# Liquid Nicotine, E-Cigarettes, and Vaping
## *Information for the Pediatric Emergency Medicine Provider*

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**Abstract:** E-cigarettes, or electronic cigarettes, are electronic nicotine delivery systems that are marketed as a healthier alternative to tobacco cigarettes. There has been an exponential increase in their use among youth since their introduction to the United States market in 2007. With increased use and popularity, there has been an increase in calls to poison control centers regarding liquid nicotine toxicity in children and adolescents. Recent US Food and Drug Administration and other federal regulations of e-cigarettes have attempted to limit availability to youth. This article reviews trends in e-cigarette use among youth, the background and mechanism of action of e-cigarettes, liquid nicotine toxicity, management of liquid nicotine toxicity, and recent policy updates regarding e-cigarettes.

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

(*Pediatr Emer Care* 2022;38: 399–405)

### TARGET AUDIENCE

This article 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. Describe the trends in e-cigarette use among youth since introduction to the US market.
2. Summarize the background and mechanism of action of e-cigarettes.
3. Discuss the toxicity and management of liquid nicotine toxicity.
4. Explain current regulation of e-cigarettes.

Electronic nicotine delivery devices (ENDS), including electronic cigarettes (e-cigarettes), are handheld devices that produce an aerosol (commonly known as a vapor) for inhalation from a solution that typically contains nicotine, flavoring, and other solvents.[1] Often advertised as a healthier alternative to regular tobacco cigarettes, nicotine remains the major psychoactive ingredient in e-cigarette solutions, which is both highly addictive and toxic.[2] The marketing, design, and flavoring of e-cigarettes appeals to youth and has led to a concerning increase in nicotine use in children and adolescents. There is a critical need for provider education regarding current patterns of use and toxicity, as well as regulation and counter promotion to protect children.

### POPULARITY/EPIDEMIOLOGY

E-cigarettes were first introduced to the US tobacco market in 2007. While initially designed as a means for smoking cessation for adults, the use of e-cigarettes by adolescents rapidly increased. In 2011, e-cigarettes were added to the National Youth Tobacco Survey (NYTS), a survey primarily conducted on school campuses, when the prevalence of current e-cigarettes use rose from 1.5% to 2.8% among high school students and from 0.6% to 1.1% in middle school students.[3,4] In contrast to conventional cigarette use, which declined significantly over the last decades,[5] by 2014, e-cigarettes had become the most common type of tobacco product used by US youth.[6] In 2016, the Surgeon General issued the first comprehensive report by a federal agency on e-cigarette use by adolescents and young adults and declared e-cigarette use a "major public health concern."[7] This declaration, along with public health campaigns, coincided with a decrease in e-cigarette use in 2016, followed by a plateau in 2017, and a subsequent rise in 2018.[8] In 2021, the NYTS registered a decrease in e-cigarette use among youth, with current use recorded at 11.3% among high school students, a decrease from 19.6% in 2020, and 2.8% among middle school students, a decrease from 4.7% in 2020.[3,4] While fewer youth using e-cigarettes is encouraging, the estimated number of youth using e-cigarettes remains high at 2.06 million.[9] Of important note, the 2021 NYTS was conducted during the COVID-19 pandemic, which may have led to underreporting of e-cigarette use among youth completing the surveys in locations other than school.[9] In another online anonymous cross-sectional survey conducted in 2020, underage youth reported cessation or decreased use of e-cigarettes during the pandemic due to increased time spent at home with parents, who would discover use, decreased availability of products, and concern that "e-cigarettes may weaken the lungs."[10]

Multiple factors have contributed to the popularity and use of e-cigarettes in youth, including exposure to advertising, the introduction of small easy-to-hide devices, and use of various flavorings.[3] In particular, the introduction of "pod mods" in 2015 increased the use of e-cigarettes by adolescents. Their design, closely resembling a flash drive, makes them easily concealable, including in schools.[11] The delivery of nicotine, using nicotine salts and softening chemicals, allows for higher delivery of nicotine while avoiding throat and mouth irritation.[11] Among the "pod mod" market, JUUL largely dominated the market. In December of 2018, JUUL sales accounted for approximately 75% of total US e-cigarette sales.[12] Most recently, based on the NYTS surveys in 2021, Vuse has supplanted JUUL as the most popular pod mod.[4] A majority of youth report use of flavored e-cigarettes, with fruit being the most common type.[9] The use of disposable e-cigarettes was noted as a worrisome new trend in the 2020 NYTS survey, with use increasing approximately 1000% among high school students and 400% in middle school students from 2019 to 2020.[4] In 2021, disposable e-cigarettes were the most common type of device used by youth, with Puff Bar being the most common brand.[9]

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The authors, faculty, and staff have no financial relationships with any ineligible organizations regarding this educational activity.

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ISSN: 0749-5161

Coinciding with increased e-cigarette use, liquid nicotine poisonings of children have increased. The colorful packaging and flavoring of many e-liquids (Fig. 1) make them appealing not only for adolescent recreational use, but exploratory ingestions by young children. The high nicotine concentration in these e-liquids makes them dangerous, even fatal, in exploratory ingestions and exposures.[1] Exposures, primarily ingestions, of e-liquids increased by 1398.2% from 2012 to 2015, peaking in 2015 and subsequently decreasing in 2016 by 19.8%.[13] The observed decrease in 2015 has been attributed, in part, to the Child Nicotine Poisoning Prevention Act of 2015, which required e-liquids be sold in child proof packaging.[14]

## MECHANISM OF ACTION

### Delivery Devices

E-cigarettes are electronic delivery devices that vaporize nicotine and other byproducts of solvents that are then inhaled. They may or may not resemble traditional cigarettes and are available in both rechargeable and disposable forms. Most e-cigarettes consist of 3 parts. First, a cartridge filled with the e-liquid (electronic liquid) containing humectants, flavorings, and varying concentrations of nicotine. Second is a battery powered component that heats the solution. When heated, the liquid is vaporized into an aerosol. The user then inhales the aerosol through a tube.[15]

### Nicotine Content

Nicotine is highly addictive and long-term health effects of e-cigarettes are being studied. There is significant concern regarding harm of e-cigarettes to the developing brain of adolescents.[7] The levels of nicotine can vary widely between commercially available e-liquids, with most labeled with concentrations between 0 and 35 mg/mL.[7,16] The known lethal dose of nicotine is approximately 10 mg in children,[17] and e-liquids, such as JUUL, contain approximately 59 mg/mL.[18] While some options are marketed as "nicotine-free," these often contain synthetic nicotine, as well as other potentially harmful solvents and additives.[19]

E-cigarettes are often marketed as a smoking cessation tool. While a recent Cochrane review demonstrated moderate evidence that e-cigarettes may help adults stop smoking, other meta-analyses demonstrate more equivocal results.[20,21] For adolescents, e-cigarette use is not only associated with subsequent cigarette use[22,23] but also associated with additional substance use including marijuana, alcohol, and amphetamines.[24,25] A meta-analysis of 9 studies concluded that adolescents using e-cigarettes were 3.5 times more likely to go on to smoke conventional cigarettes.[26]

## NICOTINE TOXICITY AND POISONING

### Presentation

Nicotine is readily absorbed through the respiratory tract, mucosal surfaces, skin, and intestines. It has a high rate of first-pass metabolism through enterohepatic circulation. Nicotine is metabolized primarily by CYP2A6 in the liver to cotinine, an inactive metabolite. The half-life of nicotine averages 2 hours, and the half-life of cotinine averages 16 hours. Because of its extended half-life, cotinine is widely used as a quantitative marker for exposure to nicotine.[27]

Nicotine mimics the effects of acetylcholine by binding nicotinic receptors throughout the body. Activation of these receptors stimulates dopamine, GABA, and serotonin release. The release of these neurotransmitters in various pathways leads to the


**FIGURE 1.** Food and Drug Administration warning of e-liquid products with labels similar to food products and candy. (Adapted from US Food and Drug Administration. Misleadingly Labeled E-Liquids that Appeal to Youth. Available at: https://www.fda.gov/tobacco-products/ctp-newsroom/misleadingly-labeled-e-liquids-appeal-youth).

cognitive and mood enhancement, appetite suppression, and anxiety reduction associated with nicotine use. Clinical effects of nicotine are dose dependent. Low doses stimulate central nicotine receptors, resulting in sympathetic agonism. With higher doses, prolonged nicotinic stimulation causes receptor blockage, and parasympathetic and neuromuscular-blocking effects result.[27]

Nicotine exposure from cigarette smoking in nicotine-naive patients produces fine tremor, cutaneous vasoconstriction, increased gastrointestinal motility, nausea, and increased heart rate. In severe poisonings, clinical symptoms are biphasic because of the early central stimulation, followed by depression (Table 1). Nicotine toxicity often initially presents as increased salivation, nausea, vomiting, diaphoresis, and diarrhea, within minutes of systemic absorption. Vomiting is the most common adverse effect reported. Pallor, hypertension, and tachycardia result from vasoconstriction. Neurologic symptoms include headache, dizziness, ataxia, confusion, and, in severe ingestions, seizures. Delayed symptoms include bradycardia, hypotension, coma, and neuromuscular blockade.[27]

### Management

Immediate evaluation is indicated for any symptomatic nicotine exposure or any ingestion of nicotine-containing liquids. Liquid nicotine is rapidly absorbed, making orogastric lavage unhelpful, and timely activated charcoal administration imperative. There is no specific antidote; treatment is symptomatic and supportive. Airway protection, respiratory, and circulatory support are priorities. Atropine can be used to treat symptoms associated with parasympathetic stimulation, such as salivation, wheeze, or bradycardia. Seizures are treated with benzodiazepines (Table 1).[27]

## LIQUID NICOTINE INHALATIONAL TOXICITY

### Presentation

Although e-cigarettes do not produce combustion products like conventional cigarettes, vaping liquids still pose a significant health hazard. In addition to nicotine toxicity and addiction, there are multiple other harmful chemicals present. Concentrations of carbonyls, including the carcinogen formaldehyde, correlate with device power. Flavoring chemicals used in e-cigarettes have been shown to have cytotoxic properties.[28] Metal and silicate particles have also been found in e-cigarette aerosols.[29] In rare cases, the explosion of e-cigarettes has caused severe burns.[30] Unfortunately, long-term safety data are not available for many of the chemicals found in vaping products.[28]

In 2019, the Centers for Disease Control (CDC) identified a nationwide outbreak of lung injury associated with vaping, referred to as "E-cigarette or vaping product use associated with lung injury" (EVALI).[31] Although EVALI has not been attributed to any one type of vaporization device or liquid, many patients with EVALI report using tetrahydrocannabinol-containing vaporization devices, in isolation or in conjunction with nicotine products.[31,32] Use of tetrahydrocannabinol-containing cartridges that were obtained from informal sources, such as friends, online suppliers, or illicit dealers, is also common in these cases.[31,33] There is evidence to suggest that vitamin E acetate may be one of the culprits for lung injury in EVALI.[34]

To meet diagnostic criteria for EVALI, the CDC has put forth the following requirements: (1) use of vaping products within 90 days, (2) pulmonary infiltrates on chest imaging, (3) a negative workup for pulmonary infections, and (4) no other alternative plausible diagnosis.[31] Patients with EVALI present with respiratory

**TABLE 1.** Signs and Symptoms of Nicotine Exposure and Toxicity

| | Exposure | Toxicity |
|---|---|---|
| Symptoms | Tachycardia, tachypnea, hypertension | Early: |
| | Euphoria | Central stimulation (similar to exposure) |
| | Tremor | Late: |
| | Vomiting | Bradycardia, hypotension |
| | Diarrhea | Confusion |
| | Diaphoresis | Paralysis |
| | Bronchorrhea | Coma |
| | Salivation | Seizures |
| | | Respiratory failure |
| Management | Intravenous fluids | Intravenous fluids |
| | Respiratory support | Activated charcoal (if ingested)<br>• Dose: 1 g/kg up to 50 g orally<br>Respiratory support (intubation as needed)<br>Atropine<br>• Dose: 0.02 mg/kg to up to 0.5 mg in a single dose IV, may repeat once in 3–5 minutes, max total dose child 1 mg, adolescent 3 mg<br>Seizure control (benzodiazepines) as needed<br>• IV or IO access:<br>○ Lorazepam: 0.1 mg/kg per dose, max 4 mg<br>○ Midazolam: 0.1 mg/kg per dose<br>○ Diazepam: 0.2 mg/kg per dose, max 10 mg<br>• If no IV or IO access:<br>○ IN midazolam: 0.2 mg/kg per dose; max 10 mg<br>○ IM midazolam: 0.2 mg/kg, max 10 mg<br>○ Rectal diazepam: 0.5 mg/kg, max 20 mg |

IM indicates intramuscular; IN, intranasal; IO, intraosseous; IV, intravenous.

complaints, including shortness of breath, cough, and chest pain.[32] Laboratory values for patients with EVALI are often notable for leukocytosis, elevated inflammatory markers, and elevated liver transaminases.[35] Chest imaging often reveals infiltrates in the absence of infectious causes and may also demonstrate ground-glass opacities with areas of lobular or subpleural sparing.[35,36] Most reported EVALI cases have required hospitalization, with some requiring mechanical ventilation or ECMO.[32,35] While steroids may have some role in decreasing inflammation, the optimal dose and duration are not yet agreed upon.[35,37] While the COVID-19 pandemic has led to a shift in monitoring and research efforts by the CDC and scientists, EVALI continues to be an ongoing outbreak.[38] Furthermore, the COVID-19 pandemic has complicated the diagnosis of EVALI in that many of the presenting signs and symptoms are similar to COVID infection and multisystem inflammatory syndrome in children.[39,40] While it remains a diagnosis of exclusion, EVALI should continue to be on the differential of patients presenting with respiratory complaints and a history of vaping.

## E-CIGARETTE REGULATIONS

Important regulations have been put in place since 2016 to attempt to address the dramatic increase in e-cigarette use among US youth. In 2016, as mentioned previously, the Surgeon General declared that e-cigarettes represented a "major public health concern."[7] Subsequently, e-cigarettes were deemed subject to the Food and Drug Administration's (FDA) tobacco authorities. Regulatory and legal requirements that were in place for manufacturers of cigarettes now also applied to manufacturers of e-cigarettes such that the FDA's Center for Tobacco Products could regulate the manufacture, import, packaging, labeling, advertising, promotion, sale, and distribution of ENDS.[41]

With the rise in e-cigarette use fueled by pods, such as JUUL, and to address the outbreak of EVALI, the Surgeon General officially declared e-cigarette use among youth an epidemic in 2018. In 2019, the federal minimum age of sale of tobacco was raised from 18 to 21 years.[42] To address the appeal of flavorings of e-cigarettes, on January 2, 2020, the FDA announced a ban on the unauthorized sale of flavored cartridge-based e-cigarettes, other than menthol and tobacco flavors. The sale of these products requires premarket authorization.[43] Any ENDS product now requires an application to the FDA demonstrating that the product is "appropriate for the protection of the public health," such that the possible benefits to adults trying to quit smoking outweigh the risks of addiction in young people. The FDA reviewed and issued Marketing Denial Orders for more than 946,000 e-cigarette products[44] but has yet to rule on whether some major manufacturers, such as JUUL, which account for most sales nationally, will be allowed to continue selling their products in the United States. In October 2021, the FDA deemed some tobacco flavored Vuse products "appropriate for the protection of public health" and authorized their sale in the United States. This constitutes the first authorized sale of e-cigarette products by the FDA.[45]

In 2021, in a worrisome new development, some companies, including Puff Bar, the popular brand of disposable e-cigarettes, announced the launch of flavored disposable e-cigarettes using synthetic nicotine. This raises the concern that FDA regulations may not apply to these nontobacco-derived products. In response to this action by Puff Bar, several organizations, including the American Academy of Pediatrics, sent a letter to the FDA Acting Commissioner on March 18, 2021, urging the FDA to remove Puff Bar from the market, arguing that it has neither been approved as a drug by the Center for Drug Evaluation and Research nor received premarket tobacco product authorization by the Center for Tobacco Products and to clearly delineate the regulatory status of synthetic nicotine.[46]

## CONCLUSIONS

With the exponential rise in e-cigarette use since their introduction to the US market, liquid nicotine, a highly toxic and addictive product, has become widely available. Although recent regulations have attempted to slow the rate of increase in use among adolescents, e-cigarettes remain widely accessible. Clinicians should be aware of the high prevalence of use, the potential for toxic ingestions, their clinical presentation, and management.

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