PEDIATRIC ALLERGY, IMMUNOLOGY, AND PULMONOLOGY
Volume 28, Number 1, 2015

DOI: 10.1089/ped.2015.0490

REVIEW ARTICLE

Electronic Cigarettes: Vulnerability of Youth

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Electronic cigarettes have become popular and are heavily promoted as a safer cigarette and an aid to quit smoking. Although they may have value in reducing cigarette use among smokers, they are of limited value in smoking cessation and pose many problems, particularly in children. Nicotine is highly addictive and affects virtually all cells in the body. It is particularly harmful to developing brains and other organs. The electronic nicotine delivery systems are largely uncontrolled and safety risks are manifold. Initiating nicotine use and increasing dependence in the population may be linked with increased tobacco and other addictive substance abuse even if the individual electronic cigarette delivers less harm than a combustible cigarette does.

Introduction

Electronic cigarettes are one of the world's fastest growing products and have overtaken traditional cigarette use among school children in a recent United States government survey. In 2014, 8.7% of 8th graders, 16.2% of 10th graders, and 17.1% of 12th graders used electronic cigarettes within the month of the survey, whereas only 1.4% of 8th graders, 3.2% of 10th graders, and 6.7% of 12th graders smoked combustible cigarettes.[1] With this trend, electronic cigarettes are on pace to become more popular than combustible cigarettes in the not-too-distant future.

What Are They and How Did They Come to be?

Electronic cigarettes are devices with a liquid cartridge container, batteries, a heating element, and electronic controls. When activated, they vaporize and can deliver an inhalable liquid. The vapor usually contains nicotine, propylene glycol, flavorings, and other substances. The nicotine is derived from the tobacco plant. Although called electronic cigarettes, they need not look like a cigarette and come in many forms. For example, devices that appear like a USB flash drive could be used by persons trying to hide their nicotine use. The devices are also termed electronic nicotine delivery systems because they are designed to deliver nicotine. Yet, this is not fully correct either, because the inhaled liquid may not contain nicotine. To enhance the experience, flavorings are added. A massive number of flavorings are available, which can give the vapor a candy or fruity taste.

In the 1960s, tobacco companies experimented with adjusting the nicotine content in cigarettes—the amount of nicotine delivered can be altered by adjusting the pH of the product. In 1971, Lichtneckert and Lundgren developed a nicotine gum for Swedish submarine sailors to prevent nicotine withdrawal. This was later made for medicinal use for smoking cessation and was eventually marketed as Nicorette®.

In 2003, Hon Lik, a pharmacist in China, first developed the electronic cigarette. By 2007, electronic cigarettes had reached Europe and North America, and sales soon skyrocketed.[2] In 2009, only 16% of Americans were aware of electronic cigarettes, but by 2010, 32% were aware of them.[3] By 2012, this had increased to 73% of Americans, 54% of the British, 40% of Canadians, and 20% of Australians.[4] Awareness in developing countries was slower. In 2011, only 11% of Indonesians were aware of them and 0.3% used them.[5] Currently, electronic cigarettes are a multibillion dollar business and nearly everyone in the United States and Western Europe is aware of them. By 2012, more than 2.5 million Americans had used them.[6]

Who Uses Them and Why?

Early surveys showed that the main users were white young persons with higher incomes. About 70% were smokers or former smokers; 39% who tried them were current users.[4] Exposure to advertising was an important factor in trying and using them.[7] More than 80% of users felt they were less harmful than combustible cigarettes and three-fourths of individuals started them to reduce smoking or avoid relapsing. Smokers or former smokers often began electronic cigarettes to deal with nicotine craving or withdrawal symptoms. Others stated that they used them because they were cheaper than smoking tobacco cigarettes (57%) or could be used in situations where smoking was prohibited (39%). An average user, according a study by Etter and Bullen, took about 120 puffs per day and used about five refills per day; 97% of consumers used them to deliver nicotine.[8]

Although many smokers used electronic cigarettes to stop smoking, the record of electronic cigarettes for smoking cessation is poor. It was generally not different from a placebo.

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The studies also did not find a difference from medicinal nicotine patches, but the patches were often not used by the study participants.[4,9–11] In these studies, almost all individuals, including the controls, reduced combustible cigarette use. Recently quit smokers felt that electronic cigarettes were not associated with success.[12]

Youth Is the Growing Market

Among children in the United States, the use of electronic cigarettes more than doubled between 2011 and 2012, increasing from 3.1% to 6.8% for all students and from 4.5% to 10.0% for high school students. Current use went from 1.4% to 2.8% in high school students. By 2012, 1.78 M American teenagers had tried them. Of these, 160,000 (9.3%) had never tried combustible cigarettes.[13] By 2013, more than 90% of American high school students were aware of them; 25% had tried them and 12% were current users.[14] Caucasians, males, and current cigarette smokers were more likely to use them. Over half of the persons polled said that the electronic cigarettes were the first tobacco product they tried. Users preferred electronic cigarettes to combustible cigarettes. Sweet flavors were most popular. Current smokers usually started with nicotine-containing liquids, but never smokers more often started using electronic cigarettes without nicotine. Sources of information for users included television advertising, social media, and peers.[14] Flavorings, which appeal to children, have been banned (except menthol) for combustible cigarettes, but not for electronic cigarettes.

Today, in the United States, the greatest increase in the percentage of current users is in the 18–24-year-old age group (14%) compared with 25–44 years (8.6%), 45–64 years (5.5%), and over 65 years (1.2%). Although smokers are most likely to use the product, a third of electronic cigarettes users are never smokers, indicating that electronic cigarettes may cause nicotine addiction instead of being a cessation tool.[15]

Marketing of e-cigarettes has been directed at the young adults and children according to the United States Food and Drug Administration documents.[2] Electronic cigarette manufacturers advertise heavily through social networking systems and avoid using the word cigarette because of its negative connotations. Teenagers may deny using electronic cigarettes, but vape, for example, on a nicotine-containing, flavored hookah pen. This may underestimate self-reported electronic cigarette use in surveys. The Stanford Research into the Impact of Tobacco Advertising website shows how many of these advertisements are designed to appeal to children (http://tobacco.stanford.edu/tobacco_main/index.php).[16]

Children and young adults are more likely than older individuals to have unplanned purchases in response to point-of-sale advertisements. Youth are more attuned to the cost and respond to price-reducing coupons and promotions. Tobacco imagery in film is a well-established influence on youth. In the United States, more than 90% of persons smoke their first cigarette before the age of 18.[17] Youthful experimentation and susceptibility to the brain-modifying effects of nicotine may be the start of a lifelong addiction.

DiFranza et al. followed sixth graders prospectively for 4 years to study nicotine addiction using standardized methods. They found that the most susceptible children (10%) lost their autonomy over tobacco within 2 days of nicotine use, 25% lost their autonomy within 30 days of inhaling their first cigarette, and half had lost autonomy by the time they were smoking seven cigarettes per month. The average salivary cotinine level of the current smokers was 5.35 ng/mL, which is below the level that distinguishes active from passive smokers. This study showed that nicotine withdrawal symptoms and failed attempts to quit precede daily smoking and occur with low levels of tobacco use in children.[18]

Among middle school and high school students, the use of e-cigarettes was associated with a higher combustible cigarette smoking rate and less chance of abstinence. Teenagers who tried even one puff of an electronic cigarette were more likely than those who had never tried them to become regular cigarette smokers.[19]

Are They Safe? The Premise

Electronic cigarettes are widely promoted as a safe alternative to smoking and even many health advocates and medical journals declare how much safer they are than combustible cigarettes. Their premise is that electronic cigarettes produce less tar than combustible cigarettes, and tar causes emphysema, bronchitis, and cancer. Therefore, electronic cigarette use is a harm reduction strategy compared with combustible cigarettes. There are several problems with this reasoning: (1) the comparator, tobacco, is the most deadly substance to which humans are commonly exposed; (2) it assumes that electronic cigarettes are well-manufactured regulated products; (3) it ignores nicotine and its harmful effects; (4) it assumes that the harms of electronic cigarettes are known; and (5) it does not account for population effects, including the potential harm to nonsmokers.

The comparator, tobacco, is the most deadly substance to which humans are commonly exposed

Any product should compare well against tobacco. Tobacco is the world's most lethal toxin. It kills about 6,000,000 people each year. About 600,000 are from indirect smoke. It kills up to half its users and causes $500 billion in economic damage each year.[20] Using tobacco as a comparator is only valid for weighing, quitting, or reducing tobacco consumption; it is not a valid comparison for someone starting to use nicotine.

The major producers of electronic cigarettes are the tobacco companies. Tobacco companies have a long deceitful history of promoting their products under healthful disguise.[21] These companies convinced the public that filtered cigarettes and later light cigarettes were healthier. There was no scientific basis for these claims. An important other question to ask is, ''Where is the harm coming from?'' Of course, it is tobacco, and tobacco use is declining in many parts of the world. The logical argument would be to increase efforts to reduce tobacco use and not risk increasing the world's addiction to nicotine.

It assumes that electronic cigarettes are well-manufactured regulated products

There are hundreds of electronic nicotine delivery products; many are poorly regulated and often lack production standards. This lack of regulation affects safety. In many places, electronic cigarettes are uncontrolled. They are not licensed as drug or tobacco products. There is no restriction on sales to minors and no control of advertisements and promotions. There is no requirement to state the ingredients and their quantities. The ingredients may vary with products and with different batches of the same product. The lack of

requirements for uniform ingredients and quality control violates best manufacturing practices. Variation in the nicotine doses delivered could cause serious toxicity.

Many studies have found contaminants, such as fungi and bacteria, toxic metals, silicates, and carcinogens, which could have serious health consequences even in low levels.

The lack of child-proof containers for candy-flavored products poses a serious threat to young children. Sophisticated advertising, which targets youth, lack of tax, and internet availability make electronic cigarettes easily accessible to youth. The availability of nicotine and flavorings allows anyone to make their own solutions at home. The familiarity of nicotine masks the risk of careless handling of this toxic substance. The fluid chambers could also be filled with cannabis oil or a cocaine solution to deliver these drugs unnoticed.

It ignores nicotine and its harmful effects

Nicotine is a highly active chemical that affects many bodily cells, pathways, mediators, and tissues. It has a complex pharmacology that includes both stimulating and desensitizing receptors, which often result in unpredictable actions, for example, its effect on the heart rate. Nicotine excites sympathetic ganglia and paralyzes parasympathetic ganglia, which increase the heart rate, but at a different level, it paralyzes sympathetic ganglia and excites parasympathetic ganglia, which decrease the heart rate. Nicotine affects the carotid and aortic bodies, which also affect the heart rate. It affects blood pressure by its effect on baroreceptors, which in turn affects the heart rate. And, nicotine causes epinephrine release from the adrenal, which also affects the heart rate and blood pressure.

The effect of nicotine is more complicated in neural tissue than any other organ, with its stimulation and suppression of autonomic ganglia. It stimulates the central nervous system. At low doses, it is a weak analgesic, but at high doses, it causes tremors and seizures. It stimulates respiration, but at large doses, it causes respiratory failure from central and peripheral blockade and respiratory muscle failure. Nicotine causes the release of excitatory amino acids, such as dopamine, but chronic use causes an increase in nicotine receptors and therefore tolerance. Nicotine increases the tone of the neurotransmitter systems of dopamine, norepinephrine, acetylcholine, glutamate, vasopressin, serotonin, gamma-aminobutyric acid, and beta-endorphins.

Nicotine withdrawal results from α4ß2-receptor desensitization in proportion to dependence. Nicotinic acetylcholine receptors are present in all areas of the mammalian brain, but addiction is located primarily in the mesolimbic dopaminergic system and locus ceruleus, areas of critical importance for survival and motivational behavior, as well as influencing the cognitive processes.

The effects of nicotine on the cardiovascular system are also diverse. In naïve subjects, nicotine, given as 4-mg gum, increases the heart rate by 10–15 beats per second, increases blood pressure by 5–10 mmHg, increases cardiac output, and increases myocardial contractility.[22] It constricts skin blood vessels and dilates muscle blood vessels. It increases myocardial oxygen demand, which increases the need for coronary blood flow, but its α-adrenergic effects decrease coronary blood flow, which could result in ischemia. Release of catecholamines causes endothelial cell injury and lipolysis. Free fatty acids are toxic to the endothelium, although it appears that the nicotinic acetylcholine receptor signaling may be more responsible for the atherogenic effect of nicotine.[23]

Nicotine affects essentially every organ through neuroeffector, chemosensitive, sympathetic, and parasympathetic activities, blood flow, endothelial cell injury, epinephrine and cortisol release, and lipid effects. Nicotine causes peptic ulcer and gastrointestinal cancers.[24] It affects bone metabolism and fracture repair.[25] Nicotine is associated with erectile dysfunction and decreased sexual arousal.[26] It interacts with several drugs, such as theophylline, caffeine, imipramine, pentazocine, levodopa, and oral contraceptives, through enzyme induction and other drugs through its effect on organ function, such as delayed gastric emptying and the effects on blood pressure and heart rate, already mentioned.

Nicotine has major effects on development, especially on the neurologic system,[27] and it is directly toxic to chromosomes of fetal cells.[28] Nicotine contributes to the decreased lung function and increased respiratory infections that occur in the children of smoking mothers.[29] Wang et al. fed 1% nicotine to pregnant mice and found an increase in the neuroepithelial bodies in the fetal and newborn pups.[30] These structures are important for the development of branching and the full arborization of the bronchial tree. Neuroepithelial cells are the cell type involved with small cell carcinoma of the lung. Maritz reported that nicotine caused DNA changes that affect lung growth and maintenance of structure, resulting in smaller lungs with increased cell turnover and type II cells.[31] Fetal lungs exposed to nicotine age more quickly and have lifelong effects on the offspring.[32] Nicotine may have a negative impact on adolescent brain development and may increase the risk for nicotine addiction.[13]

Exposure to nicotine *in utero* causes decreased birth weight, prematurity, neonatal morbidity, and mortality, including sudden infant death syndrome.[33] It can also cause adult disease and has been linked to impaired fertility, type 2 diabetes, obesity, hypertension, atherosclerosis, aortic aneurysm, neurobehavioral defects, and respiratory dysfunction later in life.[34]

Nicotine is highly toxic with a lethal dose of 0.5–1.0 mg per kg body weight in adults and probably as little as 0.1–0.2 mg per kg body weight in children.[35] A refill may contain up to 24 mg of nicotine. Children are clearly more susceptible than adults. Cutaneous nicotine toxicity, green tobacco sickness, has been reported in children working with the tobacco leaves.[36]

A small child who swallows the flavored contents of a nicotine cartridge may be at risk of lethal nicotine poisoning.[37] Pregnant women, nursing mothers, people with heart disease, and the elderly are also more sensitive than the general population. In the United States, the Centers for Disease Control and Prevention tracks Poison Center calls. In September 2010, calls for nicotine poisoning averaged 1 per month. In February 2014, they averaged 215 calls per month; 51% were for children between 0–5 years of age. The toxicity breakdown was inhalation 16.8%, eye 8.5%, skin 5.9%, and ingestions 68.9%.[38]

It assumes that the harms are known

Electronic cigarettes are new products that have not been adequately studied. The toxicity of nicotine is known, but many other things are unknown. There is limited information about the effects of nicotine, as delivered through electronic nicotine delivery systems, on lung function.[39]

Users of electronic cigarettes may inhale differently than smokers of combustible cigarettes. The nicotine effect partly results from the temperature to which it is heated. This varies between combustible cigarettes and electronic cigarettes and between different delivery systems. A combustible cigarette delivers nicotine for a fixed time—until the cigarette is finished, but electronic nicotine delivery systems continue to make nicotine available as long as the user is inhaling it. Since nicotine satisfaction may depend on the rate of absorption, a delay in its effects on the brain could result in overdosing.

The safety of inhaled flavorings is largely unknown. Products approved for flavoring food cannot be assumed to be safe if inhaled. Lethal bronchiolitis obliterans developed in workers at a microwave-popcorn plant who inhaled the butter flavoring, diacetyl.[40] Workers at flavoring manufacturing facilities had respiratory symptoms and lung function abnormalities related to their work.[41] Asthma can arise from exposure to food flavoring.[42]

Passive exposure to inhalation of the vaporized fine and ultrafine inhalable droplets and particles, nicotine, and cancer-causing substances in indoor air may have significant adverse health effects.[43]

It does not account for population effects

The major concern of electronic nicotine delivery systems is that nicotine is a powerful addictive substance. The risk of new large-scale population addiction harkens the tragedy of tobacco use and cautions against endorsement of these products.

Gateway to Addiction

Kandel and Kandel recently reviewed how nicotine is associated with addiction to other substances.[44] Smoking cigarettes, almost always, precedes cocaine use, and those who smoked cigarettes when starting cocaine have a more difficult time quitting. Chronic nicotine use causes histone acetylation, which controls how DNA is activated. Histone acetylation changes the chromatin of the *FosB* gene, enhancing the promoter, *FosB*, in the corpus striatum of the brain. The striatum is essential for establishing addiction to most drugs. The *FosB* pathway is closely tied to CREB-1, a gene transcription response element that is important in switching short- to long-term memory and is part of the addiction mechanism. Chronic nicotine use causes synaptic plasticity in nucleus accumbens, which is involved in integrating rewarding (dopaminergic) and excitatory (glutamate) neurons.[44] The nicotine cholinergic receptors influence addiction potential. Chronic exposure of these receptors to nicotine generates tolerance. Brains of children and adolescents are more susceptible to the risk for nicotine addiction.[13]

Normalization of Smoking

The most powerful tools to reduce tobacco use have been increased taxes, bans on smoking in public places, and denormalizing its use. Denormalizing tobacco use is a cultural change from one where cigarette smoking was accepted and an encouraged behavior to one where it is considered abnormal and unacceptable. This powerful driver developed over many years by many activities, such as bans on advertisement and glamorous depiction of tobacco use in the cinema, negative advertisement, health warnings, and sustained activity of healthcare workers,[45] and nonprofit organizations advocating in many spheres. Regulating smoking mimics, such as candy cigarettes, is another example of a denormalizing tool. The hazard is that electronic cigarettes normalize this behavior. Glamorizing vaping euphemizes and disguises the willful ingestion of an addicting and highly toxic substance. The risk is that electronic cigarettes will create a new nicotine-dependent world similar to what tobacco did in the last century.

In conclusion, the benefit that may be gained by certain smokers in reducing the amount of combustible cigarettes they use must be weighed by the great potential of increasing nicotine addiction in the world. Youth are particularly vulnerable because of the effect of nicotine on developing neural tissue, risk of lifelong addiction, heavy and clever promotion by the industry, and the ease of access of these products.

Author Disclosure Statement

There is no external funding. There is no financial conflict of interest. Dr. Schraufnagel chaired the tobacco committee of the Forum of International Respiratory Societies (FIRS) in the development of its position article.

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Received for publication January 24, 2015; accepted after revision February 14, 2015.