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AHC Media

Electronic Cigarette and Nicotine Toxicity

The electronic cigarette industry and the limited knowledge of the products' health effects are newly debated topics, both nationally and internationally. This review attempts to summarize the most recent developments in the increasing popularity of electronic cigarettes, including their potential use as a tobacco cessation device, their health effects, their potential toxicity with inappropriate consumption, their role as a portal to other drugs, and their lack of adequate regulation.

Introduction

The first smokeless non-tobacco cigarette was actually patented in 1965.[1] Electronic cigarettes, also referred to as e-cigarettes or electronic nicotine delivery systems, were introduced to the United States market in 2007 after being developed in China in 2003. Advertised by manufacturers and websites as a smoking cessation aid and an alternative to tobacco use, the electronic cigarette market and "vaping" culture have grown exponentially in the past several years. Especially with stricter indoor tobacco laws being enforced, traditional cigarette smokers are looking to other methods for nicotine use in public establishments. Adolescents and young adults are being targeted specifically by electronic cigarette companies, generating a whole new generation of individuals potentially addicted to nicotine.

With the rapid increase in the utilization of electronic cigarettes and vaping, much attention is being paid to the short- and long-term health effects of this new trend. Little is known regarding the consequences of acute or chronic use on consumers and the secondhand effects of this new smoking fad. Concerns include the potential dangers of a highly concentrated nicotine product for accidental ingestion or intentional misuse. New research has also suggested that nicotine can serve as a "gateway drug" for more dangerous substances and addictive behaviors. In addition, the emergence of electronic cigarettes has presented a new method for inhalation of cannabinoids and other recreational drugs.

One area that remains controversial is the federal regulation of electronic cigarettes. At the present time, a uniform guideline for production and marketing of these devices does not exist on a national level, with regulation being difficult to enforce under poorly coalesced state laws.

Anatomy and Physiology of an Electronic Cigarette

Electronic cigarettes are battery-powered systems that deliver nicotine, propylene glycol, glycerol, distilled water, flavorings, and other chemicals by

EXECUTIVE SUMMARY

- E-cigarettes are not regulated in the United States and can therefore be legally sold and used by minors. They aerosolize nicotine and other flavorings, and can be used to deliver other drugs of abuse.
- Nicotine causes increased mental alertness, as well as mood enhancement and mild euphoria. It is also an appetite suppressant.
- Ingestion of nicotine in large amounts often leads to nausea and vomiting, thereby limiting toxicity.
- Nicotine toxicity includes bronchorrhea, wheezing, seizures, and rhabdomyolysis. Use of succinylcholine in patients with nicotine toxicity is not recommended.

inhalation of aerosol. The fundamental difference between an electronic cigarette and a traditional cigarette is the aerosolization of nicotine and other chemicals rather than combustion of tobacco. Electronic cigarettes are composed of a battery, a heating element, a vaporizing chamber, and a solution cartridge. The cigarette may have a refillable solution tank or have a disposable cartridge that is pre-filled. The battery supplies electrical current to the heating element, creating sufficient temperatures to aerosolize the liquid nicotine solution. The aerosolized nicotine remains in the vaporizing chamber until the consumer inhales or presses a button, depending on the design.[2]

Original electronic cigarettes were meant to resemble the appearance and feel of traditional cigarettes, but newer designs often do not.[3] Newer models have more advanced technology like electronic chips to adjust the heating element's voltage and atomizers, which more efficiently convert the liquid inhalants to gas form.[4] The latest models include a voltage potentiometer that can control the amount of aerosol produced, allowing the individual to choose the desired amount of inhaled nicotine.[2] Innovative designs also allow recharging of the battery through a USB computer drive.

Electronic cigarette refill solution has a fairly short list of ingredients, including nicotine, water, propylene glycol, glycerol, and various flavor additives. Solution for electronic cigarettes can be sold in a pre-filled container or with a refillable cartridge that comes in various volumes and concentrations of nicotine.[5] Nicotine, the primary psychotropic ingredient, gives the user a familiar high consisting of increased mental alertness, mood enhancement, appetite suppression, and euphoria.[6] From a toxicological perspective, the concentrated nicotine liquid refills can pose a problem for accidental ingestion by a child or intentional misuse. This will be examined further in the section about nicotine toxicity.

Propylene glycol, well-known for its role as a diluent in intravenous phenytoin and diazepam, comprises about 90% of the electronic cigarette solution.[7] Glycol and glycerin are commonly used in the theater and aviation industries to create artificial smoke. The aerolisolization of these liquids generates the "smoke" that is inhaled by electronic cigarette users and potentially bystanders.[8] Other medications, including rimonabant for appetite suppression and amino-tadalafil for sexual stimulation, have been added to some nicotine solutions.[9] The Food and Drug Administration (FDA) has released several warnings, chastising electronic cigarette companies for manufacturing products with these components.[7] The only tobacco found in electronic cigarettes is the minute amount present in the tobacco flavoring, making some question the FDA proposal of regulating these devices as "tobacco products" under the Federal Food, Drug, and Cosmetic Act.[2] The debate on how to classify these products is likely to continue as electronic cigarettes were developed — and continue to morph — faster than governmental regulation can keep up.

Characteristics of Vapors

In general, electronic cigarette users are men, younger, more educated, and come from a higher socioeconomic status when compared with nonusers.[3,9] These consumers are more likely to identify smokeless cigarettes as a healthier alternative to combustible tobacco, thereby increasing their usage.[1] Interestingly, though, most electronic cigarette users also smoke traditional tobacco cigarettes and are called "dual users." The Centers for Disease Control and Prevention (CDC) states that 78.6% of adults who smoked electronic cigarettes in the past 30 days were also current tobacco users.[10] It is not entirely clear whether dual users are tobacco smokers who have unsuccessfully tried to quit smoking or have intentionally chosen to use both styles of cigarettes. Recent epidemiological investigations suggest that many consumers intend to use electronic cigarettes to help with tobacco cessation but instead end up utilizing both.[11]

Increasing Popularity

Secondary to aggressive advertising and ever-increasing availability of product, the electronic cigarette market has skyrocketed during the past several years. From 2009 to 2013, the percentage of adults in the United States who had tried electronic cigarettes multiplied from 0.6% to 8.1%.[3] Smaller online companies are being joined by big tobacco manufacturers in the expanding billion-dollar electronic cigarette industry. Companies like Newport, Marlboro, Camel, and Philip-Morris have all generated their own versions of electronic cigarettes for mass consumption.[2] In 2013, this industry reported an estimated $2 billion in sales, with a predicted increase to $10 billion by the year 2017.[3] Wells

Fargo anticipates electronic cigarette sales margins will surpass those of traditional tobacco by 2017, with smokeless cigarette consumption exceeding conventional cigarettes by 2023.[12]

Increased Use in Adolescents

One of the most concerning trends in the electronic cigarette fad is the increasing popularity in the middle school and high school demographic. The CDC announced that between 2013 and 2014, the utilization of electronic cigarettes in this age group tripled. About 13.4% of high school students and 3.9% of middle school students reported using electronic nicotine delivery systems in the past 30 days.[13] Public health officials worry that electronic cigarettes will serve as a gateway for nicotine addiction and tobacco consumption in youth and nonsmokers, as well as a portal for reintroduction of tobacco to past users.[14] Even more alarming is the usage of electronic cigarettes for inhaling marijuana and synthetic cannabinoids like K2 and spice. These illegal substances can be converted into a concentrated liquid that can be poured into electronic cigarette refill tanks and easily aerosolized for human use.[15]

The rise in the use of electronic nicotine devices in adolescents and young adults is not surprising when considering the advertising techniques of manufacturers. A recent study by Duke et al in *Pediatrics* looked at trends in exposure of youth and young adults to electronic cigarette advertising from 2011 to 2013. During this short two-year period, the exposure to electronic cigarette ads skyrocketed in both youth and young adults, increasing by 256% and 321%, respectively.[16] Advertising for electronic cigarettes has centered on social media and other Internet conduits. While focusing largely on newer mediums, electronic cigarette manufacturers also utilize traditional media to market their devices. Television, radio, and print publications are traditional avenues long banned for tobacco cigarettes but still open for the vaping market.[17]

Electronic cigarette companies are also borrowing techniques used previously by large tobacco corporations to advertise and increase product consumption by young users. The 2012 Surgeon General's Report "Preventing Tobacco Use Among Youth and Young Adults" describes historically proven techniques to attract youth, such as candy-flavored liquid, celebrity advertisements, support from sports and music personalities, and themes relevant to young people.[18] Electronic cigarettes come in more than 7000 flavors, including cotton candy, gummy bear, bubble gum, and other flavors that appeal to children and young adults.[19] Because of the sheer escalation in exposure to electronic cigarettes, as well as advertising and products directly aimed at them, it becomes easier to explain the dramatic increase in adolescent and young adult use of nicotine delivery products.

One alarming and novel habit is the use of electronic cigarettes by consumers in inconspicuous locations. Unlike traditional cigarettes, where the use of the product saturates an area with an odor, making smoking difficult to conceal, electronic cigarettes are essentially odorless, and vapors dissipate quickly. Adolescents are vaping in schools, even in the back of classrooms. Even if observed, it is almost impossible to determine exactly what substances are inhaled. The trend is not confined to teenagers in schools. An emergency physician in Florida reported that patients in his hospital are using electronic cigarettes at bedside. With no way to regulate what consumers are vaping or where they are using, teachers, physicians, and law enforcement officers are stuck in a difficult position.[15]

Explanations for Increased Popularity

One major proposed explanation for the increase in the vaping culture is the highly touted health benefits of electronic cigarettes. Advertisements claim a healthier alternative to smoking, with decreased risk for cancer and the ill effects of tobacco smoke to users and secondhand bystanders. Electronic cigarettes are publicized as tobacco cessation products. In fact, the majority of electronic cigarette users do so to assist in tobacco smoking cessation, stating that vaping decreases the craving for nicotine.[9] As will be examined in much more detail, these are statements are not adequately scientifically studied or validated.

In a 2011 study by Etter et al, the authors concluded that concerns about the price for traditional tobacco could be another potential contributing factor to the rise in recent electronic cigarette popularity. Study participants spent an average of $33 per month on electronic cigarettes compared to $150 to $200 on traditional cigarettes. Nicotine replacement therapy, if taken at the dose recommended, can cost about the same as smoking one pack per day.[9] If used alone, electronic nicotine delivery devices might offer an economical alternative to traditional smoking. However, the most common pattern of consumption is the dual use of tobacco and electronic cigarettes, thereby eliminating or, at a minimum, significantly reducing the cost effectiveness of this habit.

Electronic cigarette users cite social convenience as another explanation for their attraction to this new trend. Some use e-cigarettes to avoid exposing others to smoke.[9] In addition, with modern tobacco laws, consumers dislike having to step outside restaurants and bars to smoke traditional cigarettes. Companies advertise the use of their electronic cigarettes in smoke-free public places, including bars, restaurants, hotels, offices, and airplanes.[1] Electronic cigarettes offer the potential to "smoke" socially in some smoke-free bars or restaurants if indoor use is permitted at that specific establishment.

Electronic Cigarette Health Effects

The safety of electronic cigarettes is in question with the rampant upsurge in their use in the United States and worldwide. The inhalation effects of electronic cigarettes on consumers and "secondhand vapors" is obviously

based on the number of devices in use, climate, air flow, room size, etc.[8] To investigate the potential danger and toxicity of these novel devices, researchers are now scrutinizing the contents of the refill liquid and vapors, short-term health consequences, and longer-term health effects.[3]

Because of the lack of any regulation by the FDA or other governmental agency, however, it is difficult to make broad statements regarding the hazards of electronic cigarette use. An unregulated market has resulted in inconsistent ingredients and inaccurate labeling. Additionally, with the recent introduction and surge in electronic nicotine delivery systems, it is difficult to ascertain long-term health effects, as few individuals have utilized these products for a prolonged time period.[20]

Several initial studies discovered toxic chemicals in electronic cigarette vapor, although the concentrations were much less when compared with tobacco smoke. One 2013 study by Goniewicz et al investigated noxious components like formaldehyde, acetaldehyde, nitrosamines, heavy metals, and volatile agents. They found that these toxic compounds were present in atomized electronic cigarette vapor, although at levels nine to 450 times less than in traditional cigarette smoke.[21] At the very least, this gives the impression that electronic cigarettes might decrease exposure to the dangerous carcinogens present in tobacco smoke.

Conversely, a recent study published in *Reproductive Toxicology* demonstrates the potent cytotoxicity of electronic cigarette liquids and vapors. Human embryonic stem cells, pulmonary fibroblasts, and murine neural stem cells were exposed to electronic cigarette extracts. Certain flavors were lethal to all cell lines, while others were intermittently toxic, again revealing the potential unreliability of products in an unregulated market. Researchers noted that cellular toxicity was secondary to concentration and quantity of flavor additives instead of nicotine. Additionally, immature cell lines were much more influenced.[22] This is important in light of the increased use of electronic cigarettes in adolescents.

With these conflicting data, the CDC warns consumers to be cautious. Manufacturers of electronic cigarettes state that using propylene glycol, glycerin, and chemical flavors in their vapor fluid is harmless, as they fall under the FDA classification for compounds "generally recognized as safe." This status pertains to food additives, though, and cannot be extrapolated to use in inhalational agents. The CDC maintains that the impact of inhaling these agents is not currently known.[10] Additional research is vital to determine the toxicity of electronic cigarette flavor additives and other components.

Short-term Effects

The negative short-term consequences of electronic cigarettes affect the respiratory system, augmenting blood nitrous oxide levels and total lung resistance. Use of electronic nicotine delivery devices can increase heart rate and blood pressure, leading to potential adverse cardiac events in patients who have cardiovascular disease or significant risk factors.[23] A recent study investigated the immediate effects of tobacco compared to electronic cigarettes on coronary artery function, assessed by echocardiogram. Researchers measured the flow velocity reserve of the left anterior descending (LAD) artery, as well as change in arterial resistance. Use of tobacco cigarettes was correlated with a 16% decrease in LAD flow velocity and a 19% increase in resistance to blood flow. No difference was noted in these hemodynamic measurements after electronic cigarette use. Baseline carboxyhemoglobin levels were elevated in chronic tobacco smokers compared to electronic cigarette users. Tobacco smokers had additional elevation of carboxyhemoglobin after use, while vapors had no change in their levels.[24] There have not been any studies performed to date regarding electronic cigarettes and their effects on clot formation, platelet function, and atherosclerosis.[25]

Long-term Effects

The harmful long-term effects of electronic cigarettes are not currently well known. The Center for Tobacco Products, a branch within the FDA, collects data on adverse events reported by consumers. Electronic cigarette users relayed complaints as serious as hospitalization for pneumonia, congestive heart failure, seizure, disorientation, and partial thickness burns to the face after explosion of the smoking apparatus.[26] Other case studies describe occurrences of atrial fibrillation and exogenous lipoid pneumonia after electronic cigarette use. Both of these problems, however, improved after users abstained from nicotine delivery devices.[27,28]

Secondhand Vaping Effects

Similar to traditional tobacco cigarettes, electronic cigarettes create secondhand effects for bystanders. From 2012 through 2014, 29% of adverse event reports received by the FDA regarding electronic cigarettes were by non-users. These were related to passive vapor exposure and injury sustained with the product overheating or exploding. Most commonly, bystanders reported respiratory symptoms such as cough, shortness of breath, respiratory tract irritation, asthma exacerbation, and pneumonia.[29] While the effects were much less in bystanders when compared to those who were actively vaping, they were still reliably present.[30] Secondhand exposure to electronic cigarette vapor has the potential to subject nonsmokers to nicotine, particulate matter, and toxic chemicals, although at a much lower concentration than with traditional cigarettes.[1]

Further studies are warranted to determine the health consequences on electronic cigarette users and second-hand vapors. The 2014 Surgeon General's Report "The Health Consequences of Smoking — 50 Years of Progress" recognized and commented on the importance of determining the health hazards of long-term nicotine replacement therapy and other "non-combusted sources of nicotine"

like electronic cigarettes.[20] With this rapidly expanding new and youthful market, continued research into future health consequences will be paramount.

Electronic Cigarettes and Tobacco

Useful for Tobacco Cessation? Several FDA-approved nicotine replacement therapies are on the market and have been scientifically proven to help aid smoking cessation. Therapeutic gum, lozenges, transdermal patches, and inhalers provide various concentrations of nicotine to reduce craving for cigarettes. Nicotine receptor partial agonists like varenicline (Chantix) and cytisine have also been shown by multiple randomized controlled trials to decrease nicotine cravings. Varenicline enhances the likelihood of successful smoking cessation but also increases the risk for depression and suicidal ideation.[6]

Most people state that help with smoking cessation is the primary reason for initially using electronic cigarettes.[20] Manufacturers suggest the positive health potential of e-cigarettes. However, in 2012 to 2013, the majority of adults who had used electronic cigarettes in the past 30 days (76.8%) were also current traditional smokers.[10] Instead of actually utilizing electronic cigarettes in place of tobacco cigarettes, consumers are now "dual users," inhaling vaporized nicotine in places where smoke-free laws preside.

Conflicting data exist about the efficacy of electronic cigarettes for smoking cessation. The largest study to date is a randomized controlled trial of 657 patients, comparing electronic cigarettes to nicotine patches. Adult patients were randomized into an electronic cigarette group, a nicotine patch group, or a placebo electronic cigarette group (nicotine absent). The researchers found that electronic cigarettes were "modestly effective" in assisting smokers with quitting, even without nicotine. When exhaled carbon monoxide was measured after six months, smoking cessation was more successful in the electronic cigarette group (7.3%) when compared with the nicotine patch group (5.8%). The study participants in the placebo cigarette group had a verified quit rate of 4.1%. These findings, however, were not statistically significant. Additionally, there was inadequate statistical power to infer that electronic cigarettes were superior to nicotine patches or placebo cigarettes, likely related to the study's small sample size.[31] Dual use of both tobacco and electronic cigarettes persisted after six months for about one-third of the participants.[1] Although not sufficiently powered to suggest noninferiority of electronic cigarettes to traditional nicotine replacement therapies, this study paves the way for future investigations of this prominent new health topic.

Limiting Tobacco Use? Several studies have suggested that electronic cigarettes have the potential to assist chronic smokers in at least limiting their consumption of traditional tobacco cigarettes, if not assisting with complete cessation. The 2013 ECLAT study looked at the efficiency and safety of electronic cigarettes as an alternative to tobacco. This 12-month prospective randomized trial studied smokers who were not attempting to quit tobacco and had no desire to quit within the next 30 days. The participants were told that the electronic cigarette product was a healthier alternative to tobacco smoke and they could use this tobacco substitute as frequently as they desired. No other explicit instructions were given. The three groups of participants were supplied cigarette cartridges with varying nicotine concentrations (ranging from 0 mg to 7.2 mg). Both participants and researchers were blinded to which group received specific cartridges.

Following the use of nicotine-containing electronic cigarettes, participants were found to have a reduction in all of the following factors: exhaled carbon monoxide, cough, dry mouth, shortness of breath, throat irritation, and headache. Participants also reported less frequent nicotine withdrawal symptoms like anxiety, depression, irritability, hunger, and insomnia when compared to other cessation studies. They described enjoying the use of electronic cigarettes and having less frequent cravings for tobacco cigarettes.[32]

Most importantly, the use of electronic cigarettes significantly reduced the consumption of traditional tobacco, confirmed by exhaled carbon monoxide measurements. The decrease was seen in electronic cigarettes *both with and without nicotine*, suggesting secondary addictive properties of tobacco smoking beyond the effects of nicotine. The ECLAT study suggests that electronic cigarettes hold future potential for limiting tobacco use, but much more research is needed.

Electronic cigarettes may also contribute to the social aspect of decreasing tobacco consumption. A study of focus groups published in the *Journal of Addiction Science and Clinical Practice* compared the effectiveness of electronic cigarettes to traditional FDA-approved nicotine replacement therapy. Their conclusions suggest that electronic cigarettes were more successful in tobacco cessation compared to nicotine patches, gum, and inhalers. Researchers found that the behavioral and social aspects of vaping more closely mimicked conventional tobacco smoking, making it easier to transition to electronic cigarettes than other methods of cessation.[7]

In contrast, cross-sectional data from the National Youth Tobacco Survey in 2011 and 2012 assert that electronic cigarettes do not discourage use of conventional cigarettes but instead promote nicotine addiction.[33] Moreover, emerging evidence implies that baseline use of electronic cigarettes in adolescents and young adults is correlated with progression from tobacco abstinence to combustible cigarette smoking. A study published in 2015 in *JAMA Pediatrics* cites that electronic cigarette use was independently associated with advancement to combustible tobacco use in individuals aged 16 to 26 years, with an adjusted odds ratio of 8.3.[34] As with any new health topic, more studies are necessary to tease out the long-term benefits and dangers that

Table 1. Nicotine's Effects
• Increased alertness • Mood improvement • Appetite suppression • Anxiety reduction • Energy expenditure

Table 2. Signs of Acute Nicotine Toxicity
• Bronchorrhea • Wheezing • Salivation • Seizures • Vomiting • Paralysis

come along with electronic cigarette use.

Nicotine: An Overview

Nicotine is the main addictive component in tobacco and electronic cigarettes and can cause toxicity if used or abused at high doses. Other historical sources of nicotine toxicity include pesticides and dermal exposure by farmers handling tobacco plants.[6] Nicotine is well absorbed from the respiratory system, skin, intestines, and oral mucosa. Its absorption is increased in an alkaline environment, noteworthy when considering electronic cigarette refills are intentionally synthesized to be alkaline solutions.[1]

Physiologically, nicotine simulates the effects of acetylcholine, binding to parasympathetic nicotinic receptors. When smoking a cigarette or using an electronic smoking device, nicotine excites the reticular activating system, making the user more alert and awake. It also causes the release of dopamine in the brain, an important contributor to the highly addictive potential of nicotine. The release of several other neurotransmitters is induced by nicotine's presence, resulting in mood improvement, enhanced cognition, appetite suppression, increased energy expenditure, and reduction in anxiety.[6] (*See Table 1.*)

The CDC discourages the use of nicotine by pregnant women, children, and adolescents. Nicotine can impede the development of fetal brain and lung tissue, making the substance dangerous for a healthy pregnancy. Additionally, nicotine damages the maturation of still-developing adolescent brains and can interrupt the progression of healthy neurological pathways for acquisition of knowledge, attention, and vulnerability to addiction.[10] This becomes even more concerning when discussing the aforementioned trends of increased electronic cigarette use in middle and high school students.

Acute nicotine exposure, in doses seen with cigarette smoking, results in fine tremor, nausea, and enhanced gastrointestinal motility. Additionally, heart rate, respiratory rate, and blood pressure all increase. Chronic nicotine exposure has classically been known to cause cardiovascular damage secondary to release of catecholamines and vasoconstriction. It also stimulates angiogenesis, toxicity to neurons, and promotes development of some cancers.[6]

Nicotine Toxicity

Nicotine toxicity is marked by cholinergic manifestations, including increased salivation, vasoconstriction, nausea, vomiting, diaphoresis, and diarrhea. Patients might present with hypertension and pallor from peripheral vessel constriction. Headache, dizziness, ataxia, and confusion might be presenting neurological signs that accompany nicotine toxicity. Ingestion of nicotine gum or other nicotine products can cause irritation of the mouth and oropharynx. Because nicotine is metabolized quickly, the majority of symptomatic patients will recover completely within 12 hours. Patients with toxicity from transdermal nicotine patch therapy, however, must be observed for a longer time period. The patch can sometimes create a nicotine reservoir in the skin, allowing for continued absorption even after removal.[6]

The lethal dose of nicotine ranges from 10-60 mg in adults.[2] In children, it is estimated to be about 1-10 mg/kg.[35] Nicotine is quickly absorbed via the respiratory tract, skin, and mucous membranes.[2] It is broken down mostly by the liver to its inactive metabolite cotinine. Hepatic metabolism of nicotine is also inducible, making metabolism by chronic nicotine users much faster than in non-users. A lethal dose can cause seizures, respiratory failure secondary to paralysis, and death within minutes after ingestion.

The diagnosis of nicotine toxicity is a clinical one. Serum or urine nicotine or cotinine concentrations are not useful in the acute setting and may be positive coincidentally or secondary to chronic use. At baseline, chronic cigarette smokers will have a serum nicotine level of 30-50 mcg/mL.

The majority of patients will not necessitate formal medical evaluation and treatment of accidental or low-dose nicotine exposure. Symptomatic patients, however, should be assessed.[6]

Management of Acute Nicotine Toxicity

The acute nicotine toxic patient should be treated as all critically ill patients are, with airway management as the first priority. High levels of nicotine exposure can result in excess muscarinic signs, including increased salivation, wheezing, increased bronchial secretions, vomiting, and diarrhea. (*See Table 2.*) Patients should be treated with atropine to the clinical endpoint of drying up secretions and protecting the patient's airway. Intubation and mechanical ventilation may be required. Of note, succinylcholine metabolism will be delayed in nicotine toxicity, causing prolonged paralysis. If possible,

Table 3. Acute Nicotine Toxicity Management

- Use atropine to decrease respiratory secretions.
- Avoid succinylcholine in intubation.
- Use benzodiazepenes, then phenobarbital for refractory seizures.
- Watch for rhabdomyolysis.

succinylcholine should not be used as a paralytic agent for these patients. (*See Table 3.*)

Excess nicotinic receptor stimulation can result in seizures, respiratory and skeletal muscle fatigue and breakdown, and paralysis. First-line treatment for seizures in acute nicotine toxicity is benzodiazepenes, followed by phenobarbital. Fosphenytoin and phenytoin are *less* effective for all toxin-mediated seizures. Patients should be evaluated for rhabdomyolysis with urinalysis and total creatine kinase. If present, admission to the hospital and aggressive fluid resuscitation with normal saline is warranted to prevent renal failure.[36] Case reports of intentional liquid nicotine ingestion report patients presenting with cardiac arrhythmias, refractory seizures, and cardiopulmonary failure.[37] In the case of cardiac arrest, patients should be managed according to the Advanced Cardiac Life Support guidelines.

Nicotine in Electronic Cigarettes

The concentration of nicotine in most electronic cigarette refill liquids varies from 2-3% (20-30 mg/mL) but can reach 10% (100 mg/mL) in some brands. A 30-mL refill of fluid, even at the most dilute concentration, could potentially contain 600 mg of nicotine. If ingested all at once, this could easily prove deadly for a curious child or a suicide attempt. In fact, the first child fatality directly related to electronic nicotine devices was reported in late 2014. A 1-year-old child died in New York from presumed nicotine toxicity after ingesting bubble gum flavored electronic cigarette solution.[35] A second case report of a suicide occurred in 2013 when a 29-year-old Kansas man intravenously injected an electronic cigarette liquid refill solution. Initially found in asystole, the patient was resuscitated successfully but continued to have intermittent seizures. Multiple electroencephalographs were captured, showing brain wave patterns consistent with hypoxic injury.[38]

In comparison, the concentration of nicotine present in a tobacco cigarette fluctuates based on the brand, ranging from 10 mg in those advertised as "low nicotine" and 30 mg in some European products. Nicotine absorption is much less than this, on the order of 0.05-3 mg per cigarette, secondary to loss in secondhand smoke and remnants in the filter. Absorption also depends on the individual's rate and volume of puffing, length and depth of smoke inhalation, and the size of the remaining cigarette butt.[6]

A study done by Schroder and Hoffman showed that electronic cigarettes dispense less nicotine per puff when compared to traditional cigarettes. They comment, however, that an individual's smoking technique influences how much nicotine is distributed. Seasoned electronic cigarette smokers are able to alter inhalation methods to obtain higher serum nicotine levels, comparable to the levels of a traditional smoker.[39] Compared to older electronic cigarettes, newer designs show a plasma nicotine concentration increase of 35-72%.[40] With the continued goal of increasing the rate of nicotine delivery to the body, certain laboratories have replaced the use of nicotine salts in vaping liquid with free-base nicotine, allowing for an escalation in the body's absorption of nicotine. The result of these adaptations is concentrations of nicotine delivery on par with traditional tobacco smoking.[41]

Fortunately, the possibility of nicotine toxicity from using electronic and tobacco cigarettes appropriately is nearly impossible. The drug's inhaled effects take place within seconds. An acute excess of inhaled nicotine causes nausea and vomiting, limiting a user's further nicotine consumption.[6]

Poison Center Data

Despite the explosion of electronic cigarette use, traditional tobacco cigarettes are the most common cause of acute nicotine exposure and poisoning. Ingestion of one or more unsmoked cigarettes or three or more cigarette butts will result in symptomatic toxicity in children younger than 6 years old. This type of exposure is very uncommon and comprised less than 1% of accidental poisonings in children in the United States from 1983 to 2009.[6]

While traditional tobacco products continue to comprise the majority of nicotine poisoning, the prevalence of electronic cigarette toxicity is still relatively undocumented. Because of the novelty of electronic cigarettes, exposures to the actual device and nicotine solution were not recorded by U.S. poison centers until about five years ago. From June 2010 to September 2013, there were 840 pediatric exposures to electronic cigarettes or refill fluid, with children younger than the age of 6 years comprising 85% of the exposures. The number of monthly exposures began with fewer than five and increased to more than 140 per month in this time period. Luckily, the most commonly described symptoms were minor nausea and vomiting without severe toxic effects.[5]

In a recent *Morbidity and Mortality Weekly Report* by the CDC, the number of monthly exposures increased to 215 by February 2014. When compared to traditional tobacco cigarettes, electronic cigarette exposures were more likely to be described as causing inhalation injury, eye exposure, and skin exposure and less likely to be reported

as ingestions.[42] However, given the flavoring additives and the increased concentrations of nicotine by comparative volume, the potential danger and lethality from accidental liquid nicotine ingestion should not be ignored.

A Potential Gateway Drug

A recent study published in 2014 in the *New England Journal of Medicine* concluded that nicotine can act as a "gateway drug" on the brain at a molecular level. The study found that nicotine's effects — especially important for the developing adolescent — were found not only in traditional cigarettes and secondhand smoke, but also with the use of electronic cigarettes. Researchers observed that nicotine has a priming effect in murine models, changing the wiring of the brain so that it strengthens the effects of subsequent drug consumption. Consequently, the use of nicotine puts individuals at risk for progression to much more dangerous and addictive drugs.[43] While in an ideal scenario, utilization of electronic cigarettes could potentially decrease the undesirable carcinogenic effects of combustible tobacco, society must also be aware that these nicotine delivery devices could prove to increase the risk for even more addictive and deadlier behavior patterns.

A Vehicle for Other Drugs

The physiological gateway effect caused by nicotine is further compounded by the ease of users to exploit electronic cigarette devices for the ingestion of illicit drugs and other chemicals. Water-soluble synthetic drugs simply can be converted into a concentrated liquid that is consumed similarly to nicotine and other legal products.[15] Unregulated websites abound with step-by-step instructions for manufacturing liquid cannabinoids for vaping. There have also been reports of electronic cigarettes being used for inhalation of synthetic cannabinoids (spice), methamphetamine, cocaine, heroin, and bath salts (cathinones).

Besides abusing the ability of converting solids into liquids, the designs of electronic cigarettes are also changing for easier use with illicit drugs. Several electronic cigarette manufacturers have adapted their designs to make it easier to aerosolize dry herbs, oil concentrates, and cannabis-based liquids. Others are producing equipment dedicated to vaporizing wax or solid plant material, without the need for liquids.[4] Use and abuse of electronic cigarettes will continue unchecked without formal regulations and enforcement of stricter guidelines.

Electronic Cigarette Regulation

Regulation in the United States. As mentioned, one dramatic issue at the forefront of electronic nicotine delivery systems is regulation of content and product consistency. The ingredients of electronic cigarette liquid cartridges and refill solutions can differ greatly and are sometimes inconsistent with their labeling.[20] As the past 50 years of product liability has demonstrated, misleading labeling information can lead to dangerous scenarios for electronic cigarette users and secondhand bystanders.

With the explosion of the electronic cigarette fad seemingly overnight, the federal government has struggled to keep up with the advancing market in terms of meaningful regulation. Buying electronic cigarettes, cartridges, or refill solution is relatively easy online. Anyone is able to purchase electronic cigarette merchandise, including minors, only needing a virtual payment source to do so. The ease of access to these products is compounded by the attraction younger consumers have to the innovative and technological qualities of nicotine delivery systems. A previously mentioned study by Duke et al reported an enormous increase in exposure to electronic cigarette ads in youth and young adults, increasing by 256% and 321%, respectively.[16] This exposure includes multiple advertising arenas that have been banned for traditional cigarettes, including television, print media, and radio. Without any formal federal regulation, the exposure to and use of novel nicotine delivery systems will likely continue to increase in the coming years, especially in this targeted youth demographic.

At the time of this writing, only electronic cigarettes marketed for therapeutic purposes (smoking cessation) are regulated by the FDA Center for Drug Evaluation and Research. Currently, at least 46 states and two territories prohibit the sale of electronic cigarettes and vaping equipment to minors.[44] However, there is no federal consensus on regulation of these products.

In April 2014, the FDA proposed making electronic nicotine delivery devices regulated as tobacco products. If approved, this measure would force companies to make a number of dramatic changes to their current operations, including accurately reporting ingredients in the cartridge or cigarette refill fluid. Electronic cigarette sales would be banned to consumers younger than 18 years of age. New products could only be advertised after formal FDA assessment, and "free samples" would be forbidden. Manufacturers would be required to print health warnings on the package and would only be able to publicize claims about decreased risk compared to traditional smoking if scientifically validated. Child-resistant packaging would be required for liquid nicotine and refill solutions.[20] The FDA stated that it would accept comments, research data, and other information on this proposal through September 2015.[45] With the proposal still open to the statutorily required comment period, the FDA will likely not make a final recommendation until mid to late 2016.

Although the FDA's proposition for electronic cigarette regulation is a step in the right direction, much criticism has surrounded the continued delay of a formal recommendation on the health effects of nicotine delivery devices. In April 2015, a year after the initial FDA proposal, 31 health and medical groups sent a letter to President Obama and his

administration. Organizations like the American Heart Association, the American Academy of Family Physicians, and the American Academy of Pediatrics banded together and urged the government to complete its assessment of unregulated products like cigars and electronic cigarettes. They specifically commented on the substantial effects of direct advertisement to youth, stating that the CDC estimated about 2.4 million adolescents reported using electronic cigarettes in 2014, a number that tripled from 2013. They also affirmed the dramatic increase in number of poisonings from electronic cigarettes and liquid nicotine reported to poison control centers, citing a 13-fold increase in calls from 2011 to 2014.[19]

Regulation Internationally. In October 2014, a tobacco-control branch of the World Health Organization (WHO) met in Moscow to discuss the new trend of electronic nicotine delivery systems. This conglomeration of 180 countries agreed to create regulations as needed to limit or ban the use of electronic cigarettes and similar equipment. The goals set at this conference included preventing tobacco-naïve individuals and young people from ever starting to use electronic cigarettes. They also aimed to prevent secondhand emissions, reduce potential health risks, and challenge unconfirmed health claims made by cigarette manufacturers.[46]

As of July 2015, the WHO reports that 25 countries currently ban electronic cigarettes. Mexico, Australia, Brazil, and Argentina are just a few examples of countries that have fully outlawed newer nicotine delivery systems. The WHO 2015 report on the global tobacco epidemic also states that an additional 18 countries regulate the production and sale of electronic cigarettes as tobacco products.[47] Beginning in 2016, all 28 nations of the European Union will be following stricter regulations on electronic cigarettes. Packaging will be required to be childproof and have warning labels, and the maximum nicotine concentration permitted for refill solutions will be 20 mg/mL.[1]

Conclusion

Both in the United States and internationally, electronic cigarettes have exploded as a monumental public health topic since their introduction in 2003. This billion-dollar market has been flourishing as consumers look for ways to "smoke" indoors, enjoy the stimulating physiologic effects of nicotine, and attempt to decrease their tobacco exposure. However, the majority of electronic cigarette users are still smoking traditional cigarettes in addition to their vaping habit. At the present time, electronic cigarettes are not approved by the FDA for smoking cessation and cannot be advertised as such. Limited studies suggest that electronic cigarettes could potentially limit the amount of carcinogenic exposure to users when compared to tobacco, but much future research is necessary to further delineate the role and long-term health effects of these devices.

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CME Questions

1. A patient who ingested electronic cigarette fluid in a suicide attempt is not protecting her airway. The most appropriate course of action is:
   A. paralyze with succinylcholine, intubate, and put on the ventilator.
   B. bag the patient until you can give the antidote.
   C. paralyze with rocuronium, intubate, and put on the ventilator.
   D. put the patient on BiPAP until she wakes up.
2. Which of the following statements is true?
   A. Electronic cigarette use is increasing most rapidly in the older adult population.
   B. The majority of electronic cigarette users do not also smoke tobacco cigarettes.
   C. To date, there have been no deaths from accidental ingestion of e-cigarette refill solution.
   D. Electronic cigarettes are not FDA approved to aid in smoking cessation.
3. A 3-year-old boy comes in seizing. He has received several doses of lorazepam without effect. His mother mentions that he was playing with her e-cigarette refill cartridge just prior to arrival. What is the next best step?
   A. Intubate the child with succinylcholine and admit to pediatric ICU.
   B. Follow the algorithm for status epilepticus and load the patient with phenytoin.
   C. Give the child activated charcoal to absorb the excess nicotine in his stomach.
   D. Load the patient with phenobarbital and admit to the pediatric ICU.
4. Why is it nearly impossible to become nicotine toxic from using electronic cigarettes appropriately?
   A. Electronic cigarettes actually do not contain nicotine.
   B. An acute excess of inhaled nicotine causes nausea and vomiting, limiting a user's further nicotine consumption.
   C. The formulation of nicotine is different in electronic compared to tobacco cigarettes.
   D. A user is able to enter his or her weight into an electronic cigarette, prompting the device to stop working when a calculated concentration of nicotine has been consumed in a given time.
5. Which statement is true regarding nicotine?
   A. Its absorption is increased in an acidic environment, like the stomach.
   B. It is absorbed from the respiratory system, skin, intestines, and oral mucosa.
   C. Nicotine use by a pregnant woman does not affect fetal brain tissue development.
   D. The lethal dose of nicotine in adults is less than 5 mg.
6. All of these statements involving nicotine toxicity are accurate *except*:
   A. Patients who are asymptomatic can be discharged home.
   B. Patients with toxicity from a transdermal nicotine patch can be discharged immediately after patch removal.
   C. Atropine should be used to decrease excessive secretions in nicotine-toxic patients.
   D. The urine of a nicotine-toxic patient might show blood without any red blood cells.

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