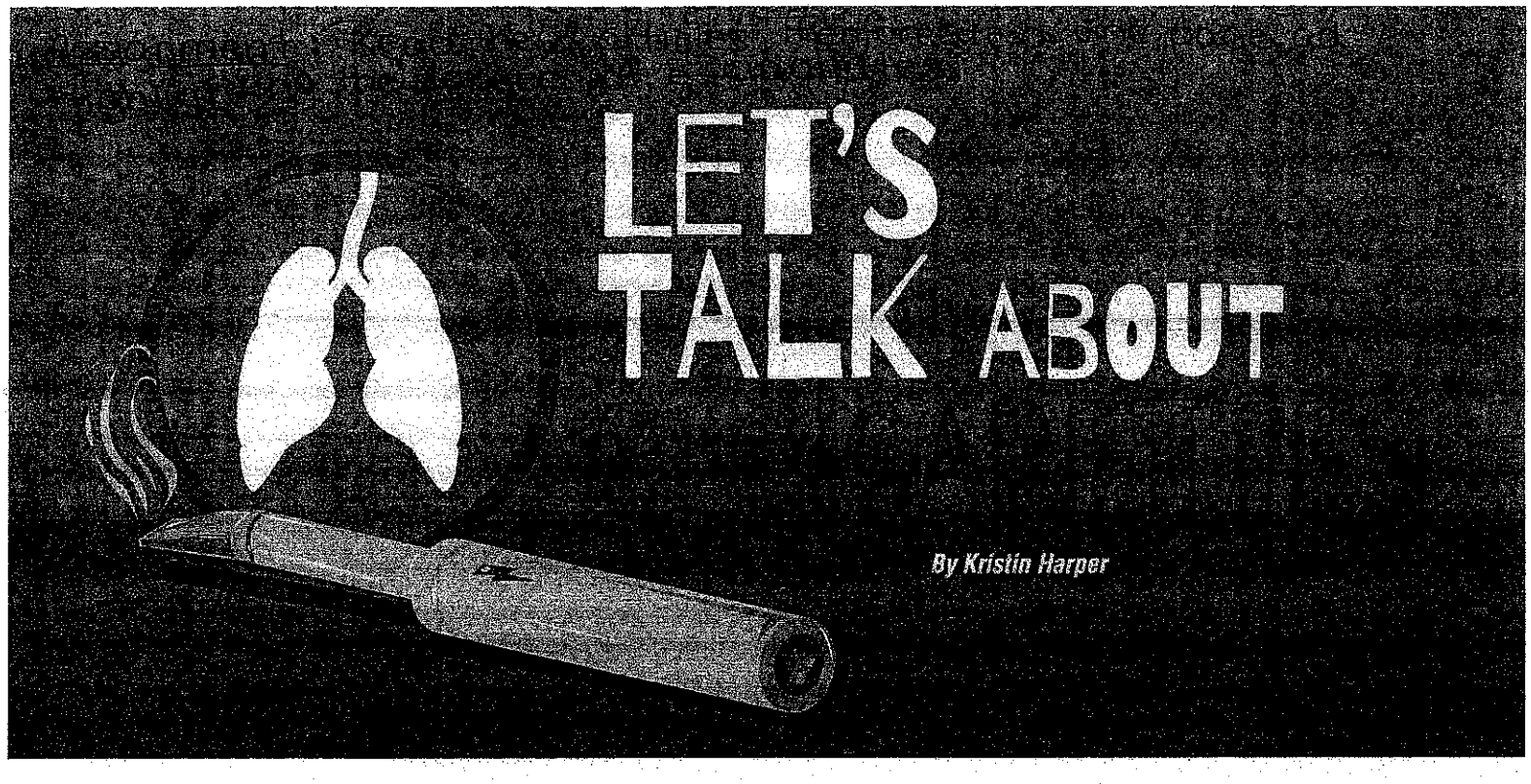
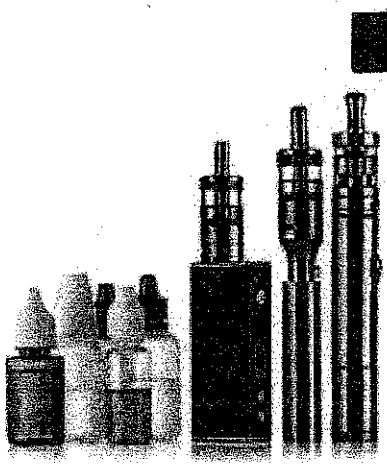


LET'S TALK ABOUT

By Kristin Harper



THEY ARE EVERYWHERE, FROM GAS STATIONS TO DRUG STORES TO BODEGAS TO VAPE SHOPS, and they come in a wide range of flavors: menthol, scotch, vanilla, and even cappuccino. Also, unlike regular cigarettes, people under the age of 18 are legally allowed to purchase e-cigarettes in many states. This helps explain why e-cigarette use by teens tripled between 2013 and 2014; in a recent survey, 17% of high school seniors reported using an e-cigarette in the previous month.

E-cigarettes are becoming more popular than regular cigarettes among high school students. Some teens say that vaping, or inhaling and exhaling the vapor produced by an e-cigarette, helps them relax; some like the flavors; some think they are a safe alternative to regular cigarettes; and others like performing smoke tricks for friends. ***But are e-cigarettes really safer than regular cigarettes—and, if so, what is the chemical basis for the difference between the two?***

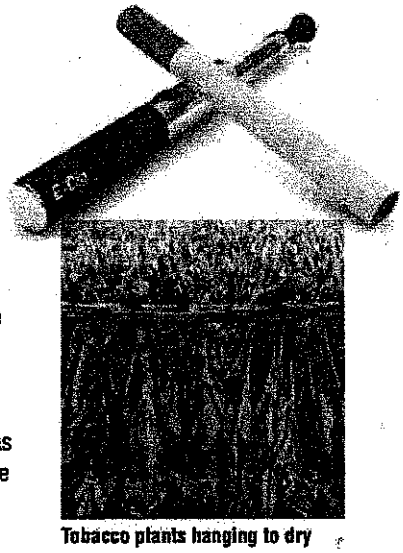
E-cigarettes versus regular cigarettes

The biggest difference between e-cigarettes and conventional cigarettes is that e-cigarettes don't burn. Instead, a battery-operated cartridge inside an e-cigarette converts liquid nicotine into a vapor. This is an important distinction because the greatest danger associated with tobacco is the smoke, which contains a toxic mix of more than 7,000 chemicals, including more than 70 substances that can cause cancer.

Some of the toxic components of cigarette smoke include carbon monoxide, hydrogen cyanide, and formaldehyde (dangerous gases); benzene (a component of gasoline); and polyaromatic hydrocarbons and tobacco-specific nitrosamines (compounds that may cause mutations in our DNA). The absence of this harmful smoke does not mean that e-cigarettes are totally safe, though. They still contain nicotine, the compound that makes cigarettes addictive.

Nicotine is derived from the roots of plants in the nightshade family, which includes tobacco plants, and accumulates in their leaves. These plants use nicotine to keep away herbivores, the animals that eat them.

At some point during human history, people discovered that the small doses of nicotine in tobacco act as a stimulant, making people who smoke it feel more alert. Tobacco was smoked in the Americas long before Christopher Columbus arrived, and European settlers of the New World introduced the practice of tobacco smoking to Europe, from which it spread across the Old World.



Tobacco plants hanging to dry

ANTHONY FERNANDEZ, SHUTTERSTOCK; DOLLARPHOTOCLUB

Although nicotine in regular cigarettes is just one component of smoke from tobacco leaves, nicotine in e-cigarettes is typically extracted from tobacco leaves in the lab, which is how it can be delivered without many of the other harmful compounds found in regular cigarettes.

Addictive nicotine

What makes nicotine so addictive? Within roughly 10 seconds, nicotine moves straight from a regular cigarette to the brain. There, it competes with a chemical called acetylcholine (Fig. 1). Acetylcholine is a neurotransmitter, a molecule that relays messages between nerve cells, called neurons. The brain uses neurotransmitters to tell your heart to beat, your lungs to breathe, and your stomach to digest. Neurotransmitters can also affect mood, sleep, concentration, and weight.

In the brain, acetylcholine binds to special molecules, called receptors, on the surface of a neuron. Once acetylcholine binds to a receptor, the receptor changes its shape and allows sodium ions to flow inside the neuron. This flow of ions is how neurons "talk" to each other. The flow of ions also causes the release of other neurotransmitters and hormones that affect your mood, your memory, and even your appetite.

Because the chemical structures of nicotine and acetylcholine are similar, nicotine can bind to the same receptors that acetylcholine does; in chemical terms, both molecules have an affinity for the same receptors. In fact, some acetylcholine receptors are called nicotinic receptors, for their ability to bind nicotine! In Fig. 2, the similar parts of the acetylcholine and nicotine structures are shown in red.

Acetylcholine binds to its receptor through its trimethylammonium group, which consists of a nitrogen atom bound to three methyl groups ($-CH_3$). The trimethylammonium group binds to two types of amino acids that are part of the receptor (Fig. 3). These amino acids each contain a benzene ring—a hexagonal arrangement of six carbon atoms—which has a partial negative charge in the center of the ring and a positive charge around the outside. So, the trimethylammonium group, which is positively charged, binds to the negatively charged center of the benzene rings in each type of amino acid. This type of bond is called a cation-π interaction.

Nicotine binds to the same receptor using a group of atoms similar to acetylcholine's trimethylammonium group. It is positively charged and contains a nitrogen atom bound to one methyl group and two $-CH_2$ groups (Fig. 2).

By binding to acetylcholine receptors, nicotine stimulates the adrenal glands to produce epinephrine, a hormone and neurotransmitter also known as adrenaline. This chemical increases heart rate and blood pressure while constricting blood vessels, which explains why smoking helps people feel energized and alert. It also stimulates the production of dopamine, a neurotransmitter that controls the brain's pleasure center, which keeps smokers coming back for more.

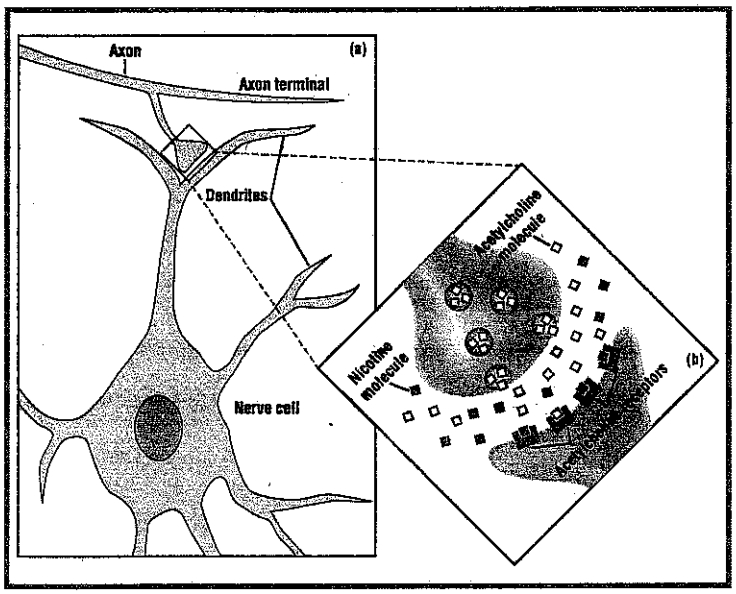
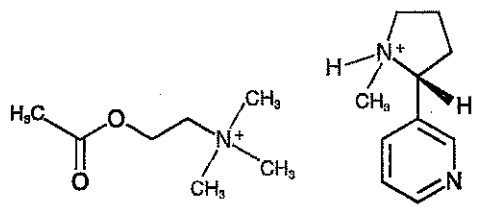


Figure 1. Neurons are nerve cells that carry messages. (a) A neuron is made up of three parts: the cell body, which contains the nucleus and other organelles; dendrites, which receive nerve impulses from other cells; and axons, which pass the nerve impulses on to other cells. (b) Neurons use neurotransmitters, such as acetylcholine, to send messages to each other. Nicotine imitates acetylcholine, sending the same messages—but in much greater quantities.



acetylcholine **nicotine**

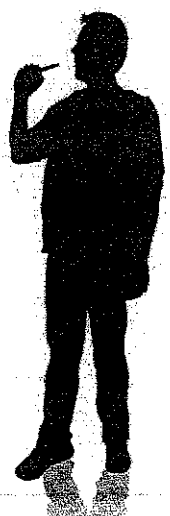
Figure 2. The chemical structures of acetylcholine and nicotine. The similar parts of the molecules are highlighted in red.

Nicotine's effects on the body

Normally, your body carefully monitors the concentration of acetylcholine, to ensure that you are receiving the right amount of this chemical. Your cells can produce more acetylcholine, store it, release it, or break it down, depending on how much you need at a given time. For example, when you are concentrating hard on a test question, lifting weights, or facing off with a scary figure in a dark alley, the cells in your body will release more acetylcholine.

When you are relaxing with friends or watching your favorite TV show, your cells can work on breaking down unneeded acetylcholine molecules that are loose in the body and rebuilding stores for the next time the chemical is needed. When nicotine binds to nicotinic receptors, this system doesn't work as well, because nicotine is not regulated by the body.

Although neurons typically release small amounts of acetylcholine in a regulated manner, nicotine activates neurons in many different regions of the brain simultaneously. All of this unregulated stimulation causes cells to release acetylcholine, leading to heightened activity throughout the brain—whether the situation requires it or not.



ANTHONY FERNÁNDEZ; ADAPTED FROM HTTP://SCIENCE.HOWSTUFFWORKS.COM/NICOTINE3.HTM

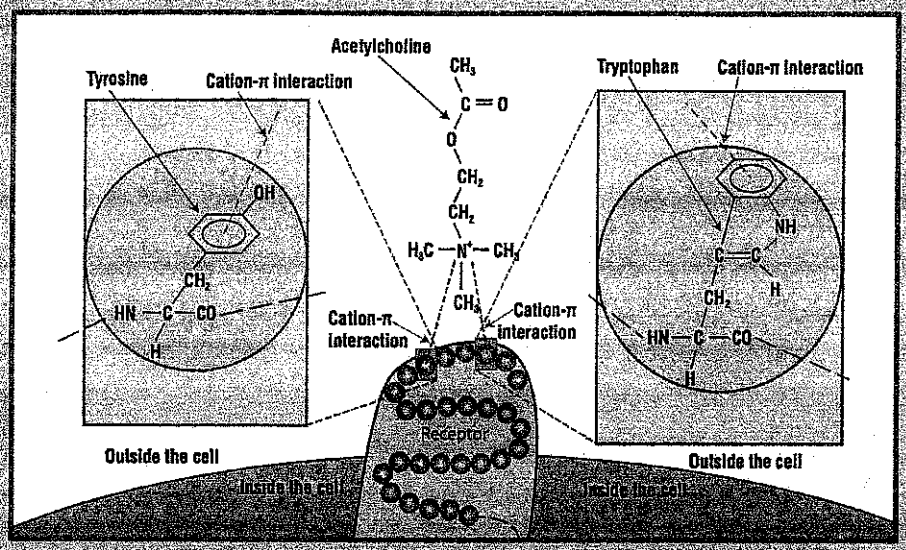


Figure 3. Acetylcholine binds to two types of amino acids, tyrosine (left) and tryptophan (right), which are on a cellular receptor, through a type of molecular interaction called a cation-π interaction. These amino acids belong to the protein that makes up the receptor, shown here in a simplified way as a chain of amino acids. In reality, the chain of amino acids is folded in a complex three-dimensional structure.

One difference between acetylcholine and nicotine is that frequent exposure to nicotine causes long-term inactivation of the receptors to which it binds (Fig. 3). In other words, after nicotine binds to and activates receptors, they cannot respond to new nicotine and acetylcholine signals for a longer period than usual. This is why people who smoke often find that cigarettes have less and less effect after a while—causing them to smoke more and more. Because of exposure to nicotine, their cells' receptors are not responding to acetylcholine in the way they used to and need time to return to their normal state.

This also explains why smokers often feel relaxed and even sleepy after the initial stimulating effect of nicotine disappears. Nicotine is not readily cleared from the receptors, so the activity of muscles, particularly the heart, slows. This causes blood circulation to slow, and oxygen is delivered to the body at a lower rate.

Nicotine's inactivation of these receptors is the biological basis of nicotine addiction, and it explains why, when people quit smoking or have too little nicotine in their bodies, they may feel irritable, restless, hungry, and experience cigarette cravings.

The health effects of nicotine

By essentially hijacking the acetylcholine system, nicotine can affect brain development. Teens' brains are still developing—especially the prefrontal cortex, which is the area of the brain involved in decision-making and planning. The prefrontal cortex does not finish maturing until around age 25.

Researchers have studied what happens to the prefrontal cortex in adolescent mice and rats exposed to nicotine. By measuring currents inside their brains, they have found that nicotine can alter the connections that develop between neurons. These types of changes can affect learning and impulse control, which are important for success in school and life.

Nicotine also has effects on other parts of the body. For example, it constricts blood vessels by causing cells to release a chemical called norepinephrine. Norepinephrine helps keep you alert in difficult or dangerous situations, but too much of it for too long causes blood pressure to rise, which increases the risk for heart attack and stroke. More smoking leads to a higher concentration of nicotine in the body and more pronounced health effects.

Are e-cigarettes safe?

Whether e-cigarettes should be considered a healthier alternative to regular cigarettes is controversial. Research suggests that e-cigarettes are a better choice than regular cigarettes for someone who chooses to smoke, because they allow users to avoid the toxic slew of chemicals contained in cigarette smoke. So, e-cigarettes may be an alternative for people who are already using nicotine [illegible] e-cigarettes can help people to quit smoking, presumably by allowing them to gradually decrease their exposure to nicotine (similar to how nicotine patches work). But this research is contentious, because other studies have found that e-cigarettes do not seem to help people who want to quit smoking. In fact, a recent study funded by the National Institutes of Health found that students who have used e-cigarettes by the time they start ninth grade are significantly more likely to start smoking regular cigarettes within the next year than students who have not tried e-cigarettes.

Many people are concerned that fun flavors, easy accessibility, and big advertising budgets may lure teens into trying e-cigarettes and potentially becoming addicted. Evidence from animals, paired with what we know about the development of the human brain, clearly indicates that nicotine is addictive, no matter the form in which it is delivered, and that it has health consequences. *CM*

SELECTED REFERENCES

Tavernise, S. E-Cigarettes Top Smoking among Youths, Study Says. *The New York Times*, Dec 16, 2014: http://www.nytimes.com/2014/12/17/science/national-institute-on-drug-abuse-e-cigarette-study.html [accessed Nov 2015].

Tavernise, S. Use of E-Cigarettes Rises Sharply among Teenagers, Report Says. *The New York Times*, April 16, 2015:http://www.nytimes.com/2015/04/17/health/use-of-e-cigarettes-rises-sharply-among-teenagers-report-says.html [accessed Nov 2015].

Griffin, B. M. E-Cigarettes 101. Smoking Cessation Health Center, WebMD: http://www.webmd.com/smoking-cessation/features/electronic-cigarettes [accessed Nov 2015].

Kristin Harper is a science writer who lives in Seattle, Wash. Her latest *ChemMatters* article, "Bacteria Buster! Triclosan Kills Bacteria, but Is It Safe?" appeared in the December 2015/January 2016 issue.

ANTHONY FERNANDEZ, ADAPTED FROM WALSH, C. T.; SCHWARTZ-BLOOM, R. D. LEVINE'S PHARMACOLOGY: DRUG ACTIONS AND REACTIONS, 7TH ED. TAYLOR & FRANCIS: UNITED KINGDOM 2005; P 41

By Michael Nedelman, CNN

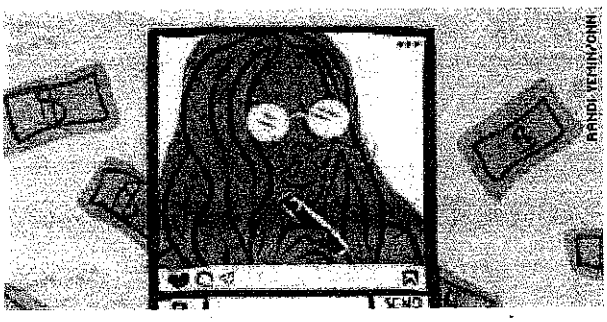
Updated 8:00 PM ET, Thu January 17, 2019

CNN investigates Juul's social media practices 02:28

(CNN) — Most of what we know about nicotine addiction in teens, we know from cigarettes. But experts say the technology and chemistry of vaping might pose an entirely different threat.

"It turns out that e-cigarette use by kids doesn't look the same at all," said Dr. Sharon Levy, director of the Adolescent Substance Use and Addiction Program at Boston Children's Hospital. "How you're delivering [nicotine] and how much you're delivering ... everything you change really matters."

Levy said she's seen vape-addicted kids in her program showing what appear to be psychiatric symptoms rarely seen with traditional cigarettes or among adults. Some have anxiety and cannot focus, for example.



Meanwhile, vaping has become ubiquitous in many high schools, prompting the US Food and Drug Administration to tackle "epidemic" levels of use among minors.

On Friday, the agency will hold a public hearing to discuss the role of smoking cessation drugs for kids in order to get them off vapes. There currently are no FDA-approved nicotine cessation products for e-cigarette users under 18.

Despite early fanfare that e-cigarettes might offer a less

tion

Their long-term health effects are still unclear.

"We let this Frankenstein loose without knowing what was going to happen," Levy said.

Teen vaping was a 'predictable problem'

Experts say that one Juul pod -- a cartridge of nicotine-rich liquid that users plug into the dominant e-cig brand -- contains the same amount of nicotine as a pack of cigarettes.

"That may be true, but that's not the only consideration here," said Levy, adding that it's yet unclear "how high those peaks go and how quickly it gets into the bloodstream and into the brain."

Levy said that it's not uncommon for kids to report symptoms that "sound a lot like nicotine toxicity," including headaches and stomach aches. She suspects these devices cause nicotine levels in the blood to peak higher than they do with traditional cigarettes -- but experts say more research is needed to better understand how vapes work on the body and brain.

Related Article: When your child vapes, what's a parent to do?

"These new generations of electronic cigarettes, like Juul ... they actually deliver a really high dose of nicotine, probably even higher than tobacco cigarettes," said Maciej Goniewicz, an associate professor of oncology and pharmacology at Roswell Park Comprehensive Cancer Center who specializes in toxicology.

In a study last year, Goniewicz found higher levels of cotinine -- a breakdown product of nicotine -- in the urine of adolescent vapers than had been reported in prior research of teenage cigarette smokers.

According to Goniewicz, vape manufacturers may be able to pack more nicotine into their products by creating "nicotine salts," which may mask nicotine's naturally unpleasant taste and lead the drug to be absorbed by the body quicker.

The salt is created by combining nicotine -- a base in its natural form -- with an organic acid, he said. Experts worry that inhaling these and other added ingredients may cause other health problems down the line, but e-cigarettes haven't been around long enough to know.

Beyond the chemistry of the nicotine itself, e-cigarette companies have come under fire for adding pleasant, often sweet flavors to their "e-liquid" that are known to appeal to young people. And the absence of the harshness of inhaling combustible cigarettes may allow vapers to take deeper or more frequent puffs, Levy added.

FDA commissioner Dr. Scott Gottlieb proposed in November to strengthen the agency's policies against flavored e-cigarette products. These proposals could ultimately prompt their removal from shelves and websites that are accessible to minors. But the proposed changes do not include mint, menthol and tobacco flavors. Gottlieb said he wanted to leave the door open for adults who might use these products to quit smoking cigarettes, "but it can't come at the expense of addicting a generation of kids on nicotine," he previously told

its new regulations

combustible cigarettes.

Ashley Gould, chief administrative officer at Juul Labs, told CNN last year, "We were completely surprised by the youth usage of the product." The company has maintained that its product is intended to convert adult former smokers to what Juul describes as a less-harmful alternative, and it says it is taking steps to limit kids' use of e-cigarettes.

But Levy describes vapes' popularity among teens as an "entirely predictable problem."

Teens' brains might be more vulnerable to nicotine

Levy said the impact of vapes on teens is changing the way people think about nicotine products.

Smoking was largely seen as a "medical problem" that could lead to cancer and other physical ailments, she said. Now, vaping is increasingly being seen as a psychiatric problem over concerns that nicotine is cultivating addictive behaviors among kids and interfering with their brain development.

"There's concern that the adolescent brain may be more vulnerable to the addictive effects of nicotine," said Adam Leventhal, director of the Health, Emotion, and Addiction Laboratory at the University of Southern California.

"The circuits underlying pleasure and the pursuit of novel, enjoyable experiences develop much faster than the circuits that promote decision making, impulse control and rational thinking," Leventhal said.

Related Article: What parents should know about the 'huge epidemic' of vaping

We know from cigarette users that those who try nicotine products early in life are more likely to develop dependence to the drug, said Leventhal. This may also lead to the disruption of brain circuits that underlie attention and cognitive skills, he added.

What makes kids uniquely vulnerable to vapes is not merely biological; it's also psychosocial, according to Leventhal. This may come in the form of peer pressure or stress, which may increase the likelihood of addictive behaviors, he said.

More broadly, the cultural and policy shifts that prevent many kids from picking up cigarettes -- including FDA regulation and a "long history of prevention programs" -- simply haven't kept pace with the vaping boom, Leventhal added.

Kids and adults also tend to vape for different reasons, Goniewicz said. Adults tend to be former smokers who can handle a high dose of nicotine and want to avoid withdrawal symptoms, such as the inability to sleep or focus on work.

"They don't really need nicotine to feel good," he said. "They need nicotine not to feel bad -- because they are already addicted."

But e-cigarettes may be kids' first experience with nicotine. "Nicotine hits the brain," he said, tinkering with molecules that affect mood and other pathways. And they aren't used to it, he said.

"Nicotine is a potent chemical that changes our brain."

Health experts worry that getting hooked on nicotine early in life may be a gateway to cigarette smoking and other drugs, and there are few tried-and-true resources out there for teens.

"Kids are often really struggling with this, and there are just not a lot of resources for them," Levy said, adding that many addiction programs may not be equipped to deal with some of the younger, nicotine-addicted kids she's seeing. Far better would be to ensure that primary care doctors are equipped to work with kids in their own communities, she said.

Some parents have pursued nicotine gum and other cessation tools off-label for their children under doctors' guidance. Levy said that can be tricky because some kids may use these products as a "bridge" between puffs of vapes and tobacco products.

Medications can be important in some advanced cases, but they're not enough, she said; kids also need "good, solid counseling."

"We end up needing to teach kids how they can deal with cravings, how they can identify high-risk situations, how they can actually deal with being surrounded by people who are using these things," Levy said. "Because the reality is that, for most kids, we treat them and put them back in school, and then they go to the bathroom, and everybody's Juuling."

Still, she said kids and their parents seem largely unaware of the potential dangers.

"Even to this day, I have kids saying, 'well, I thought it was safe' or 'I know it's safer than cigarettes,' " Levy said.

"And 'safer than cigarettes' is a really low bar."