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Review

Reduced nicotine product standards for combustible tobacco: Building an empirical basis for effective regulation

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ABSTRACT

Introduction. Both the Tobacco Control Act in the U.S. and Article 9 of the Framework Convention on Tobacco Control enable governments to directly address the addictiveness of combustible tobacco by reducing nicotine through product standards. Although nicotine may have some harmful effects, the detrimental health effects of smoked tobacco are primarily due to non-nicotine constituents. Hence, the health effects of nicotine reduction would likely be determined by changes in behavior that result in changes in smoke exposure.

Methods. Herein, we review the current evidence on nicotine reduction and discuss some of the challenges in establishing the empirical basis for regulatory decisions.

Results. To date, research suggests that very low nicotine content cigarettes produce a desirable set of outcomes, including reduced exposure to nicotine, reduced smoking, and reduced dependence, without significant safety concerns. However, much is still unknown, including the effects of gradual versus abrupt changes in nicotine content, effects in vulnerable populations, and impact on youth.

Discussion. A coordinated effort must be made to provide the best possible scientific basis for regulatory decisions. The outcome of this effort may provide the foundation for a novel approach to tobacco control that dramatically reduces the devastating health consequences of smoked tobacco.

Contents

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"Without nicotine… there would be no smoking"
[*Phillip Morris scientist, William* Dunn, 1972]

Introduction

A billion individuals may die from tobacco use by the end of the 21st century if current trends continue (Jha, 2009). Tobacco control policies such as taxation, restricting youth access, prohibiting smoking in public places, anti-smoking media campaigns, and the wide availability of effective treatments will be important tools for improving public health for the foreseeable future (USDHHS, 2010). However, these efforts are not enough; new strategies are needed.

Reducing the addictiveness of tobacco by reducing nicotine may be particularly effective. Nicotine is the primary psychoactive constituent of tobacco that results in the development and maintenance of tobacco dependence, a fact that has been formally recognized by numerous bodies including the U.S. Surgeon General and the World Health Organization (USDHHS, 1988b; WHO, 2003). Recent changes in the regulation of tobacco products allow public health agencies and governments to directly address the role of nicotine in tobacco products. In the U.S., the Family Smoking Prevention and Tobacco Control Act (FSPTCA) enables the Food and Drug Administration to establish product standards, including for nicotine, that are "appropriate for the protection of public health" (Congress, 2009). Worldwide, Article 9 of the Framework Convention on Tobacco Control, a World Health Organization treaty with over 170 state parties, states that the Parties agree to establish guidelines that all nations may use in measuring and regulating the content and emission of tobacco products (WHO, 2003). The purpose of this paper is to review the current science on nicotine reduction and discuss some of the challenges in establishing the empirical basis for regulatory decisions about reduction of nicotine in smoked tobacco. The paper focuses on the FSPTCA, although the principles also likely apply outside the United States.

How might reducing nicotine improve health?

The detrimental health effects of smoked tobacco are primarily due to the non-nicotine constituents of tobacco smoke (USDHHS, 2014). Consequently, the impact of nicotine reduction on health is likely to be largely determined by changes in smoking behavior that result in a net decrease in exposure to tobacco smoke. A reduction in the nicotine content of cigarettes may reduce smoking behavior in at least three ways. First, nicotine reinforcement and dependence may be reduced in current smokers, providing users with the freedom to smoke less or stop smoking altogether. Second, new users may be less likely to develop dependence and continue to smoke. Finally, ex-smokers who lapse may be less likely to become regular smokers again. Additional benefits may occur as a consequence of reduced exposure to secondhand smoke; however, these benefits are not discussed in this paper.

Nicotine reduction: not just another "light" cigarette

A distinction must be made between the reduction of nicotine content in tobacco and the twentieth century public health disaster of "light" cigarettes. The critical difference between these two approaches is that light cigarettes were capable of providing relatively high yields of nicotine to smokers who changed their behavior to increase nicotine exposure (e.g., vent blocking, increasing puff volume) whereas very low nicotine content (VLNC) cigarettes cannot. VLNC cigarettes contain substantially less nicotine *in the tobacco*, making it extremely difficult or impossible for the smoker to adjust their behavior enough to yield large doses of nicotine. Hence, although we must be careful not to repeat the mistake of "light cigarettes", we must also not pay an additional cost for history if reduction in the nicotine content of cigarettes is likely to improve public health.

Generating the empirical basis for regulatory decisions

A new field of tobacco regulatory science is emerging. Ashley and colleagues describe tobacco regulatory science as "the scientific discipline that supports the evaluation of the risks and benefits of tobacco regulatory decisions and provides a robust scientific foundation for regulatory policies" (Ashley et al., 2014). Because the regulation of tobacco is based on a public health standard, the purpose of tobacco regulatory science is to enable regulators to make the best possible estimate of the potential impact of a regulatory decision on population health.

Regulatory scientists must understand what actions can be taken by FDA (or any other regulatory body), which questions are critical for estimating the potential public health impact, and how to translate these regulatory questions into testable hypotheses if they are to provide the "robust scientific foundation" required by regulators (Ashley et al., 2014). No single scientific study can, or should be expected to, determine an appropriate nicotine standard or how such a standard should be implemented. Instead, regulatory action will be based on an evaluation of the available scientific evidence and a determination that, on the whole, a ruling is *likely* to benefit public health (Villanti et al., 2011). In short, the translation of science to policy will be based on the weight of all the empirical evidence and regulators, not scientists, will determine if a product standard should be enacted.

Methods

Clinical research: questions, challenges and limitations

Hatsukami and colleagues have summarized some of the critical questions facing the FDA with regard to nicotine reduction including: 1) whether VLNC products (i.e., <2 mg/g tobacco compared to approximately 10–14 mg/g in a typical cigarette) result in reliable decreases in exposure to tobacco smoke; 2) whether nicotine should be reduced gradually over time or rapidly; and 3) whether any adverse outcomes result from nicotine reduction (Hatsukami et al., 2010b, 2013a). Translating these questions into testable hypotheses is complex and challenging. One cannot, for example, test the effect of reducing nicotine gradually over many years. However, one can test the hypothesis that gradually reducing nicotine over a shorter period of time leads to greater total toxicant exposure and/or fewer withdrawal symptoms. Such data would help regulators weigh the risks and benefits of gradual vs. abrupt reduction even though the exact parameters of the potential regulation are not tested.

Regulatory science aimed at determining the effects of nicotine reduction faces several limitations. First, the principle underlying nicotine reduction is that smoking should gradually decline or cease as a result of decreased reinforcement

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from and dependence on tobacco products. However, these processes are experience and context-dependent (e.g., extinction; (Bouton, 2004)). Whether the typical study duration of several weeks to months is adequate to result in behavior change is uncertain (Hatsukami et al., 2010a, 2013c; Benowitz et al., 2009, 2012). Second, testing the hypothesis that nicotine reduction in combustible tobacco would lead to decreased smoking depends on participants being compliant with the use of experimental tobacco products. However, the current marketplace provides easy access to high nicotine content products, thereby potentially undermining compliance. Third, the impact of nicotine reduction is typically evaluated using experimental cigarettes (Hatsukami et al., 2013b). However, experimental cigarettes do not mimic the complex product design and marketing tactics that increase product appeal of commercial cigarettes. Furthermore, research tools for other smoked products (e.g., hookah, little cigars) are not available. Fourth, clinical trials often poorly represent individuals who use other nicotine or tobacco products. Although inclusion of users of other products would help to address this concern, it presents other challenges (e.g., biomarker measurement; dynamic nature of the current market). Finally, cigarettes are generally provided free of charge in clinical studies. Providing free cigarettes will likely increase smoking. In sum, clinical research is limited by numerous factors that must be kept in mind when interpreting the results of such studies. Indeed, many of these challenges may lead to underestimates of the potential public health impact of nicotine reduction.

Primary outcome measures

The primary outcome measure for clinical trials that aim to understand the health impact of nicotine reduction in current smokers is a change in smoking behavior that results in a change in exposure to smoke constituents. However, as foreshadowed above, it is important to distinguish the goal of a clinical trial in current smokers – e.g., to test whether nicotine reduction leads to decreased smoking – from the assessment of nicotine reduction as a regulatory strategy. The latter is based not only on the impact on users, but also non-users. Given the limitations for clinical trials, the extensive evidence that supports nicotine as the addictive agent in cigarettes (USDHHS, 1988a, 2010, 2014), and the potential for nicotine reduction to address the burden of tobacco for future generations, nicotine reduction could still be a viable policy even if current smoking behavior does not decrease within the context of a clinical trial, as long as the safety of current smokers is not compromised.

Hence, safety must also be considered a critical outcome measure. Safety concerns fall into three broad categories: 1) changes in smoking or other tobacco use behaviors that could represent increased potential for harm (e.g., compensatory smoking); 2) adverse outcomes directly related to the reduction of nicotine (e.g., cardiovascular changes, severe withdrawal symptoms); 3) adverse outcomes indirectly related to the reduction of nicotine and/or changes in smoking behavior (e.g., alcohol consumption, drug use). Many of these effects may be relatively short-lived and mitigated with nicotine replacement or other interventions. Ultimately, accurate assessment of safety is critical as these data will inform estimates of the risks of nicotine reduction that must be weighed against the potential health benefits of reductions in smoking (USDHHS, 1990, 2014).

Biomarkers of exposure and harm

Biomarkers of nicotine intake such as cotinine or urine total nicotine equivalents (the sum of nicotine and its metabolites) can be used to assess actual exposure to nicotine. These measures are important for assessing compensatory changes in smoking which could increase exposure to toxic tobacco smoke constituents. Furthermore, toxicant exposure can be measured more directly with biomarkers such as breath carbon monoxide, urine NNAL (metabolite of the carcinogenic tobacco specific nitrosamine NNK), urine metabolites of polycyclic aromatic hydrocarbons and urine mercapturic acid metabolites of volatile organic chemicals. If daily cigarette smoke intake remains constant (i.e., no compensatory smoking), there will be no change in many of these biomarkers (unless they are reduced in the product/smoke; e.g., NNK), as has been observed in several studies (Hatsukami et al., 2010a, 2013c; Benowitz et al., 2009, 2012).

Compensatory smoking when switching from conventional cigarettes to cigarettes with less nicotine can be computed based on biomarkers of exposure in comparison to the emissions or content of the cigarettes. Thus, if a person switches from a high to low nicotine cigarette and there is no change in cotinine, compensation is 100%. Conversely if the yield or content is reduced by 50% and the cotinine levels drop by 50% there is 0% compensation. The following equation is commonly used to compute compensation (Benowitz et al., 2005):

$$\text{Compensation} = 1 - \frac{[\log(\text{marker 2}) - \log(\text{marker 1})]}{[\log(\text{yield 2}) - \log(\text{yield 1})]}.$$

Biomarkers of biological effect may also be included in nicotine reduction studies. Such markers include indicators of inflammation, platelet activation, oxidative stress and others. Thus far, nicotine reduction studies have not seen changes in biomarkers of biological effect as nicotine levels are reduced (Benowitz et al., 2009, 2012). It will be important to also continue to evaluate the relationship between biomarkers and health, as changes in biomarkers alone may not be sufficient to result in changes in public health.

Compliance

Non-compliance in clinical studies may limit estimates of the impact of nicotine reduction and, consequently, it is an important outcome to measure effectively. Accurate self-report of all (study and non-study) products should be carefully considered when evaluating study procedures and weighed against the potential benefits of strategies for minimizing non-compliance (e.g., financial incentives). Furthermore, whenever possible, biochemical measures of compliance (e.g., cotinine, anabasine, NNAL) should be considered given the demand characteristics of clinical trials. However, validated cutoffs for assessing non-compliance have not been developed to date. It should also be recognized that products with reduced abuse liability are most likely to result in reduced compliance. Lastly, given the goal of regulatory science is to inform decisions about product standards, analytic approaches may need to take compliance into account when considering the effects of nicotine reduction (Benowitz et al., 2009).

Additional measures

Numerous other measures can provide important information for regulatory decisions. Factors that are predictive of use, particularly those that may serve to mediate the likelihood of quitting, would be important indicators of potential behavior change. For example, a decrease in nicotine dependence (TTURC et al., 2007) might be expected to precede actual change in behavior. Conversely, current smokers may be less likely to attempt to quit because they perceive VLNC cigarettes as less harmful (Shiffman et al., 2004). Likewise, outcomes that may occur as a result of nicotine reduction but do not pose a significant threat to safety may be important. For example, withdrawal symptoms are generally not serious threats to health, but may limit public acceptability of a standard and lead to unnecessary discomfort.

Heterogeneity of response

Researchers should be cognizant of the potential heterogeneity in response to nicotine reduction. While numerous sources for variability could be discussed (e.g., metabolic differences, race/ethnicity, gender, smoking rate), two subpopulations readily illustrate this concern: youth and individuals with co-morbid psychiatric disorders.

The long-term public health impact of nicotine reduction lies in the prevention of dependence in new, typically young, smokers. Ethical challenges make effects of reduced-nicotine cigarettes on initiation and early use in young smokers difficult to study; however, research on young non-smokers that does not involve smoking can reveal important information about the antecedents of tobacco use (e.g., risk perception). Furthermore, the reinforcing effects of VLNC cigarettes can be studied in current teen smokers, which could prove important given developmental differences in the neurobiology related to nicotine reinforcement (Counotte et al., 2011; Leslie et al., 2004; Ernst et al., 2006). Finally, additional research on young adults (e.g., 18–25) with minimal smoking experience may provide useful information for estimating the impact on youth under 18.

People with psychiatric illness smoke almost half of the cigarettes consumed in the United States (Lasser et al., 2000). The obstacles that smokers with psychiatric comorbidity have with initiating and maintaining abstinence likely include heightened sensitivity to the relative reinforcing effects of nicotine, use of nicotine to ameliorate psychiatric symptoms and cognitive deficits, and difficulty accessing effective smoking cessation treatments (Kalman et al., 2005; Hall and Prochaska, 2009; Spring et al., 2003; Tidey and Williams 2007; Ziedonis et al., 2008). A nicotine reduction policy has the potential to surmount some of these barriers, but could also have unintended negative consequences for comorbid smokers.

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Preclinical models

Animal models also have much to contribute to the evaluation of whether a tobacco product standard of very low nicotine levels might benefit public health (Donny et al., 2012). Preclinical work encompasses two broad categories of studies. One category includes studies that complement work in human subjects. For example, initial studies in experimental animals can examine whether nicotine reduction that occurs gradually vs. abruptly result in different rates of self-administration. The second, and potentially more important, category of studies relates to questions that cannot, at present, be addressed in humans. For example, preclinical experiments can evaluate the effects of reduced nicotine on adolescent, nicotine naive animals. Experiments can also assess interactions between nicotine and other chemicals in cigarette smoke that may interact with nicotine (and each other) to initiate and/or maintain behavior.

Results

Daily smokers

Several clinical trials of the effects of VNLC cigarette use for at least a week have been conducted. Two of the clinical trials have examined smokers motivated to quit smoking. One trial (N = 165) randomly assigned smokers to one of two different nicotine-yield cigarettes (0.05 mg vs. 0.3 mg nicotine; Quest™ 3 & 2, respectively) or nicotine lozenge (Hatsukami et al., 2010a). Smokers were asked to completely switch over to using these products for a period of six weeks and to quit all tobacco product use at the end of this period. In another trial (N = 235), smokers underwent the same protocol but were randomly assigned to 0.05–0.09 mg nicotine-yield (0.7–1.2 mg nicotine content; 8–11 mg tar) cigarettes, with or without nicotine patches, or to nicotine patch alone (Hatsukami et al., 2013c). The results from both these studies showed that switching to cigarettes with 0.05–0.09 mg nicotine yield significantly decreased the number of cigarettes smoked per day (~18–37%) and biomarkers of exposure such as cotinine or total nicotine equivalents (~88–95%) and carbon monoxide (~11–25%). On the other hand, switching to 0.3 mg nicotine-yield cigarettes significantly increased both cigarettes per day (~8%) and carbon monoxide levels (~20–35%) through much of the 6 week period, although it decreased cotinine levels (~50%), suggesting partial compensation. In addition, with the 0.05 mg nicotine content cigarette, significant decreases in perceived risk for addiction and nicotine dependence were observed, and participants did not experience increases in withdrawal symptoms when they stopped using this product. In contrast, use of the 0.3 mg nicotine-yield cigarette decreased perceived risk for addiction but did not change nicotine dependence severity, and nicotine withdrawal symptoms significantly increased upon cessation. Finally, when rates of cessation from all tobacco products were examined, 0.05–0.09 mg nicotine yield cigarettes had very similar rates of cessation as the nicotine replacement products.

In contrast, Benowitz et al. examined the effects of gradual reduction of nicotine yield each week (N = 20) (Benowitz et al., 2009) or month (N = 135) (Benowitz et al., 2012) among smokers unmotivated to quit smoking. Both studies showed minimal increases in cigarettes smoked per day (~5–10%) and no change in carbon monoxide when the nicotine content in cigarettes was greater than 4 mg (or 0.4 mg nicotine yield) but a decrease in cotinine levels at this content and lower (~40–56%). The larger, longer study found a decrease in cigarettes smoked per day, but only after participants reached 1 mg nicotine content (0.1 mg nicotine yield; 11 mg tar); however, daily smoking rate was similar to the rate observed during a usual brand baseline (Benowitz et al., 2012). It is possible that levels <0.1 mg nicotine yield are required to reduce the number of VLNC cigarettes smoked. Because of the differences in level of motivation to quit across the studies conducted by Hatsukami vs. Benowitz, it is difficult to discern the impact of gradual versus immediate approaches to reducing nicotine content in cigarettes.

With regard to safety, in the studies that assessed cardiovascular biomarkers (Benowitz et al., 2009; Benowitz et al., 2012; Hatsukami et al., 2013c) or exposure to toxicants (Benowitz et al., 2009; Benowitz et al., 2012; Hatsukami et al., 2013c; Hatsukami et al., 2010a) there was no evidence of adverse effects of VLNC cigarettes. In fact, at the lowest nicotine content, decreases in exposure biomarkers were observed. In addition, in the Hatsukami et al. studies (Hatsukami et al., 2013c; Hatsukami et al., 2010a) of a total of 202 smokers, only 3 were discharged due to compensatory smoking (i.e., >100% increase in CO).

Several approaches can be used to mitigate any adverse effects of reduced-nicotine cigarettes. These include providing nicotine replacement therapies, non-nicotine therapeutic agents (e.g., varenicline) or possibly non-combusted potential modified risk tobacco products (e.g., electronic nicotine delivery systems). Little research has been conducted in this area. One study randomized smokers (N = 68) to use the Quest 3™ (0.05 mg nicotine yield) cigarettes while wearing a placebo, 7 mg or 21 mg nicotine patch or smoke Quest 1™ (0.6 mg nicotine yield) cigarettes while wearing a placebo patch (Donny and Jones, 2009). Smokers assigned to nicotine patch (21 mg or 7 mg) plus VLNC cigarettes compared to placebo patch plus VLNC cigarettes showed a greater decrease in the number of VLNC cigarettes smoked and less severe withdrawal symptoms. In another study (Hatsukami et al., 2013c), smokers (N = 235) who were randomly assigned to VLNC cigarettes plus the 21 mg nicotine patch smoked fewer study cigarettes, had lower carbon monoxide levels, and experienced less severe withdrawal symptoms than those smokers assigned to VLNC cigarettes alone. No difference in abstinence rates was observed across patch conditions. However, among smokers who called a smoking cessation quitline (N = 1410), those assigned to both usual treatment (which involved nicotine replacement therapies) plus low nicotine content cigarettes (Quest 3™, 0.05 mg nicotine yield) had a 1.5 fold higher continuous abstinence rate at the six months compared to usual treatment alone (Walker et al., 2012).

Youth

Little direct evidence addresses the potential impact of nicotine reduction on youths (<18 years of age) initiating smoking or on the progression from initial use to dependence. In the only study published to date, adolescents (N = 35) tended to engage in compensatory smoking when given VLNC (0.06 mg nicotine yield, 17.9 mg tar) cigarettes acutely, increasing the number of puffs compared to a high nicotine (1.14 mg nicotine yield, 15.9 mg tar) cigarette (Kassel et al., 2007). This effect has also been observed in adult, daily smokers, but tends to dissipate with repeated use (Macqueen et al., 2012).

Ex-smokers

Similarly, little is known about the effects of nicotine reduction in ex-smokers. Given the ethical constraints of providing ex-smokers with tobacco products, the most informative studies may rely on experimental models of relapse. In one study, current smokers who were not seeking treatment were given incentives to abstain from smoking (Juliano et al., 2006). After 4 days of abstinence, smokers (N = 60) were randomly assigned to smoke 5 normal-nicotine-content cigarettes (0.6 mg nicotine yield, 11 mg tar), 5 VLNC cigarettes (0.07 mg nicotine yield; 11 mg tar), or not smoke. Participants were then given additional financial incentives to abstain from smoking for 6 days. Regardless of the nicotine content of the cigarettes, smoking (compared to not smoking) increased the likelihood of relapse. This study suggests that nicotine reduction may not alter the effect of a first lapse on subsequent smoking of normal nicotine content cigarettes. Whether ex-smokers would resume smoking if only VLNC cigarettes were available is unknown.

Smokers with co-morbid psychiatric conditions

One of the psychiatric illnesses most closely associated with tobacco dependence is schizophrenia (de Leon and Diaz, 2005). Human laboratory comparisons of smokers with and without schizophrenia have

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collectively found that smokers with schizophrenia puff faster, attaining higher nicotine intake levels than equally-heavy smokers without psychiatric disorders. They also experience more severe nicotine withdrawal symptoms and cognitive impairment when abstinent, relapse sooner and smoke more intensely after a period of abstinence (Olincy et al., 1997; Sacco et al., 2005; Tidey et al., 2005; Tidey et al., 2008; Tidey et al., 2013; Tidey et al., 2014; Weinberger et al., 2007; Williams et al., 2005; Williams et al., 2010). Among smokers with schizophrenia, acute VLNC cigarette use is equally effective at reducing cigarette craving, withdrawal symptoms and usual-brand smoking, but is less effective at reducing negative symptoms and cognitive deficits than high-nicotine cigarettes use (Smith et al., 2002; Tidey et al., 2013). If their intense smoking topography characteristics arise from attempts to ameliorate their symptoms and cognitive deficits, a dramatic reduction in the nicotine content of cigarettes could result in compensatory increases in smoking topography among these smokers.

Smokers with mood or anxiety disorders are important groups to consider because they comprise approximately 20–30% of people with tobacco dependence in the U.S. (Grant et al., 2004; Kandel et al., 2001; Tsai et al., 2011). These smokers report more severe negative affect and craving to relieve negative affect during abstinence, and greater sensitivity to the positive mood-enhancing effects and relative reinforcing effects of nicotine than do non-psychiatric smokers (Breslau et al., 1992; Dedert et al., 2012; Leventhal et al., 2014; Malpass and Higgs, 2007; Perkins et al., 2010; Piper et al., 2011; Weinberger et al., 2010). As a result, smokers with mood disorders may be particularly sensitive to abrupt changes in nicotine, raising the possibility that they might respond better to a gradual, rather than immediate, reduction in nicotine content, or may benefit from nicotine replacement when transitioning to VLNC cigarette use.

Data from animal models

Recent studies have found that gradual reduction of nicotine resulted in some compensatory increases in behavior at intermediate doses, but no compensation with lower doses. The dose of nicotine below which self-administration was no longer maintained was similar whether the nicotine dose was reduced gradually or abruptly (Smith et al., 2013). The nicotine dose required to establish self-administration among nicotine-naive animals appears to be similar to or higher than that which maintains self-administration among nicotine-experienced animals (unpublished observations), suggesting that a product standard established in experienced users may be effective for preventing initiation in current non-users.

Studies addressing the interaction between nicotine and other chemicals in cigarette smoke, while preliminary, suggest that other tobacco constituents may moderate the effects of nicotine reduction on behavior. In one study, a mixture of 5 minor alkaloids (nornicotine, cotinine, anatabine, anabasine, and myosmine) significantly enhanced responding for nicotine in adult male rats, at least under some reinforcement conditions (Clemens et al., 2009). Similarly, another psychoactive chemical in cigarette smoke, acetaldehyde, may increase responding for nicotine, at least under some conditions in adolescent rats (Belluzzi et al., 2005). Thus, the data available are consistent with the notion that other chemicals in cigarette smoke could alter the reinforcing and addictive properties of reduced nicotine tobacco products.

Discussion

A reduction in the nicotine content of combustible tobacco products has the potential to dramatically improve public health (Tengs et al., 2005). Studies to date strongly suggest that VLNC cigarettes produce a desirable set of outcomes, including reduced smoking, reduced nicotine exposure, reduced nicotine dependence, and/or increased abstinence. Importantly, they appear to engender no more harm than normal-nicotine-content cigarettes and, in fact, lead to reduced exposure to toxicants and very few adverse events. Furthermore, nicotine replacement may enhance outcomes.

Regulatory science should continue to build upon recent studies of nicotine reduction and the decades of research that highlight the central role of nicotine in maintaining smoking. Studies that would be most useful for FDA to estimate the public health impact of a nicotine standard should be prioritized. For example, one issue pertains to whether nicotine content should be reduced abruptly or gradually. Gradual reduction may initially provide less discomfort and may be more acceptable to the smoker, but abrupt reduction would have a more rapid public health benefit and be less likely to lead to significant compensatory smoking which tends to occur at intermediate levels of nicotine. Likewise, we also know relatively little about the impact of VLNC cigarettes on vulnerable populations (e.g., psychiatric co-morbidity) and on the use of other products that contain nicotine and/or other psychoactive constituents. Finally, additional information that would improve estimates of the likely impact on non-users, especially youth would be helpful.

Conclusion

In summary, a coordinated effort must be made to provide the best possible scientific basis for regulatory decisions as to whether nicotine should be reduced in combustible tobacco products. The science that emerges will build on decades of research on the behavioral and neurobiological effects of nicotine that has supported the conclusion reached in 1972 by Phillip Morris scientist William Dunn — "without nicotine… there would be no smoking" (Dunn, 1972). The outcome of this research effort may be to provide the foundation for a novel approach to tobacco control that dramatically reduces the devastating health consequences of smoked tobacco in the 21st century.

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Conflict of interest statement

Dr. Hatsukami was funded by Nabi Biopharmaceuticals and NIDA to be a site for a nicotine immunotherapy trial. Dr. Benowitz serves as consultant to several pharmaceutical companies that market smoking cessation medications and has been a paid expert witness in litigation against tobacco companies. Drs. Donny, Tidey, Sved and Cassidy have no conflicts to report.

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