



Supplement Article

Anticipated Effects of Nicotine Reduction on Youth Smoking Initiation and Maintenance

Suzanne M. Colby PhD^{1,✉}, Rachel N. Cassidy PhD¹, Rachel Denlinger-Apte MPH¹, Tracy T. Smith PhD², Lauren R. Pacek PhD^{3,✉}, F. Joseph McClernon PhD³, Jennifer W. Tidey PhD¹

¹Center for Alcohol and Addiction Studies, Brown University School of Public Health, Providence, RI; ²Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC; ³Department of Psychiatry and Behavioral Sciences, Duke University School of Medicine, Durham, NC

Corresponding Author: Suzanne M. Colby, PhD, Center for Alcohol and Addiction Studies, Brown University School of Public Health, Box G-S121-4, Providence, RI 02912 USA. Telephone: 401-863-6655; Fax: 401-863-6647; E-mail: Suzanne_colby@brown.edu

Abstract

This commentary summarizes emerging findings on the potential impact of a nicotine reduction policy on youth and young adults. We conclude that: (1) adolescent smokers and nonsmokers alike are likely to be less sensitive to reinforcement from very low nicotine content (VLNC) cigarettes compared with adults; (2) reducing nicotine in cigarettes to 0.4 mg/g would reduce the abuse potential of cigarettes in adolescents and young adults; (3) findings to date do not support concerns that nicotine reduction leads to compensatory smoking in young smokers; and (4) if the scope of a reduced nicotine product standard were applied to all combusted tobacco products, that would likely maximize public health benefit of this policy.

As the FDA considers a tobacco product standard to reduce the maximum nicotine level for combusted cigarettes with the aim of rendering cigarettes minimally addictive, questions remain regarding the potential effects of this regulation on cigarette initiation and ongoing use among youth. Below we comment on findings from preclinical research, which inform the potential effects of cigarette nicotine reduction on smoking initiation in nicotine-naïve youth. We then summarize findings from experimental research with adolescent and young adult smokers, which inform the potential effects of cigarette nicotine reduction on ongoing use among youth who are already smokers at the time of policy implementation.

Nicotine-Naïve Individuals Who Initiate Smoking Following Implementation of a Nicotine Reduction Policy are Likely to be Less Sensitive to Reinforcement From Very Low Nicotine Content Cigarettes Than Smokers Who had Already Initiated Before a Nicotine Reduction Policy

Ethical considerations preclude experimental research that directly tests the impact of cigarette nicotine content in nicotine-naïve

individuals. Preclinical research bridges this gap, utilizing nicotine self-administration models in nicotine-naïve rodents. Smith and colleagues¹ conducted a preclinical study to examine how nicotine-naïve individuals might respond to a nicotine reduction policy. Two groups of rats were compared: “Acquirers,” analogous to nicotine-naïve individuals who first try smoking after implementation of a nicotine reduction policy, and “Currents,” analogous to those who are already current smokers when a nicotine reduction policy is enacted. Acquirers were given the opportunity to self-administer one of three low nicotine doses (3.75, 7.5, 15 µg of nicotine/kg of body weight/infusion) or saline. Currents started nicotine self-administration at a higher dose (60 µg/kg/infusion) before experiencing a reduction in nicotine to one of the same three low doses of nicotine, or saline. Acquirers and Currents did not differ in their rates of self-administration of 3.75 µg/kg/infusion, 15 µg/kg/infusion, or saline. At the 7.5 µg/kg infusion dose, Currents responded at a higher rate and earned more infusions than Acquirers did, suggesting that prior experience self-administering a higher nicotine dose may have increased sensitivity to a lower nicotine dose. This suggests that a mandated nicotine level for cigarettes set below the reinforcement threshold in current smokers will likely be below the reinforcement threshold for nicotine-naïve individuals.

Youth are Likely to be *Less Sensitive to Very Low Nicotine Content Cigarette Reinforcement Than Adults*

The study above is promising, but utilized adult rats. Because smoking tends to be initiated during adolescence, it is important to understand whether nicotine reinforcement is different in adolescents. Several studies have found adolescent rats to self-administer nicotine at higher rates than adults, raising concern that adolescents may be more sensitive to nicotine than adults. However, these studies compared adolescent and adult rats on *rate of responding* for nicotine doses that are above the reinforcement threshold in both groups. The more relevant question for nicotine reduction is whether the *threshold for reinforcement* differs by age.

Two studies have compared the threshold nicotine dose for acquiring nicotine self-administration in adolescent versus adult rats. One compared adolescent and adult rats on self-administration of three nicotine doses (3, 10, 30 $\mu\text{g}/\text{kg}/\text{infusion}$).² Both groups failed to acquire self-administration of the lowest dose, and both acquired self-administration of the highest dose, with rates of self-administration similar across groups. At the middle dose, adult rats acquired self-administration but adolescent rats did not. An earlier study³ showed that adult rats were more likely than adolescent rats to acquire self-administration of a similar dose (15 $\mu\text{g}/\text{kg}/\text{infusion}$). Thus, both studies showed that adult rats were more sensitive to the reinforcing effects of a low nicotine dose than adolescent rats. These findings suggest that a mandated nicotine level in cigarettes that is established based on data from adult smokers is likely to result in reduced smoking initiation among adolescents.

Nicotine Reduction is Likely to Reduce the Abuse Liability of Cigarettes in Adolescent Smokers

To examine the effects of cigarette nicotine reduction in adolescent daily smokers, we compared their reactions to four different doses of nicotine (15.8, 5.2, 1.3, and 0.4 mg/g of tobacco) in research cigarettes.⁴ Using a within-subjects design with counterbalanced sessions, 50 adolescent smokers who had abstained overnight completed assessments before and after smoking one cigarette. Adolescents rated cigarettes with the lowest nicotine content as *less satisfying* than those with the highest nicotine content. All of the research cigarettes significantly reduced withdrawal symptoms, negative affect, and craving. The amount of withdrawal and negative affect reduction did not differ by nicotine content. However, the highest nicotine cigarette reduced abstinence-induced craving to a greater extent than the two lowest nicotine cigarettes.⁴ We also evaluated the effects of nicotine content on behavioral economic demand for cigarettes using a cigarette purchase task.⁵ Analyses showed that all four research cigarettes were rated as equally reinforcing, and all were less reinforcing than participants' usual brand cigarettes. Overall, our findings are consistent with those in adult smokers in that very low nicotine content (VLNC) cigarettes attenuated craving and withdrawal, yet were also less reinforcing than usual brand. However, unlike adults,⁶ adolescents did not show pronounced *dose-dependent effects* of nicotine on cigarette reinforcement. In sum, the 0.4 mg/g nicotine cigarettes were rated as less satisfying and less effective at reducing craving than a normal nicotine cigarette, indicating that a cigarette nicotine standard of 0.4 mg/g nicotine or less would significantly reduce the abuse potential of cigarettes among adolescent smokers.

Nicotine Reduction is Likely to Reduce the Abuse Liability of Cigarettes in Young Adult Smokers

We conducted a secondary analysis of a 6-week RCT⁷ testing the effects of cigarettes varying in nicotine content in adult smokers. Compared to adults smokers (ages 25+),⁸ younger smokers (ages 18–24) showed greater dislike for and lower use of 0.4–2.4 mg/g nicotine cigarettes, suggesting that a VLNC standard for cigarettes may reduce the abuse potential of cigarettes among young adult smokers.

Nicotine Reduction May Lead to Lower Cigarette Health Risk Perceptions in Adolescent Smokers

One concern for a nicotine reduction policy is that adolescent smokers may misperceive VLNC cigarettes as being less harmful, which could undermine motivation to quit smoking. Lab and survey studies both indicate that adults rate VLNC cigarettes as lower in health risk.^{9,10} Reduced health risk perceptions of VLNC cigarettes are particularly concerning in adolescents, who already tend to underestimate smoking harms.¹¹

We compared the effects of smoking a 0.4 mg/g versus a 15.8 mg/g nicotine cigarette on health risk perceptions¹² in adolescents, who similarly perceived the 0.4 mg/g nicotine cigarette to be lower in risk than the 15.8 mg/g nicotine cigarette. Although participants were blind to nicotine content, providing this information may not correct these misperceptions, given that a large proportion of smokers in the United States incorrectly believe that nicotine is the constituent in cigarettes responsible for cancer development.¹⁰ If a nicotine reduction policy were to be implemented, youth who incorrectly believe that nicotine reduction in cigarettes reduces cancer risk may be more susceptible to smoking. Thus, to maximize the public health benefit of a nicotine reduction policy, educational campaigns will serve a critical role in correcting such misperceptions in a manner that young people understand.

Nicotine Reduction is Unlikely to Lead to Compensatory Smoking in Young Smokers

Another concern about cigarette nicotine reduction is that it might unintentionally increase harm by leading to compensatory smoking, that is, changes in smoking behavior such as inhaling more deeply or smoking more cigarettes in an attempt to extract more nicotine. Research in adult smokers has not found evidence that 0.4 mg/g cigarettes lead to compensatory smoking.^{7,13} In our adolescent study described above⁴ we found no effect of cigarette nicotine content on compensatory smoking, which we measured using breath carbon monoxide boost (ie, change in carbon monoxide after smoking one cigarette). Extending this research, we are conducting an RCT (NCT02587312) comparing the effects of 0.4 mg/g versus 15.8 mg/g research cigarettes over a 3-week period in adolescent daily smokers. Among the first 45 study completers, smoking rate did not change significantly across the 3-week period, despite access to free cigarettes. Results to date raise no concerns about compensatory smoking of VLNC cigarettes.

A Nicotine Reduction Policy That Covered all Combusted Products Would Increase the Health Benefits for Youth and Young Adults

If nicotine is reduced in cigarettes but not in other tobacco products, smokers will likely shift to other nicotine-containing tobacco products. Research with adults has shown that when cigarettes were made less attractive, either by reducing nicotine content or increasing price, little cigars were the most frequently chosen alternative. When little cigars were not an option, the most common alternative chosen was e-cigarettes.^{14,15} We recently conducted a study with 240 young adult dual users of cigarettes and e-cigarettes.¹⁶ When participants were faced with a hypothetical VLNC product standard for cigarettes, they reported that they anticipated either quitting or reducing cigarette smoking (55.8%) and increasing their use of e-cigarettes (41.3%). As young tobacco users are particularly prone to multiple tobacco product use,¹⁷ the likelihood that many will shift to other nicotine-containing products in response to a cigarette nicotine reduction policy underscores the need for such a policy to cover all combusted products.

Summary and Conclusions

Research evidence counters concerns that VLNC cigarettes might be more appealing to youth than normal nicotine cigarettes, and/or might lead to compensatory smoking in youth. Preclinical studies indicate that adolescent smokers and nonsmokers alike are likely to be less sensitive to reinforcement from VLNC cigarettes compared with adults. Our lab 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, we find no convincing evidence that nicotine reduction leads to compensatory smoking in young smokers.

A few qualifications should be considered: (1) Adolescent smokers associate VLNC cigarettes with lower health risks, which could promote experimentation with these cigarettes. Effective youth-targeted educational campaigns will be needed to maximize the public health impact of the policy. (2) There is the potential for adolescents to shift from VLNC cigarettes to higher-nicotine tobacco products if a nicotine reduction policy applied only to cigarettes. A policy that covered all combusted products would likely increase health benefits. (3) Much of the evidence summarized herein is based on adolescent daily smokers. Such findings may not fully generalize to the majority of young smokers whose smoking tends to be more intermittent. In an ongoing trial (NCT02989038), we are evaluating reactions to cigarettes with varying nicotine content among young adult non-daily smokers, and findings should be available later this year. In the meantime, we note that similar work in non-daily, light adult smokers found no evidence of compensatory smoking.¹⁸

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Declaration of Interests

None declared.

References

- Smith TT, Schassburger RL, Buffalari DM, Sved AF, Donny EC. Low-dose nicotine self-administration is reduced in adult male rats naive to high doses of nicotine: implications for nicotine product standards. *Exp Clin Psychopharmacol*. 2014;22(5):453–459.
- Schassburger RL, Pitzer EM, Smith TT, et al. Adolescent rats self-administer less nicotine than adults at low doses. *Nicotine Tob Res*. 2016;18(9):1861–1868.
- Shram MJ, Li Z, Lê AD. Age differences in the spontaneous acquisition of nicotine self-administration in male Wistar and Long-Evans rats. *Psychopharmacology (Berl)*. 2008;197(1):45–58.
- Cassidy RN, Colby SM, Tidey JW, et al. Adolescent smokers' response to reducing the nicotine content of cigarettes: Acute effects on withdrawal symptoms and subjective evaluations. *Drug Alcohol Depend*. 2018;188:153–160.
- Cassidy RN, Miller ME, Tidey JW, DiGuseppi G, Denlinger-Apte R, Colby SM. The impact of nicotine dose on the reinforcing value of cigarettes in adolescents. *Tob Regul Sci*. 2019;5(2):105–114.
- Higgins ST, Heil SH, Sigmon SC, et al. Addiction potential of cigarettes with reduced nicotine content in populations with psychiatric disorders and other vulnerabilities to tobacco addiction. *JAMA Psychiatry*. 2017;74(10):1056–1064.
- Donny EC, Denlinger RL, Tidey JW, et al. Randomized trial of reduced-nicotine standards for cigarettes. *N Engl J Med*. 2015;373(14):1340–1349.
- Cassidy RN, Tidey JW, Cao Q, et al. Age moderates smokers' subjective response to very low nicotine content cigarettes: Evidence from a randomized controlled trial. *Nicotine Tob Res*. 2018; doi:10.1093/ntr/nty079
- Denlinger-Apte RL, Joel DL, Strasser AA, Donny EC. Low nicotine content descriptors reduce perceived health risks and positive cigarette ratings in participants using very low nicotine content cigarettes. *Nicotine Tob Res*. 2017;19(10):1149–1154.
- Byron MJ, Jeong M, Abrams DB, Brewer NT. Public misperception that very low nicotine cigarettes are less carcinogenic. *Tob Control*. 2018;27(6):712–714.
- Halpern-Felsher BL, Biehl M, Kropp RY, Rubinstein ML. Perceived risks and benefits of smoking: differences among adolescents with different smoking experiences and intentions. *Prev Med*. 2004;39(3):559–567.
- Denlinger-Apte RL, Cassidy RN, Colby SM, Sokolovsky A, Tidey JW. Effects of cigarette nicotine content and menthol preference on perceived health risks, subjective ratings, and carbon monoxide exposure among adolescent smokers. *Nicotine Tobacco Res*. 2019;21(Suppl.1): S56–S62.
- Hatsukami DK, Donny EC, Koopmeiners JS, Benowitz NL. Compensatory smoking from gradual and immediate reduction in cigarette nicotine content. *Cancer Epidemiol Biomarkers Prev*. 2015;24(2):472–476.
- Hatsukami DK, Luo X, Dick L, et al. Reduced nicotine content cigarettes and use of alternative nicotine products: Exploratory trial. *Addiction*. 2017;112(1):156–167.
- Quisenberry AJ, Koffarnus MN, Hatz LE, Epstein LH, Bickel WK. The experimental tobacco marketplace I: substitutability as a function of the price of conventional cigarettes. *Nicotine Tob Res*. 2016;18(7):1642–1648.
- Pacek LR, Oliver JA, Sweitzer MM, McClernon FJ. Young adult dual combusted cigarette and e-cigarette users' anticipated responses to a nicotine reduction policy and menthol ban in combusted cigarettes. *Drug Alcohol Depend*. 2019;194:40–44.
- Lee YO, Hebert CJ, Nonnemaker JM, Kim AE. Youth tobacco product use in the United States. *Pediatrics*. 2015;135(3):409–415.
- Shiffman S, Mao JM, Kurland BF, Scholl SM. Do non-daily smokers compensate for reduced cigarette consumption when smoking very-low-nicotine-content cigarettes? *Psychopharmacology (Berl)*. 2018;235(12):3435–3441.