Electronic Cigarettes May Lead to Nicotine Addiction

By Mike Fillon

Are electronic cigarettes (e-cigarettes) a relatively harmless substitute for cigarettes? Or are they a Trojan horse leading to nicotine addiction and ultimately chronic smoking? Many researchers believe the latter.

E-cigarettes are battery-powered devices that deliver aerosolized nicotine and kid-friendly flavored additives, such as chocolate mint, piña colada, atomic fireball candy, and even gummy bears. Designed to mimic the look and habit of smoking, the devices are marketed as a relatively benign alternative to smoking, without the tar, carbon monoxide, and other harmful ingredients adversely affecting the heart and respiratory system. “Vaping,” the term for using e-cigarettes, emits only a cloud of vapor—not secondhand smoke.

Many people are buying into the non-smoking allure. E-cigarettes have quickly become a marketing marvel. In the U.S., sales escalated from 50,000 devices in 2008 to 3.5 million in 2012, fulfilling every marketing executive’s dream to sell a product that customers return to repeatedly. And the younger customers start, the longer they keep buying. Most smokers begin when they’re young. According to the Centers for Disease Control and Prevention (CDC) in Atlanta, nearly 90% of U.S. adult smokers began smoking by the age of 18 years.

These companies’ pro-e-cigarette marketing strategy seems to work. In a national survey by CDC appearing in the November 28, 2014 issue of Nicotine & Tobacco Research, 4.5% of high school students said they had used e-cigarettes in the previous month, up from 1.5% in 2011 and 2.8% in 2012. Former CDC researcher Shanta Dube, Ph.D., M.P.H., associate professor of epidemiology and biostatistics at Georgia State University’s School of Public Health, said that how many of them were using e-cigarettes regularly and how many tried it only once during that month is unknown.

“Cigarette among adolescents has been going down without addicting young people to another product. While it is entirely speculative whether e-cigarettes are having any impact on cigarette use among youth, it is not speculative that the widespread use of nicotine products by youth is harmful.”

“However, with the allure of popular flavors and desire to fit in with their peers, it’s not a surprise youngsters become curious and try them, and conceivably more than once,” Dube said. “Also, since e-cigarettes and conventional tobacco cigarettes are used exactly the same way, it’s possible for them to become interchangeable.”

Patrick T. O’Gara, M.D., F.A.C.C., president of the American College of Cardiology, said he finds the CDC’s report disheartening. He released a statement that after decades of progress against smoking and nicotine addiction, “we risk going backwards if a new generation of smokers becomes addicted to nicotine.”

Stanton A. Glantz, Ph.D., director of the Center for Tobacco Control Research and Education at the University of California, San Francisco, said O’Gara’s alarm is justified.

“There is no question that e-cigarettes are the way that some kids initiate nicotine addiction. We also know that there is very high dual use of e-cigarettes and conventional cigarettes among youth. The one thing that we do not yet know is the precise fraction of kids who start with e-cigarettes [and] then add cigarettes, and vice versa.”

E-cigarettes also have their defenders. In his Nov. 28, 2014, column, “Nicotine Without Death,” New York Times opinion columnist Joe Nocera wrote that the drop in smoking by teenagers coupled with a large increase in e-cigarette use by teens was actually good news. Quoting Michael B. Siegel, M.D., M.P.H., a professor of public health at Boston University, Nocera said that “e-cigarettes are not the ‘gateway’ to cigarettes that many in the public health community feared.”

Matthew L. Myers, president of the Campaign for Tobacco-Free Kids, said e-cigarette advocates are missing the critical cause-and-effect point.
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In the Aug. 5, 2014, Wall Street Journal, Siegel wrote, “The gateway hypothesis is a myth. Of the few nonsmoking youths who do experiment with e-cigarettes, there is currently no evidence that they subsequently progress to cigarette smoking.”

Sieg said she’s also a study by Theodore Wagener, Ph.D., assistant professor of general and community pediatrics at the University of Oklahoma Health Sciences Center in Oklahoma City. In a survey of 1,300 college students, average age 19 years, about tobacco and nicotine use, 43 students said their first nicotine product was an e-cigarette, and of that group, only one person claimed to go on to smoke regular cigarettes.

However, Wagener’s numbers are minuscule compared with those in a study that Glantz co-wrote, which found that e-cigarettes act as a gateway to nicotine addiction. Appearing in the July 2014 issue of JAMA Pediatrics, this study was based on answers from 17,353 U.S. middle and high school students in 2011 and 22,529 in 2012 who took part in the National Youth Tobacco Survey both years.

“The emerging data is showing rapid market penetration of e-cigarettes among never cigarette smokers, particularly low-risk kids. While about 10%–20% of kids using e-cigarettes have never smoked a cigarette (we believe) there is high dual use among kids. It is highly likely that many of these kids started with e-cigarettes and added cigarettes later.”

Denise Kandel, Ph.D., professor of Sociomedical Sciences in Psychiatry at Columbia University, said senior investigator, Howard Hughes Medical Institute, Chevy Chase, Maryland who proposed the gateway theory of drug addiction years ago, said the main concern shouldn’t be whether e-cigarettes are better for the respiratory system, but rather how nicotine affects the developing brain. In the Kandels’ latest study (N. Engl. J. Med. 2014:371:932–43; doi:10.1056/NEJMa1405092) Denise Kandel wrote, “Nicotine acts as a gateway drug on the brain, and this effect is likely to occur whether the exposure is from smoking tobacco, passive tobacco smoke, or e-cigarettes.”

Denise Kandel said she’s concerned that “the behavior is outpacing the science, and this is a serious problem. There is a tremendous increase in the use of these cigarettes, and there’s very little research carried out to address the basic questions that we need answers for. Could it possibly undo 50 years of public-health work to reduce nicotine addiction? I think so.”

Myers echoes a similar sentiment and adds that it is imperative that the U.S. Food and Drug Administration speed up enactment of its proposed set of rules issued last April.

“This is truly using America’s youth as guinea pigs in one of the largest experiments ever conducted, with no rules,” he said. “While we debate whether the large numbers of youth who are using e-cigarettes will go on to using cigarettes, basic public health principles say we should be doing everything possible to prohibit marketing and sale of these products to kids.”

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Checkpoint Blockade Immunotherapy for Cancer Comes of Age

By Vicki Brower

Cancer immunotherapy—Science’s 2013 breakthrough of the year—took off in 2014. Almost weekly, reports described patients on immunotherapies living longer than those taking combinations of chemotherapy and targeted drugs.

One immunotherapy has reenergized the field. Ipilimumab (Yervoy), the first checkpoint inhibitor developed, approved in the U.S. in 2011, is the culmination of more than two decades of research. Ipilimumab is an antibody that inhibits cytotoxic T lymphocyte-associated protein 4 (CTLA-4), an immune checkpoint receptor found on T cells. CTLA-4 normally acts as a brake on the immune system’s ability to unleash T-cell attack on cancer cells. But ipilimumab releases the brake, allowing T cells to attack cancer.

About 20% of patients with advanced melanoma who take the drug live 3 years or longer, whereas previously median survival was 7–8 months. However, ipilimumab works well only in one-fifth of patients. Scientists recently discovered the reason and, for the first time with any immunotherapy, could predict who will benefit. Jedd D. Wolchok, M.D., Ph.D., chief of the melanoma and immunotherapeutics service at Memorial Sloan-Kettering Cancer Center in New York, and team analyzed tumor samples from 64 patients treated with ipilimumab or a similar drug, tremelimumab (N. Engl. J. Med. 2014:371:2189–99; doi:10.1056/NEJMoa1406498). The researchers discovered an association in many, but not all, patients, between mutational load and clinical benefit.

“We then asked, What did the immune system ‘see’ to evoke a reaction in responders?” Wolchok said. A genetic signature in these patients caused tumors to express new antigens (neoepitopes) that T cells recognize and become more reactive to. The researchers then validated the signature in a second set of 39 melanoma patients treated with anti–CTLA-4 antibodies. The reactive antigens are similar to many viral and bacterial antigens to which the body normally reacts as well.

“These data suggest that the neoepitopes in patients with strong clinical benefit from CTLA-4 blockade may resemble epitopes from pathogens that T cells are likely to recognize,” Wolchok said.

“This is the first reliable way to predict which patients with melanoma will respond to ipilimumab, which will help guide upcoming trials and therapy design,” said coauthor Timothy A. Chan, M.D., Ph.D., vice chair of the radiation oncology department and director of the