability among the general population as well as vulnerable populations such as youth, young adults, smokers with mental illness or who are economically disadvantaged, and who smoke menthol cigarettes. Based on subjective responses to cigarettes that are reflective of abuse potential, an immediate as opposed to a gradual nicotine reduction approach is likely to lead to more rapid and greater public health benefit. As policy-makers consider rule making, attention is needed to ensure public communication is fact-based and corrects misperception about the harms of nicotine and reduced nicotine cigarettes, and that industry marketing, labeling, and packaging is regulated. Recent studies are demonstrating what type of messages can be used to correct misperceptions but also to facilitate abstinence. It has also been made clear that in order to mitigate any negative consequences, the availability of regulated alternative nicotine products is important and protective measures to reduce the use of illegal cigarettes need to be implemented. Although several gaps in research have been identified, some of these gaps are currently being addressed and, as stated by Berman and Glasser,[26] "given the overwhelming amount of harm caused by combusted tobacco products and the substantial and rapidly growing body of literature on nicotine reduction, the remaining research gaps should not prevent the FDA from moving forward with the rulemaking process."

Declaration of Interests

None declared.

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