Maziak and colleagues reported results of a randomized crossover clinical trial investigating the impact of partial reduction in nicotine levels on puffing behaviors among electronic nicotine delivery systems (e-cigarette) users. Participants included 50 healthy adult users (aged 21 to 35 years) of e-cigarettes who preferred 5% nicotine solutions. Each participant took part in two 60-minute laboratory sessions on separate days, during which they were allowed to vape e-cigarettes with 1 of 2 nicotine concentrations (5% and 3% for JUUL or 5% and 2.4% for NJOY) ad libitum. Results indicated greater median puff duration, greater median puffing time, and greater total inhaled volume in the 3% compared with the 5% sessions, which is suggestive of compensatory changes in puff topography in response to reduced nicotine concentrations. Plasma nicotine levels, however, remained lower from 3% solutions. Greater compensatory puffing during the 3% sessions was observed among those with higher levels of nicotine dependence and in men.

Vaping has emerged as the most popular form of nicotine and tobacco use among youth, with approximately 1 in 10 high school students reporting use in the past 30 days. While the long-term health consequences remain to be determined, vaping nicotine is associated with a variety of acute cardiovascular and pulmonary effects. Although the levels of most toxins in the aerosol generated by e-cigarettes are substantially lower than those found in combustible tobacco smoke, the presence of known carcinogens, heavy metals, and volatile organic compounds is reason for concern. Vaping is also associated with significant exposure to nicotine, which is harmful to the developing brain and over time, leads to dependence. Opinions differ regarding the role that e-cigarettes should play in harm reduction for adults who use combustible tobacco. For young people who do not use tobacco or other recreational nicotine products, however, vaping is accompanied only by risk. Reducing use among this group, therefore, is a public health priority.

One potential strategy for decreasing the risks associated with vaping is to establish product standards for maximum nicotine levels. If successfully implemented, this approach would limit the potential for becoming dependent on nicotine, reduce the likelihood that those who experiment with vaping would transition to regular use, and increase success with quitting. However, this approach is not without its complications. A variety of factors influence nicotine yield from e-cigarettes including the nicotine concentration of the solutions, the form of nicotine (ie, free-base vs protonated), heating temperature, and wattage. Puffing behaviors, including frequency and depth of inhalation, also significantly impact nicotine absorption levels. It has long been recognized that reducing nicotine content in nicotine and tobacco products could lead to compensatory changes in puff topography (eg, more intense inhalation, greater frequency of puffing) that would allow users of these products to maintain consistent nicotine levels. This could counteract benefits of reduced nicotine concentration on the addictiveness of recreational nicotine and tobacco products and even potentially increase harm through greater exposure to toxicants from compensatory overvaping or oversmoking.

Fortunately, it appears that these unintended consequences can be prevented while maintaining the benefits of nicotine reduction, at least with combustible cigarettes. Minimally addictive nicotine levels can be achieved using very low nicotine content (VLNC) cigarettes for which changes in consumption and puffing behaviors sufficient to compensate for reduced nicotine levels are not possible. Critically, exposure to toxic chemicals also does not increase after switching to...
VLNC cigarettes. Thus, combustible cigarettes can be manufactured with minimal potential for nicotine dependence without increasing health risks. Much less is known, however, about the utility of this approach for e-cigarettes. Given the differences in use patterns and the wide range of device characteristics, it is critical to investigate nicotine reduction strategies separately for e-cigarettes and combustible cigarettes. The study by Maziak and colleagues is a critical step in that process.

Importantly, results from the study by Maziak and colleagues demonstrated compensatory changes in puff topography when using e-cigarettes with partially reduced nicotine levels. Although the reasons for different findings from nicotine reduction using e-cigarettes and what has been reported for combustible cigarettes require further investigation, the reduced harshness and irritation associated with e-cigarette vapor, particularly generated from nicotine salts, relative to cigarette smoke may make greater compensation possible. It is also important to note that the lower nicotine level used in the study by Maziak and colleagues (3%) does not likely correspond to nicotine delivery levels from VLNC combustible cigarettes and almost certainly exceeds minimal thresholds for dependence. As a result, compensatory changes in puff topography are more likely to facilitate nicotine levels that maintain positive reinforcement and alleviate withdrawal symptoms. To be successful as a regulatory strategy, mandated nicotine levels in e-cigarettes will need to be significantly lower than were tested in their study.

Although it was a well-designed and methodologically rigorous study with potentially important implications, certain limitations were also evident. First, while the carefully controlled laboratory environment plays a critical role in this type of work, it does come at a cost to ecological validity. The 60-minute–focused vaping sessions were arguably more representative of how combustible tobacco products are consumed than how e-cigarette users typically vape. Furthermore, the extent to which the physical and social environment mirrored that in which e-cigarettes are commonly used was difficult to discern. It is also unclear whether the compensatory changes in puffing that were evident in an acute laboratory paradigm would be sustained over time in a natural environment. Studies with VLNC combustible cigarettes suggest that this may not be the case.

The clinical significance of the observed differences in topography between sessions was also not readily apparent. For example, the implications of a 0.12-minute difference in median puffing time over 60 minutes or a 0.13-second difference in median puff duration between conditions and whether differences of this magnitude meaningfully impact nicotine absorption, dependence, and (potentially) toxicant exposure is unclear.

Finally, the external validity of the findings was likely impacted by the inclusion and exclusion criteria, which resulted in a rather selective sample. The characteristics of those who were enrolled do not appear to reflect the general population of young adult e-cigarette users.

The Family Smoking Prevention and Tobacco Control Act that was signed into law in 2009 grants the US Food and Drug Administration the authority to regulate nicotine levels in recreational nicotine and tobacco products. To date, it has not exercised this authority. Product standards that lower the addictive potential of e-cigarettes have great promise for reducing the harms associated with vaping nicotine in young people. Results from the study by Maziak and colleagues suggest that it will be important to establish nicotine levels that have minimal potential for dependence, as has been done with combustible cigarettes. It is also critical to consider the broader landscape of tobacco, nicotine, and vaping products, which is rapidly evolving. Although mandates regarding a maximum nicotine concentration in e-cigarettes may ultimately reduce their potential to foster nicotine dependence, the public health benefits of that approach will be limited if the mandates lead to substitution with products with higher nicotine levels and greater exposure to harmful chemicals. Therefore, a comprehensive strategy, rather than one focused specifically on e-cigarettes, will be critical. Finally, the industry has a long history of manipulating its products to maintain their addictiveness. If reduced nicotine levels are mandated, it is reasonable to assume that the industry would attempt the same with e-cigarettes.
Lowering Nicotine Levels to Reduce E-Cigarette Dependence

ARTICLE INFORMATION
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REFERENCES