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Nicotine Reduction Strategy: State of the science and challenges to tobacco control policy and FDA tobacco product regulation

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Potential Conflicts of Interest:

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

Keywords: nicotine reduction, addiction, FDA, regulation, alternative nicotine delivery systems, cigarette end game

Abstract

Nicotine addiction is the proximate cause of disease and death from cigarette smoking. In 1994, we proposed reducing the nicotine content of cigarettes to non-addicting levels to reduce the risk of youth becoming addicted smokers and promoting quitting in established smokers. In 2009, the Family Smoking Prevention and Tobacco Control Act provided the authority to FDA to reduce nicotine levels as appropriate to benefit public health. Over the past 15 years, considerable research has determined that nicotine reduction is feasible and safe, resulting in reduced nicotine dependence with little evidence of compensatory over-smoking. The availability of acceptable non-combusted form of nicotine would provide support and enhance acceptability of nicotine reduction in tobacco. Most recently, the FDA promulgated a nicotine-based regulatory framework, which includes nicotine reduction combined with ready availability of noncombustible nicotine products. Nicotine reduction could contribute to a virtual end to the use of cigarette smoking, with enormous benefits to public health.

Commentary

The proximate cause of disease and death from cigarette smoking is addiction to nicotine. However, the most of the direct harm from smoking comes not from nicotine, but from tobacco combustion products. The addicting role of nicotine in cigarettes and smokeless tobacco supported FDA's conclusion in its 1996 rule to regulate cigarettes and smokeless tobacco products as nicotine delivery devices in which nicotine's drug effects on the structure and function of the brain caused and sustained addictive use of these products (FDA, 1995, FDA 1996). Although, the US Supreme Court rejected the FDA's Tobacco Rule in 2001, many of the findings of FDA's investigation that led to the 1995 Proposed Rule and 1996 Final Rule provided the foundation for the 2009 Family Smoking and Prevention Tobacco Control Act. (FDA, 2009)

In parallel with FDA's deliberations on regulating nicotine as a drug, in 1994 Drs. Benowitz and Henningfield proposed consideration of reducing the nicotine content of cigarettes to non-addictive levels as a strategy to reduce the risk that future generations would become addicted to cigarettes (Benowitz and Henningfield, 1994). Most smokers begin smoking as children or adolescents socially with friends, but soon transition to smoking for pharmacologic effects of nicotine, leading to addiction. Reducing the nicotine levels in cigarettes to non-addictive

levels would be a highly effective way to prevent the transition from experimental to addictive smoking. In addition, nicotine reduction would lower the level of nicotine dependence and promote quitting in established smokers (Hatsukami et al., 2010). In our original paper, based on the daily intake of nicotine by non-addicted smokers and data on the bioavailability of nicotine from cigarettes, we estimated that a threshold level of 0.4 mg per cigarette rod (compared to 10-15 mg in a conventional cigarette) would result in a minimally addictive cigarette (Benowitz and Henningfield, 1994). A recent experimental study found that reducing the nicotine level to 0.4 nicotine per rod resulted in reduced dependence and smoking of fewer cigarettes per day (Donny et al., 2015). Other analysis suggest that the threshold for addiction may be lower (Hatsukami et al., 2010b; Sofuoglu and Lesage, 2012), suggesting the need for ongoing surveillance of any policy, as discussed below.

In 1998, the American Medical Association commissioned Henningfield, Benowitz and Slade to develop a report identifying the specific research issues, barriers to implementation of such a strategy and how any barriers might be addressed (Henningfield et al., 1998). Eventually in 2009, the Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act) that made tobacco regulation by FDA the law of the land, authorized the FDA for the benefit of public health to reduce nicotine to non-addictive levels, but not to zero. The Tobacco Control Act also authorized regulatory tools that could enable implementation as well as funding for relevant research (FDA, 2009).

The FDA Advisory Committee and FDA Commissioner David Kessler concluded that the potential public health strategy of reducing cigarette nicotine levels to non-addictive levels was promising but needed more research before action to implementation would be warranted because FDA understood that the issues were complex. That is, research was needed on an appropriate standard for the maximum nicotine content of a minimally addictive cigarette, whether nicotine in cigarettes should be reduced abruptly or gradually over years, and how to minimize the risks to heavily addicted smokers and vulnerable populations. Thus, nicotine reduction was not recommended in FDA's proposed or final Tobacco Control Act rule. Key research challenges related to implementation of such a proposal and the need for alternative nicotine delivery systems were discussed by Henningfield, Benowitz, Slade and others in their 1998 review for the American Medical Association (Henningfield et al., 1998).

In the two decades since its initial consideration, there has been extensive research on nicotine reduction as well as the emergence of more viable approaches to ensuring alternate means of nicotine intake for smokers who need or strongly desire it (FDA, 2018; Gottlieb and Zeller, 2017). Several clinical trials have demonstrated that nicotine reduction is feasible (Benowitz et al., 2012; Benowitz et al., 2007; Donny et al., 2015; Hatsukami et al., 2010). Smokers switched from conventional cigarettes to very low nicotine content cigarettes reduce daily nicotine intake by an average of 70%, smoke fewer cigarettes per day, report lower levels of dependence, and demonstrate a trend toward greater quitting. Furthermore, there is little evidence of nicotine withdrawal or compensatory over-smoking of cigarettes such that smokers are not exposed to greater levels of tobacco smoke toxicants compared to when they were smoking their usual brand of cigarette (Donny et al., 2015, Hatsukami et al., 2015). However, smokers switched to very low nicotine content cigarettes do have a higher dropout rate compared to higher nicotine content cigarette smokers, and do smoke occasional conventional cigarettes, presumably reflecting a compelling need for nicotine by certain individuals and/or in certain situations.

The idea of having alternative nicotine delivery systems (ANDS) that deliver nicotine without exposing the smoker to toxic combustion products as a way to reduce harm from smoking has been discussed by tobacco and health researchers and policy makers for many years (Benowitz and Henningfield, 2013; Slade and Henningfield, 1998; Warner et al., 1997). Moreover, it has been increasingly recognized that ready access to acceptable non-combusted alternate nicotine delivery systems and a nicotine reduction policy should be considered as complementary strategies because nicotine reduction may not be viable without increased access to acceptable alternative products; and conversely, nicotine reduction could accelerate the migration away from cigarettes (Benowitz et al., 2017; DHHS, 2014). It is important to recognize that nicotine reduction in cigarette tobacco is not proposed because nicotine is the main source of harm, but rather because nicotine sustains cigarette smoking, and cigarette smoke is the primary cause of the harm.

Recently, the world has seen the development and a marketing of electronic cigarettes and other electronic nicotine delivery systems that deliver nicotine to the lungs in a manner more similar to that of cigarettes, and in products that appear appealing to a broad range of cigarette smokers, including males and females. Whereas, alternatives such as oral smokeless tobacco

remain largely unappealing to females and nicotine replacement therapy product labeling and design is intended to primarily address smoking cessation efforts and not long term nicotine substitution (Warner et al., 1998; Warner et al., 1997). While there is much controversy among health professionals about the population benefits vs risks of electronic cigarettes, there is general agreement that e-cigarettes are less hazardous than tobacco cigarettes and that some individual smokers are able to quit smoking using e-cigarettes (Kozlowski and Warner, 2017; McNeill et al., 2018; Henningfield, Higgins and Villanti, 2018 – this issue of Prev Med).

In May 2016, FDA issued a deeming rule that extended their authority to include regulation of ANDS and other non-cigarette tobacco products (FDA, 2016) In the context of a national policy to reduce the nicotine of cigarettes, ANDS could be potentially used by smokers to manage nicotine withdrawal symptoms, to provide smokers who are addicted and have difficulty quitting with a safer source of nicotine, and to alleviate concerns that nicotine reduction is nicotine prohibition.

These advances provided the scientific basis for the 50th Anniversary Surgeon General's report to discuss nicotine reduction in the context of a comprehensive tobacco control policy intended to greatly accelerate the reduction of combusted tobacco use as part of what it termed the "end game" (DHHS, 2014). More recently, on July 28, 2017 FDA Commissioner Scott Gottlieb and FDA Center for Tobacco Products Director Mitch Zeller announced FDA's a new plan for tobacco regulation (Gottlieb and Zeller, 2017). The focus of the plan was nicotine, and included the intent to develop a rule to reduce nicotine to non-addictive levels while also promoting the conditions to enable such implementation. The plan included making medicinal and other noncombustible nicotine products readily available to facilitate transition from cigarette smoking. On March 15, 2018, FDA issued an Advance Notice of Proposed Rulemaking to obtain public input on the plan to reduce the nicotine levels of cigarettes to non-addictive levels (FDA, 2018).

A nicotine-focused regulatory framework could have a tremendously beneficial effect on public health. Reducing the addictiveness of cigarettes by nicotine reduction would prevent or markedly diminish the acquisition of addicted smoking in youth, and would most likely prompt many or most addicted smokers to quit smoking. The availability of acceptable and less hazardous forms of nicotine would provide support and enhance acceptability of nicotine

reduction in tobacco. Population models of the impact of nicotine reduction predict a magnitude of benefit to public health that rivals historical sanitation efforts (Tengs et al., 2005). Nicotine reduction could contribute to a virtual end to the use of combustible products within a decade or so of implementation instead of the half century or more scenario that seemed overly optimistic only a decade or so ago (Koop, 2003).

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