Abstract: E-cigarettes, also known as electronic nicotine delivery systems and electronic cigarettes, are advertised as a healthier alternative product to tobacco cigarettes despite limited data on the consequences of e-cigarette use. Currently, there are no US Food and Drug Administration or other federal regulations of e-cigarettes, and calls to poison control centers regarding liquid nicotine toxicity, especially in children, are on the rise. This article presents the background and mechanism of action of e-cigarettes as well as up-to-date details of the toxicity of liquid nicotine. We also present management strategies in the setting of liquid nicotine toxicity.

Key Words: e-cigarettes, electronic cigarettes, liquid nicotine, nicotine toxicity

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TARGET AUDIENCE

This continuing medical education activity is intended for physicians, nurse practitioners, physician assistants, and emergency medical services personnel who care for pediatric patients.

LEARNING OBJECTIVES

After completion of this article, the reader should be able to:

1. Summarize the background and mechanism of action of e-cigarettes
2. Explain the toxicity of liquid nicotine
3. Discuss management of liquid nicotine toxicity
4. Address the lack of regulation of e-cigarettes

E-cigarettes, also known as electronic nicotine delivery systems and electronic cigarettes, are gaining popularity rapidly. The first smokeless tobacco was developed and patented by Gilbert Herbert in 1963, but did not become commercialized. In 2003, a Chinese pharmacist developed and patented the modern e-cigarette, which was granted an international patent in 2007 and introduced to the market outside China. E-cigarettes are advertised as a healthier alternative to regular tobacco cigarettes, despite limited data on the consequences of e-cigarette use. Furthermore, there is lack of quality control of e-cigarettes and electronic liquid refill products.1-2

MECHANISM OF ACTION

The term “e-cigarette” refers to a heterogeneous collection of devices that are manufactured by different companies with different designs and contents. E-cigarettes are battery-powered devices that vaporize doses of nicotine and other byproducts of solvents that are then inhaled. Most e-cigarettes are composed of 3 parts. First is a cartridge containing a humectant carrier, most often propylene glycol, as well as varying concentrations of liquid nicotine. Second is a battery-powered component that heats the solution, causing it to vaporize. Third is a tube through which the user can inhale. Metals, rubbers, and ceramics may be used as materials for aerosol generation in e-cigarettes.3

POPULARITY

According to the US Food and Drug Administration (FDA) in 2010, there were more than 400 brands of e-cigarettes available, and the number of e-cigarette users more than quadrupled between 2009 and 2010.4 In addition, there were 7764 flavors of liquid nicotine available by January 2014.5 With the increasing popularity, expenditures for advertisement of e-cigarettes have risen from $6.4 million in 2011 to $18 million in 2012.6-8 Accordingly, sales of e-cigarettes in the United States have increased from $283 million in 2012 to $537 million in 2013.9 Currently, the global e-cigarette market is estimated to be $6 billion.2 A survey of 3587 participants, 70% of whom consisted of former tobacco smokers, revealed that 96% of users believed e-cigarette helped them to quit smoking or reduce their smoking. Of note, 84% of users perceived that e-cigarettes were safer than tobacco cigarettes.5 7% stated that e-cigarettes were cheaper, and 39% of users believed that e-cigarettes helped them deal with areas where smoking was prohibited.10

ELECTRONIC LIQUIDS

E-cigarette solutions, also known as e-liquids (electronic liquids), are variable. Many solutions can be found online in various flavors, including tobacco, menthol, fruit, candy, and dessert. Nicotine concentration varies in these products from 0 to 35 mg/mL, and according to an FDA study, the concentration may differ from the product labeling. Other components of e-liquids include humectants, most often propylene glycol or vegetable glycerin, which may be toxic. When heated and vaporized in e-cigarettes, the humectants produce acetaldehyde, formaldehyde, and acrolein, which are toxic.11-12 Formaldehyde, acetaldehyde, and aceto- tone levels are shown to be higher in solvents composed of propylene glycol and under higher battery output voltage.13 In addition to propylene glycol, glycerol, and nicotine, there are carbonyls, aerosol particulates, tobacco-specific nitrosamines, aldehydes, metals, volatile organic compounds, and polycyclic aromatic hydrocarbons produced from e-cigarettes,13,14 although some studies indicate that the level of toxicants are lower than in conventional cigarettes.15 A study of 28 e-liquids from Germany also showed that ethylene glycol was present in 5 of the products, and nicotine was present in products that were advertised as nicotine-free.16 A study by Geiss et al13 discovered design flaws in the e-cigarettes that allowed leakage from the cartridge reservoirs, leading to further toxicity. A study in Sweden analyzed 20 models of refill nicotine liquids and showed that nicotine content in the bottle corresponded closely to the labels on the bottles.17 However, according to multiple studies, there seems to be variability in the nicotine concentration in these e-liquids.18-21 One study evaluated nicotine concentrations in 71 e-cigarette refill products, including a do-it-yourself
product, and revealed that 65% of products had nicotine concentrations deviating by more than 10% from the manufacturers’ labels.22

In addition, several studies revealed that flavoring are also cytotoxic. A study looked specifically at Cinnamon Ceylon and found that cinnamaldehyde and 2-methoxy-1-cinnamaldehyde were highly cytotoxic and that duplicate bottles of the same product varied in concentrations of 2-methoxy-1-cinnamaldehyde.23,24 Another study on human embryonic stem cells and mouse neural stem cells demonstrated cytotoxicity secondary to chemicals used in e-cigarette flavoring fluids.25

### NICOTINE TOXICITY AND POISONING

In 2010, Pediatrics published an article regarding unintentional child poisonings through ingestion of tobacco products, including both conventional and novel products such as tobacco pellets. According to the study, conducted between 2006 and 2008, poison control center received 13,705 reports regarding tobacco ingestion, greater than 70% of which involved infants younger than 1 year.26 US poison control centers reported an increase from 1 call per month regarding e-cigarette exposure in September 2010 to 215 calls per month in February 2014.27 Specifically, between June 2010 and September 2013, poison control centers received 1700 calls regarding exposure to e-cigarettes. The average exposure from June 2010 through December 2012 was 1.36 per month, which rapidly increased to 9.60 per month from January through September 2013. Of those exposures, 42.2% involved children younger than 5 years, and 27.4% involved young adults.28 A study found that the proportion of calls that poison control centers received regarding e-cigarettes and cigarette exposures increased from 0.3% in September 2010 to 41.7% in February 2014, 51% of which were in children 0 to 5 years of age.27

Prior to the rise of e-cigarettes, transdermal patches were a common cause of nicotine poisoning, in which 1768 cases of smokeless tobacco-product poisoning in children younger than 6 years were reported between 2006 and 2008. Nicotine poisoning may present with vomiting, diarrhea, tachycardia, hypertension, and tremor of the extremities. With higher concentrations, poisoning may lead to loss of consciousness, seizures, and respiratory failure.29

Nicotine is readily absorbed through all routes of exposure (gastrointestinal, dermal, intranasal, ophthalmologic, and inhalational), has a high degree of first-pass metabolism (70%-90%), and most likely undergoes enterohepatic circulation. Nicotine is metabolized in the liver, primarily by CYP2A6, generating cotinine, which is probably inactive. The half-life of nicotine averages 2 hours, whereas the half-life of cotinine averages 16 hours. Because of the short half-life of nicotine, cotinine is widely used as a quantitative marker for exposure to nicotine (eg, as a diagnostic test for the use of tobacco).3,9

Nicotine acts as an agonist at nicotinic-type acetylcholine receptors. Acute nicotine intoxication follows a biphasic pattern. Lower-level stimulation of the nicotinic receptor results in vomiting, abdominal pain, hypertension, tachycardia, and excessive salivation. At higher levels or more sustained exposure, autonomic ganglionic blockade can occur, leading to hypotension, bradycardia, dyspnea, and eventually coma and respiratory failure.30

A qualitative study of users of e-cigarettes revealed that a learning curve exists in their use; because of complexities of the device, new users are advised to purchase extra e-liquid due to unpredictability of the amount used.30 E-liquid is sold on various third-party Web sites and can easily spill or be extracted from e-cigarettes, putting children and young adults at risk for exposure to high concentrations of liquid nicotine. Routes of exposures to e-cigarettes included ingestion, inhalational, ophthalmologic, and dermal. Most common adverse effects included nausea, vomiting, and eye irritation.27 As noted above, nicotinic binding to receptors can lead to cholinergic excess. Cardiac and neurologic changes may occur with high doses, leading to tachycardia and seizures. The estimated lethal dose of nicotine is 1 mg/kg, estimated at 30 to 60 mg in adults and 10 mg in children.16,51

There are many case reports of adverse events from e-cigarette use in the literature among both pediatric and adult patients. There are reports of adults who unintentionally instilled nicotine refill solutions into their eyes and suffered irritation; other cases document unintentionally spilled nicotine solutions onto the skin.31,32 Bassett et al44 published a case report of a 10-month-old infant who presented with vomiting, tachycardia, grunting respirations, and truncal ataxia after ingestion of a “small” amount of liquid nicotine. Gupta et al55 reported a 30-month-old in the United Kingdom who presented to the emergency department after her mother found her with a refill cartridge in her mouth. The Jerusalem Post published reports of toddler deaths from liquid nicotine ingestion in 2013.36 and in December 2014, death of a 1-year-old boy from ingesting liquid nicotine was reported in New York State.

Other serious adverse events included myocardial infarction in a patient who was using 16 mg of liquid nicotine for approximately 1 month in place of 1 pack of tobacco cigarettes per day. Nicotine has a toxic effect on the endothelium, which may change its vascular activity and cause vasospasm, leading to myocardial infarction, as well as cause increased platelet aggregation.37 In another fatal case, a poison control center reported the death in an adult who injected liquid nicotine.27

Suicide attempts using liquid nicotine have also been reported. In 1 case, a man with depression ingested 180 mg of nicotine and experienced nausea, vomiting, dizziness, hypertension, and tachycardia.38 Another young man presented to the emergency department after ingesting ethanol along with the contents of 5 e-liquid containers totaling 420 mg of nicotine. He presented with emesis, tachycardia, hypertension, and lactic acidosis.9

In addition to suicide attempts, liquid nicotine is emerging as a drug of abuse in “dripping,” during which users drip e-liquid onto the e-cigarette heating element and inhale the vapor or combine e-liquids with alcohol and other substances. Some e-cigarettes allow users to adjust the voltage, thereby altering the amount of nicotine inhaled.39 A tobacco cigarette may contain 10 to 15 mg of nicotine, but e-cigarettes and e-liquids have varying concentrations and may cause serious toxicity.7

### ADVANTAGES FOR SMOKING CESSATION

Despite the potential toxicity and abuse potential of liquid nicotine, there are numerous studies that illustrate the use of e-cigarettes in successful smoking abstinence.30,40–43 as well as therapy for ulcerative colitis.44 There are also multiple studies comparing tobacco cigarettes with e-cigarettes. One study compared tobacco smoke with e-cigarette vapor to assess indoor air quality and determined significant risk with the former but no significant risk with the latter.55 While some studies suggest that e-cigarettes prevent exposure to tobacco-specific combustion toxicants indoors46–48 and do not affect complete blood count or hemodynamic parameters,99,10,57,15 the devices may allow exposure to secondhand nicotine vapor.14

### LIQUID NICOTINE INHALATION TOXICITY

Although e-cigarettes may aid in tobacco abstinence, a recent literature review also showed that nicotine delivery via e-cigarettes
is variable among users and that e-cigarette nicotine pharmacology is not well known and may cause toxic effects when inhaled. In a human trial of active and passive e-cigarette and tobacco cigarette users, Flouris et al showed that although e-cigarette smoking did not significantly decrease lung function, serum cotinine levels were similar in e-cigarette and tobacco cigarette users, even in passive use. Another human trial demonstrated that the concentration of exhaled nitric oxide was similar between e-cigarettes and tobacco cigarettes. Yet another study examined exhaled nitric oxide and found that respiratory flow resistance and overall peripheral airway resistance were increased acutely after using e-cigarettes. In addition, Schober et al demonstrated during a vaping session that ultrafine particles can be deposited in the lung, and aerosolized nicotine may also increase inflammatory signaling in the lungs. Another study done in emission chambers also revealed that nicotine and other byproducts were released, causing chemical and aerosol exposures for both passive and active users. There are several investigations that describe the adverse effects of e-liquid in the lungs: a mouse study showed that e-liquid promoted inflammation as well as susceptibility to respiratory viral infections. Variation also exists between different generations of e-cigarettes. A study showed that newer generations of e-cigarettes resulted in 35% to 72% higher plasma nicotine concentration compared with the first-generation e-cigarettes using 18 mg/mL nicotine-containing liquid, and puffing time and nicotine concentration may also influence particle concentrations. Flavoring substances may also contain toxic components, and several studies have shown that the cytotoxic properties of e-liquid vary with the flavoring. Diacetyl, also known as 2,3-butanediol, gives a buttery flavor and is approved in food products, as it is safe when ingested, but is associated with bronchiolitis obliterans as well as decline in respiratory function when inhaled. Acetyl propionyl, also known as 2,3-pentanedione, is a popular replacement for diacetyl, but may have similar effects on the lungs. One study revealed that 74.2% of e-liquid samples analyzed contained diacetyl or acetyl propionyl, even in products claimed to be free of both compounds. This can cause potential harm in both e-cigarette users as well as those exposed to secondhand vapor. Metal and silicate particles were also found in e-cigarette aerosols.

Other adverse effects exist in the setting of e-cigarette use. In a study evaluating the use of e-cigarettes on desire to smoke, participants reported adverse effects such as mouth and throat irritation, aching jaws, nausea, flatulence, vertigo, headache, sweatiness, and palpitations. Other studies of e-cigarette users reported throat and mouth irritation, nausea, and headaches as the most common adverse effects.

More serious adverse events are rare but exist as case reports in the literature. Hureauaux et al published a case report of a 20-year-old presented with persistent cough, shortness of breath, and facial flushing 1 hour after smoking e-cigarettes and was found to have acute eosinophilic pneumonia. Although these are rare case reports, e-cigarettes are unpredictable and may have serious adverse effects. A recent literature review by the FDA revealed that there are limited data on the toxicity of e-cigarettes in the United States, which limits the ability to perform risk assessment.

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### EVALUATION AND MANAGEMENT OF NICOTINE POISONING

Symptoms of liquid nicotine poisoning include muscarinic and nicotinic effects. See Table 1 for evaluation and management of nicotine poisoning.

### LEGAL IMPLICATIONS

E-cigarettes are currently unregulated by the FDA, and most states do not restrict the sale of the devices or e-liquids to minors. A total of 34 states have implemented laws regarding e-cigarettes and other tobacco-derived products, 28 of which pertain directly to e-cigarettes. Although these laws vary in their provisions, most apply to youth access to e-cigarettes. Data from 2011 and 2012 National Youth Tobacco Survey revealed that e-cigarette use rose from 3.3% to 6.8% for children in the sixth to 12th grade. Among middle-school students, use of e-cigarettes rose from 1.4% to 2.7%, and among high school students, 4.7% to 10% during 2011–2012. In addition, according to the Centers for Disease Control and Prevention, 160,000 students in 2012 reported using e-cigarettes who had never used tobacco cigarettes in the past.

E-cigarettes are widely available and easy to purchase even for youth. A survey showed that greater than 90% of users purchased electronic cigarettes online, and in 2012, e-cigarettes were available in about one-third of US tobacco retailers, most concentrated in areas with weak tax and smoke-free-air policies. Currently, there are movements toward increased regulation of e-cigarettes. Recently, the Forum of International Respiratory Societies published a position statement regarding e-cigarettes that they should be restricted or banned until more safety information is available or closely regulated. In July 2014, Senator Bill Nelson introduced the Child Nicotine Poisoning Prevention Act, which is currently under consideration in Congress.

### CONCLUSIONS

Reports of e-cigarette use and e-liquid exposure are on the rise. Liquid nicotine is highly toxic, but e-liquid refill solutions

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### TABLE 1. Evaluation and Management of Nicotine Poisoning

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<thead>
<tr>
<th>Symptom</th>
<th>Evaluation</th>
<th>Management</th>
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<tr>
<td>Muscarinic effects</td>
<td>Vomiting</td>
<td>Intravenous fluids</td>
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<td>Diarrhea</td>
<td>Respiratory support</td>
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<td>Bronchorrhea</td>
<td>Atropine</td>
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<td>Salivation</td>
<td>Intubation as needed</td>
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<td>Wheezing</td>
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<td>Respiratory failure</td>
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<tr>
<td>Nicotinic effects</td>
<td>Muscle fasciculations</td>
<td>Intravenous fluids</td>
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<td></td>
<td>Rhabdomyolysis</td>
<td>Respiratory support</td>
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<td>(urinalysis, urine myoglobin, creatine phosphokinase)</td>
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<tr>
<td></td>
<td>Weakness</td>
<td>Seizure control (benzodiazepines) as needed</td>
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<td>Paralysis</td>
<td>Intubation as needed</td>
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<td></td>
<td>Seizures</td>
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are readily available and lack child-resistant packaging. Clinicians should be aware of the potential for danger in the use of e-cigarettes as well as the toxicity of liquid nicotine, particularly in light of the currently unregulated market.

REFERENCES


