

# E-Cigarettes: Cause for Optimism or Pessimism?

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Cigarette smoking, which leads to more than 400,000 deaths in the United States annually, remains the number-one preventable cause of sickness and mortality. Thus it is no wonder that there is so much interest in, as well as controversy over, e-cigarettes, which simulate the cigarette smoking experience but without producing tar and other combustion products in tobacco smoke. The promise—and the implication of much of the marketing of these increasingly popular devices—is that they could be a safer, less toxic alternative to conventional cigarettes and even could work as cessation aids for people who are trying to quit smoking.

E-cigarettes produce a flavored aerosol that looks and feels somewhat like tobacco smoke and, in many cases, delivers rewarding nicotine. Unfortunately the evidence for e-cigarettes' possible benefits as well as their safety remains very limited at this point, creating a challenge for policymakers, addiction counselors, and others in healthcare who are in a position to influence the health of Americans. We just don't know yet how enthusiastic versus cautious to be about vaping, particularly when it involves a substance as addictive as nicotine.

The uncertainty is reflected at the level of world public health authorities, whose reactions to the new devices are widely varied. An executive agency of the UK's Department of Health, Public Health England, asserted last August that e-cigarettes were "95% safer" than cigarettes and recommended maximizing the public health opportunities they present.<sup>1</sup> However, their report was strongly criticized in *The Lancet* for a lack of evidence base on which to make such an optimistic claim.<sup>2</sup> American authorities have been much more cautious, with the U.S. Centers for Disease Control and Prevention sounding alarms over e-cigarettes and their advertising.<sup>3</sup>

One concern is the safety of the fluids and flavorings used in e-cigarettes. Testing of some e-fluids has found known carcinogens and toxic chemicals (such as formaldehyde and acetaldehyde) in the vapor, as well as metals.<sup>4</sup> Whether there will be long-term health consequences as a result of repeated exposure to these chemicals is unknown. At the time of this writing, the U.S. Food and Drug Administration is proposing extending regulatory requirements for tobacco products to e-cigarettes and the fluids used in them, meaning that products would need to be safety tested and approved.

An even more pressing question is the relationship between e-cigarette use and traditional cigarette smoking. Much of the optimism of the Public Health England report is based on the idea that e-cigarettes may be a substitute for more harmful options. If this were true, then given the known health risks of cigarettes it might be reasonable to be optimistic about the new devices, even given the unknowns about the safety of vaping. However, increasingly there is evidence—albeit preliminary—that e-cigarettes are supplementing tobacco products without necessarily reducing the use of the latter. They may even be opening the door to cigarette use among individuals who might not otherwise smoke.

That this could happen among teen users is particularly worrying. Since their emergence on the market, e-cigarettes have skyrocketed in popularity among U.S. adolescents. According to the 2015 Monitoring the Future Survey of drug use and attitudes among middle- and high-school students,

9.5% of 8th graders, 14.0% of 10th graders, and 16.2% of 12th graders used e-cigarettes—more than use traditional cigarettes.<sup>5</sup> Cigarette smoking by teens is currently at an all-time low, after declining steadily since the 1990s. A recent NIDA-funded study found that teen e-cigarette users may be more likely to graduate to conventional tobacco products than non-users: In a sizeable, demographically diverse cohort of California 14-year-olds, e-cigarette use at baseline was associated with a greater likelihood of cigarette use over the subsequent year than no e-cigarette use.<sup>6</sup>

E-cigarettes are similarly popular among U.K. teens. Nearly one fifth of over 16,000 14- to 17-year-old school students surveyed in North West England in 2013 reported trying or purchasing e-cigarettes.<sup>7</sup> This study was interesting because it suggested British teens view e-cigarettes as a new type of recreational drug rather than as a replacement for cigarettes: E-cigarette use was linked to other risky substance-related behaviors such as drinking to get drunk, binge drinking, avoiding age restrictions to obtain alcohol, and cigarette smoking. Only 15.8% of e-cigarette users had never smoked conventional cigarettes.

Many, though not all, e-cigarettes deliver nicotine to the user, and this is a particular concern for adolescents, who are more susceptible to developing nicotine addiction. Early nicotine exposure produces lasting sensitization to nicotine and appears to alter synaptic connectivity.<sup>8</sup> Younger age at smoking initiation increases risk of later heavy smoking.<sup>9</sup> Nicotine exposure has also been found to sensitize mice to the rewarding effects of cocaine, via an epigenetic pathway (changes in gene expression), and thus nicotine may act as a "gateway drug."<sup>10</sup>





It is still unclear how teen use of e-cigarettes translates to nicotine exposure. Students in the 2015 MTF survey were asked for the first time about what was in the fluid they vaporized on the most recent occasion they used an e-cigarette, and over 60% across all grades reported vaporizing “just flavoring.” Since products are currently unregulated and their labeling often suspect, there is no way to know how accurately teens can assess what they are really consuming. Also it is possible that enjoyment of flavorings alone could lead to using nicotine fluids and/or flavored tobacco products. Most teens who ever have used tobacco started with a flavored product—63% started with flavored e-cigarettes.<sup>11</sup>

Concerns over teen e-cigarette use and possible smoking initiation must be weighed against any potential benefits of existing smokers switching to e-cigarettes—the harm-reduction potential on which the U.K. public health recommendations rest. Here again, the data are preliminary, and as yet, no head-to-head comparisons between the efficacy of e-cigarettes and FDA-approved smoking-cessation aids such as nicotine patches have been conducted. But there is some evidence that e-cigarettes may not be the smoking-cessation aids the makers and consumers had hoped. A recent review and meta-analysis

of 38 previous studies of e-cigarette use and smoking cessation funded by the National Cancer Institute found that adult smokers who had used e-cigarettes had 28% lower odds of quitting compared to smokers who had not used these devices.<sup>12</sup> Limiting the analysis to studies of smokers with an intent to quit did not alter the results.

Public health campaigns and legislation restricting smoking in public places have successfully stigmatized smoking over the past decades, which is expected to lower the burden of disease and mortality from cigarettes. It would be tragic if, by newly glamorizing a smoking-like behavior, e-cigarettes and vaping led to a reversal of the current trends by increasing cigarette use in teens or actually prolonging cigarette use in smokers trying to quit. But more research is needed to know how much weight to place on these fears. Are teens using e-cigarettes the ones who are more likely to use tobacco products anyway? Are smokers who experiment with e-cigarettes already less likely to quit? Finding some answers to these and other questions is an urgent priority, and thus NIH is supporting wide research in this area. We hope and expect to know much more in coming years.



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Control Policy (ONDCP) where, before coming back to NIDA, he served as the Chief of the Prevention Branch.

#### FOOTNOTES

- <sup>1</sup>McNeill, A. et al. *E-cigarettes: an evidence update. A report commissioned by Public Health England.* (Public Health England, 2015).
- <sup>2</sup>The Lancet. E-cigarettes: Public Health England's evidence-based confusion. *The Lancet* 386, 829 (2015).
- <sup>3</sup>E-cigarette ads reach nearly 7 in 10 middle and high-school students. at <http://www.cdc.gov/media/releases/2016/p0105-e-cigarettes.html>
- <sup>4</sup>Grana, R., Benowitz, N. & Glantz, S. A. E-Cigarettes: A Scientific Review. *Circulation* 129, 1972–1986 (2014).
- <sup>5</sup>Johnston, L. D., O'Malley, P. M., Miech, R. A., Bachman, J. G. & Schulenberg, J. E. *Monitoring the Future national survey results on drug use, 1975–2015: Overview, key findings on adolescent drug use.* (Institute for Social Research, The University of Michigan, 2016).
- <sup>6</sup>Leventhal, A. M. et al. Association of Electronic Cigarette Use With Initiation of Combustible Tobacco Product Smoking in Early Adolescence. *JAMA* 314, 700 (2015).
- <sup>7</sup>Hughes, K. et al. Associations between e-cigarette access and smoking and drinking behaviours in teenagers. *BMC Public Health* 15, 244 (2015).
- <sup>8</sup>Smith, R. F., McDonald, C. G., Bergstrom, H. C., Ehlinger, D. G. & Brielmaier, J. M. Adolescent nicotine induces persisting changes in development of neural connectivity. *Neurosci. Biobehav. Rev.* 55, 432–443 (2015).
- <sup>9</sup>National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. *Preventing Tobacco Use Among Youth and Young Adults: A Report of the Surgeon General.* (Centers for Disease Control and Prevention (US), 2012). at <http://www.ncbi.nlm.nih.gov/books/NBK99237>
- <sup>10</sup>Levine, A. et al. Molecular Mechanism for a Gateway Drug: Epigenetic Changes Initiated by Nicotine Prime Gene Expression by Cocaine. *Sci. Transl. Med.* 3, 107ra109–107ra109 (2011).
- <sup>11</sup>Ambrose, B. K. et al. Flavored Tobacco Product Use Among US Youth Aged 12–17 Years, 2013–2014. *JAMA* 314, 1871 (2015).
- <sup>12</sup>Kalkhoran, S. & Glantz, S. A. E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and meta-analysis. *Lancet Respir. Med.* 4, 116–128 (2016).