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How will alcohol research be impacted by future reduction in nicotine content in cigarettes?

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The United States (US) Food and Drug Administration (FDA) is taking unprecedented steps to regulate tobacco products in order to improve public health. The FDA recently announced its intention to set product standards to reduce the nicotine content in cigarettes available in the US to a minimally- or non-addictive level through an advance notice of proposed rulemaking (ANPRM) (Gottlieb and Zeller, 2017). Because of the strong connection of cigarette smoking to alcohol drinking, there is compelling reason for alcohol-focused researchers to consider how future mandated market-wide reductions of nicotine levels in cigarettes would have downstream impact on drinking behavior. This commentary describes four implications of the ANPRM on alcohol research, treatment, and policy, with the ultimate goal of helping to guide the alcohol field to be optimally positioned to react to and leverage the opportunity afforded by the ANPRM to reduce the alcohol-related disease epidemic.

The Family Smoking Prevention and Tobacco Control Act (TCA) of 2009 gives FDA the authority to establish tobacco product standards that it determines to be appropriate for the protection of public health. In March 2018, the FDA issued an ANPRM seeking public comment for consideration to develop a potential nicotine product standard that would lower nicotine to a minimally- or non-addictive level. Currently, the FDA has not yet decided on the actual nicotine level and will continue to evaluate the potential ramifications of new product standards before putting a standard into place.

To assess the public health impact of imposing these restrictions on all cigarettes available on the licit marketplace, the FDA has enabled a pathway for conducting clinical research

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studies examining the effects of nicotine reduction, including providing research cigarettes with varying levels of nicotine to the scientific community. In the largest clinical study to date ($N=840$), Donny and colleagues (Donny et al., 2015) reported that adults randomly assigned to smoke reduced nicotine cigarettes for 6 weeks had lower levels of nicotine exposure, had lower levels of nicotine dependence, and smoked fewer cigarettes per day during week 6 vs. adults assigned to their usual brand. Thus, there is encouraging evidence of the public health benefit of implementing a reduced nicotine standard for cigarettes. The FDA has stated that it will review results such as these, as well as all relevant science as part of a transparent, public rulemaking process (Gottlieb and Zeller, 2017). To reveal the overall public health impact of reduced nicotine cigarettes, a comprehensive evidence base is needed to examine not only cigarette smoking outcomes, but outcomes related to factors that correlate with cigarette smoking.

Studies consistently show that both dependent and non-dependent smokers have disproportionately high rates of problematic drinking (Kessler et al., 2005, Hasin et al., 2007, Vanable et al., 2003), and that individuals with more severe alcohol-related problems are more likely to be smokers and tend to smoke more heavily than those with less severe alcohol problems (Venable et al., 2003, Kahler et al., 2008b). Furthermore, alcohol use predicts poor tobacco cessation outcomes; this finding is so consistent that alcohol has been described as part of a neglected “epidemic” in tobacco cessation (Schroeder and Morris, 2010). A secondary analysis of data from the Donny et al. trial (Donny et al., 2015) has provided initial evidence of how alcohol drinking could be impacted by future reduction in nicotine content in cigarettes. In this secondary analysis, published in this journal (Dermody et al., 2016), adult daily smokers who were current drinkers, defined as reporting at the screening visit any alcohol use during the past month or reporting any alcohol use during the 2-week baseline period, there was no evidence of compensatory alcohol use or binge drinking when smoking reduced nicotine cigarettes (Dermody et al., 2016). To our knowledge, this is the only study that has examined the effects of *prolonged* nicotine reduction (i.e., 6 weeks) on alcohol drinking. Past studies of *acute* nicotine deprivation or abstinence have reported inconsistent effects on alcohol craving and drinking behavior (Cooney et al., 2003, Colby et al., 2004, Cohn et al., 2017, Palfai et al., 2000), but these studies may not closely model what is expected to occur in the marketplace as a result of new FDA product standards – a gradual reduction in nicotine content in cigarettes. As we anticipate changes in nicotine content in cigarettes, it is now time to reflect on how alcohol-focused researchers, clinicians, and policy makers, who have had a long-standing focus on harm reduction, can prepare for upcoming changes in the nicotine-focused harm reduction regulatory framework for tobacco.

First, alcohol researchers can contribute to FDA’s need for relevant and timely science to inform regulation. The aforementioned study by Dermody and colleagues (Dermody et al., 2016) is a critical piece of this evidence base, as it shows that compensatory drinking may *not* occur when smoking reduced nicotine cigarettes. However, similar studies in different subpopulations of cigarette smokers who show specific alcohol-related risks are needed to build a more comprehensive evidence base upon which FDA can justify its regulatory decisions. These different subpopulations can include: (1) smokers with current (past-year) Alcohol Use Disorder (AUD), to demonstrate whether smoking- and alcohol-related

outcomes vary by severity of AUD symptoms; (2) smokers with past (lifetime but not past-year) AUD, to demonstrate whether smoking reduced nicotine cigarettes becomes associated with relapse to problematic drinking or current AUD; and (3) smokers with current at-risk drinking according to NIAAA guidelines (for women, > 3 drinks in a day or > 7 drinks in a week, and for men, > 4 drinks on any day or > 14 per week), to show whether smoking reduced nicotine cigarettes becomes associated with low-risk drinking or, conversely, with progression to AUD. We are currently conducting a clinical study of reduced nicotine cigarettes in smokers with and without at-risk drinking, some of whom also have current or past AUD, with the goal of examining whether drinking behavior changes when smoking reduced nicotine cigarettes. A key implication of our current study, in addition to future studies with similar experimental designs, is that they will show whether the initial finding of no negative impact of reduced nicotine cigarettes on drinking is replicated across different subpopulations of drinkers. Thus, alcohol researchers can contribute to a comprehensive evidence base to show whether reductions in nicotine in cigarettes will have broad impact across drinkers or whether reductions will have more limited impact depending on typology of drinker.

Second, alcohol researchers and clinicians should consider how the clinical picture of individuals in alcohol treatment and how alcohol treatment outcomes might change as a result of the new product standard for cigarettes. Currently, much of the morbidity and mortality among smokers with AUD is due to smoking-related illness (Holahan et al., 2018, Hurt et al., 1996, Pelucchi et al., 2006). If reductions in nicotine levels in cigarettes do facilitate smoking cessation at the population level, then smoking-related disease could be expected to decrease among individuals with co-occurring AUD as well. This could mean that the demographic of individuals in AUD treatment might change, with potentially more older individuals in AUD treatment, in part due to lower frequency of premature death. This could also mean that associated clinical problems might change; because smoking cessation improves psychological functioning (Taylor et al., 2014), smokers with AUD who are successful at quitting may ultimately have fewer comorbid psychological diagnoses, psychosocial problems, and/or medical comorbidities. However, some individuals could increase their drinking under conditions of decreased nicotine exposure, such as young adults who drink heavily and women (as reviewed by Dermody and Donny, 2014). Given poorer AUD treatment outcomes for current smokers (Walitzer et al., 2015), a particularly critical area for future study is whether clinical outcomes improve as a result of reduced quantity or frequency of smoking and whether co-treatment (treating both alcohol and smoking cessation in the same context) can result in improved smoking and alcohol use outcomes. Addressing alcohol in the context of smoking cessation increases the odds of smoking cessation and reduces heavy drinking episodes (Toll et al., 2015, Kahler et al., 2008a), and addressing smoking cessation in the context of alcohol use treatment can increase the likelihood of long-term alcohol abstinence (Prochaska et al., 2004). A key implication for alcohol researchers is that synchronizing alcohol and tobacco policy and intervention approaches could maximize their net public health impact, although special attention should be paid to potentially high risk or vulnerable populations who could increase their drinking under conditions of decreased nicotine exposure.

Third, alcohol-focused researchers conducting surveillance analyses should be aware that changes in alcohol use patterns at the population level could be attributed to future expected changes in smoking behavior as a result of new FDA product standards. The proposed new product standard has the potential to decrease smoking prevalence by divorcing nicotine reinforcement from the tobacco self-administration process and associated cues. This could result in reduced alcohol consumption, as nicotine (and cigarette smoking) no longer serve as cues to drink. Alternatively, the proposed new standard could inadvertently increase population-level alcohol consumption, as smokers decide to quit and substitute cigarette smoking with alcohol use. Additionally, reducing the nicotine content in cigarettes may reduce the pleasurable and stimulating aspects of one's first smoking experience, and thus reduce conditioned cross-tolerance or sensitization to alcohol (Perkins et al., 2009). If fewer adolescents and young adults start smoking reduced nicotine cigarettes, surveillance efforts could detect a delay in initiation of alcohol drinking or in the development of alcohol-related problems at the population level. Assuming that reduced nicotine cigarettes will soon be available on the marketplace, there are unparalleled opportunities for researchers to examine changes in alcohol use in the US population before and immediately after FDA regulations go into effect.

Fourth, the increasing prevalence of non-cigarette tobacco products, such as e-cigarettes, hookah, large cigars, and little cigars/cigarillos, is worth noting. In the last 10 years, cigarette smoking has declined significantly, while use of these alternative products has increased dramatically (Kasza et al., 2017). Alcohol use commonly co-occurs with use of each of these products, although the strength of association differs across tobacco product type (Conway et al., 2017). A key mechanism by which reduced nicotine levels in combustible cigarettes will impact population-level health is to encourage combustible cigarette smokers to transition to potentially lower risk non-combustible tobacco products, like e-cigarettes, some of which may have lower levels of nicotine. However, reducing the content of nicotine in cigarettes may inadvertently drive consumers to use other combustible non-cigarette tobacco products that have similar levels of nicotine. If cigarette smokers transition to non-combustible or other combustible products, and continue a similar level of nicotine intake and frequency of tobacco product self-administration (e.g., Pope et al., 2018), there may not be downstream effects on alcohol use. The potential new product standard provides research opportunities to examine how reduced nicotine content, and the sensorimotor effects of smoking reduced nicotine cigarettes, might affect or be affected by alcohol use. An important area for future study, and for FDA's comprehensive nicotine and tobacco regulatory framework, is what effect tobacco product switching has on alcohol use.

The FDA is enacting significant measures to change the landscape of tobacco products and improve public health. Making cigarettes minimally addictive or non-addictive is expected to disrupt the progression from tobacco experimentation to regular use to tobacco-related disease and death, and could save millions of American lives. While regulation of tobacco products in the US is changing, regulation of alcoholic beverages at the national level appears relatively stable. This allows a unique opportunity to observe the downstream effects of changes in tobacco use on alcohol use. Preliminary evidence suggests positive impact on smoking-related outcomes and no sign of negative alcohol-related outcomes when smoking reduced nicotine cigarettes (Dermody et al., 2016, Donny et al., 2015), but it will be of

utmost importance to execute timely and rigorous surveillance and experimental studies to determine the short- and long-term secondary impact of tobacco product regulation on alcohol use behaviors. Indeed, ultimately reducing alcohol-related morbidity and mortality could be an important and serendipitous public health outcome of nicotine reduction.

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