# E-Cigarettes to Assist with Smoking Cessation

Belinda Borrelli, Ph.D., and George T. O'Connor, M.D.

The prevalence of tobacco smoking in the United States has declined to 14.0% but still exceeds 25% among high-risk subgroups.[1,2] Electronic cigarettes (e-cigarettes) are not approved by the Food and Drug Administration (FDA) for smoking cessation, but Americans trying to quit smoking use these products more frequently than FDA-approved cessation aids.[3] Comparative-effectiveness trials are needed to learn whether smokers have a better chance of quitting with e-cigarettes. Previous trials have had methodologic shortcomings, used first-generation e-cigarettes, or did not assess long-term outcomes.

Hajek et al.[4] now report in the *Journal* the results of a multicenter, pragmatic, randomized trial of e-cigarettes, as compared with nicotine-replacement therapy, as a smoking-cessation treatment within the U.K. National Health Service smoking-cessation program. In addition to behavioral support, participants received either a second-generation refillable e-cigarette or a 3-month supply of whichever nicotine-replacement products they preferred. After 1 year, the rate of abstinence from smoking tobacco, validated by exhaled carbon monoxide concentration, was higher in the e-cigarette group (18.0%) than in the nicotine-replacement group (9.9%). Trial limitations include a lack of objective and validated measures of adherence and the possibility that smoking-cessation counselors who were aware of the treatment assignments may have influenced patient expectations.

These findings must be considered in the context of FDA-approved medications for smoking cessation that have acceptable safety profiles. Treatment with nicotine-replacement therapy and bupropion achieves abstinence rates of approximately 25 to 26% at 6 months and 20% at 1 year,[5] with slightly higher abstinence rates for combination therapy than for monotherapy.[6] Varenicline has been shown to outperform bupropion, all forms of nicotine-replacement therapy, and placebo, with a 26% abstinence rate through 24 weeks of follow-up among participants without psychiatric diagnoses.[7] The 1-year abstinence rate of 18% reported by Hajek et al. for the e-cigarette group is similar to these outcomes.

This evidence of effectiveness must be balanced against the short-term and long-term safety of e-cigarettes. With regard to the former, the data from Hajek et al. are reassuring: the e-cigarette group had greater declines in the incidence of cough and phlegm than the nicotine-replacement group, no excess wheezing or dyspnea, and only a small incidence of oropharyngeal irritation. More frequent respiratory serious adverse events in the e-cigarette group than in the nicotine-replacement group (5 vs. 1) did not appear to be related to e-cigarette use. A limitation of this pragmatic trial is the lack of information on the presence of asthma or chronic obstructive pulmonary disease, which could confer a predisposition to short-term adverse respiratory health effects, although previous reports have suggested short-term clinical benefit among patients with these conditions who switch from tobacco smoking to e-cigarette use.[8] The use of e-cigarettes by pregnant women, who were excluded from the trial by Hajek et al., raises special safety concerns. Although nicotine-patch use during pregnancy is associated with a higher rate of smoking cessation and better child-development outcomes than placebo,[9] there are no such reassuring data for e-cigarettes.

A key finding of Hajek et al. is that among participants with sustained abstinence at 1 year, 63 of 79 (80%) in the e-cigarette group were still using e-cigarettes, whereas only 4 of 44 (9%) in the nicotine-replacement group were still using nicotine replacement. This differential pattern of long-term use raises concerns about the health consequences of long-term e-cigarette use. E-cigarette vapor contains many toxins and exerts potentially adverse biologic effects on human cells in vitro or in animal models, although toxin levels and biologic effects are generally lower than those of tobacco smoke.[10] A study involving humans showed an altered bronchial epithelial proteome in association with e-cigarette use, including some protein alterations also seen among tobacco smokers.[11] In a mouse model, inhalational exposure to nebulized e-cigarette liquid containing nicotine resulted in distal airspace enlargement that was consistent with pulmonary emphysema.[12] These findings argue against complacency in accepting the transition from tobacco smoking to indefinite e-cigarette

use as a completely successful smoking-cessation outcome.

An additional societal consideration is the effect of adult e-cigarette use on children and young adults. Adult use may not only expose children to e-cigarette vapor but also models addictive behavior. There is substantial evidence that e-cigarette use by youth increases the risk of smoking combustible tobacco cigarettes,[10] and the U.S. Surgeon General has recently declared e-cigarette use among youth "an epidemic."[13]

A consensus has emerged that e-cigarettes are safer than traditional combustible cigarettes,[10] but it remains controversial whether e-cigarettes should be recommended as a first-line treatment to assist smoking cessation, alongside FDA-approved treatments. The appropriate duration of e-cigarette "treatment" for smokers trying to quit is also uncertain. We recommend that e-cigarettes be used only when FDA-approved treatments (combined with behavioral counseling) fail, that patients be advised to use the lowest dose needed to manage their cravings, and that there be a clear timeline and "off ramp" for use. Use of e-cigarettes should be monitored by health care providers, like other pharmacologic smoking-cessation treatments. The efficacy and safety of e-cigarettes need to be evaluated in high-risk subgroups, and further research on the health consequences of long-term e-cigarette use is needed.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

From the Center for Behavioral Science Research, Department of Health Policy and Health Services Research, Henry M. Goldman School of Dental Medicine, Boston University (B.B.), and the Pulmonary Center, Boston University School of Medicine, and Division of Pulmonary, Allergy, Sleep, and Critical Care Medicine, Boston Medical Center (G.T.O.) — all in Boston.

This editorial was published on January 30, 2019, at NEJM.org.

1. Wang TW, Asman K, Gentzke AS, et al. Tobacco product use among adults — United States, 2017. MMWR Morb Mortal Wkly Rep 2018;67:1225-32.
2. Borrelli B, Busch A, Dunsiger S. Cigarette smoking among adults with mobility impairments: a US population-based survey. Am J Public Health 2014;104:1943-9.
3. Benmarhnia T, Pierce JP, Leas E, et al. Can e-cigarettes and pharmaceutical aids increase smoking cessation and reduce cigarette consumption? Findings from a nationally representative cohort of American smokers. Am J Epidemiol 2018;187:2397-404.
4. Hajek P, Phillips-Waller A, Przulj D, et al. A randomized trial of e-cigarettes versus nicotine-replacement therapy. N Engl J Med 2019;380:629-37.
5. Rosen LJ, Galili T, Kott J, Goodman M, Freedman LS. Diminishing benefit of smoking cessation medications during the first year: a meta-analysis of randomized controlled trials. Addiction 2018;113:805-16.
6. Windle SB, Filion KB, Mancini JG, et al. Combination therapies for smoking cessation: a hierarchical bayesian meta-analysis. Am J Prev Med 2016;51:1060-71.
7. Anthenelli RM, Benowitz NL, West R, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. Lancet 2016;387:2507-20.
8. Polosa R, Morjaria JB, Caponnetto P, et al. Evidence for harm reduction in COPD smokers who switch to electronic cigarettes. Respir Res 2016;17:166.
9. Cooper S, Taggar J, Lewis S, et al. Effect of nicotine patches in pregnancy on infant and maternal outcomes at 2 years: follow-up from the randomised, double-blind, placebo-controlled SNAP trial. Lancet Respir Med 2014;2:728-37.
10. Stratton K, Kwan LY, Eaton DL, eds. Public health consequences of e-cigarettes. Washington, DC: National Academies Press, January 2018.
11. Ghosh A, Coakley RC, Mascenik T, et al. Chronic e-cigarette exposure alters the human bronchial epithelial proteome. Am J Respir Crit Care Med 2018;198:67-76.
12. Garcia-Arcos I, Geraghty P, Baumlin N, et al. Chronic electronic cigarette exposure in mice induces features of COPD in a nicotine-dependent manner. Thorax 2016;71:1119-29.
13. Stein R. Surgeon General warns youth vaping is now an "epidemic." NPR. December 18, 2018 (https://www.npr.org/sections/health-shots/2018/12/18/677755266/surgeon-general-warns-youth-vaping-is-now-an-epidemic).

DOI: 10.1056/NEJMe1816406


# The Dangerous Flavors of E-Cigarettes

Jeffrey M. Drazen, M.D., Stephen Morrissey, Ph.D., and Edward W. Campion, M.D.

Nicotine is amazingly addictive. About 20 years ago, researchers in a nearby laboratory were studying the effects of cigarette smoke on lung function in mice. To expose a mouse to cigarette smoke, the mouse is placed in a plastic tube, head out. The tube is positioned in a stream of smoke, which the mouse then breathes. On the day of the first exposure, it is difficult to get the mouse to enter the tube. But on the second exposure, most mice run right into the tube. In contrast, mice not exposed to tobacco smoke on the first day continue to resist entering the tube on the second day. Exposed mice are eager to get another hit of nicotine.

Electronic cigarettes are nicotine delivery devices for humans. Since smoking is not a natural