

Therapeutics & Toxins News

Newsletter for the TDM and Toxicology Division of AACC

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E-cigarettes and vaping – pros and cons

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e-cigarettes (e-cig) started as a safer alternative to smoking. Patented in the US in 2005, they soon became very popular; for example, in 2020, there were 460 brands of e-cig in the US market (1). Some e-cigs are made to look like regular cigarettes, cigars, or pipes. Some resemble pens, USB sticks, and other everyday items. Sometimes they are for single use, but more often they are refillable. The process of smoking e-cigs is called vaping. Vaping devices are battery-operated devices that people use to inhale an aerosol, which typically (though not always) contains nicotine, flavorings, and other chemicals. E-cig market has exploded since its inception: in 2021 the US market amounted to \$7.4 billion (2). From February 2020 to March 2021, total e-cigarette sales increased by nearly 50% (from 14.8 million units to 22 million units). Sales of flavored e-cigarettes increased by 64%. The vast majority (69.8%) of this increase was from sales of disposable products. However, the most worrisome news was the increasing popularity of e-cig in children and teens, for whom a 2-mg dose of nicotine can be toxic and a 100-mg dose can be fatal.

e-cigarettes

These devices, in general, have four different components: a cartridge or reservoir or pod, which holds a liquid solution containing varying amounts of nicotine, flavorings, and other chemicals; a heating element (atomizer); a power source (usually a battery); and a mouthpiece that the person uses to inhale. When the users puff, that activates the battery-powered heating device (up to 55°C), which vaporizes the liquid in the cartridge. The person then inhales the resulting aerosol or vapor, which typically contains nicotine.

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Depending on the device design and its power, a puff contains different amounts of nicotine. In a study, three hundred puffs of e-cigarette aerosol were found to contain between 21% and 85% of the cartridge's total nicotine content (3). In terms of nicotine that amounted to as low as 0.5 mg nicotine (from a 1.6 mg nicotine cartridge) to 15.4 mg nicotine (from an 18 mg nicotine cartridge).

Pros

Many of the ills of tobacco smoking (for example, cigars, cigarettes) have been thought to be caused by the 'tar' – the residue left from smoking. When tobacco smoke is inhaled, the tar can form a sticky layer on the inside of the lungs. This damages the lungs and may lead to lung cancer, emphysema, or other lung problems. Tar yields range from a low of about 8 mg per cigarette to a high of about 43 mg per cigarette. Nicotine yields, on the other hand, range from about 0.3 to 2.6 mg per cigarette. Since e-cigs avoided combustion, they were thought to be safer. Importantly, e-cigs could circumvent the no smoking policies in most states. Though e-cigs were never marketed as smoking cessation tools, some users claim they are more effective for this purpose than traditional nicotine replacement therapies. The e-cigs and society's anti-smoking policies helped reduce the percentage of smokers in the general population from 40% (in the 1960s) to 14% in 2019. It was hoped that passive exposure to tobacco smoking (tar and nicotine) will also be less in e-cigs. Unlike smoking, e-cigs produce vapor only when the user inhales, so second-hand smoke is produced only by the user's exhaled breath. However, air exhaled by vaping users has been shown to have a comparable amount of the nicotine metabolite cotinine as air exhaled by e-cig smokers (4).

In fact, the U.S. Food and Drug Administration (FDA) recognized e-cigs as less of evil than tobacco smoking. They authorized the marketing of three new tobacco products in a memo on Oct 2021 (5). This was the first set of electronic nicotine delivery system products ever to be authorized by the FDA via the Premarket Tobacco Product Application pathway. Furthermore, these three products are tobacco-flavored and so are less popular among the young adult population. Thus FDA hopes that the authorization will not encourage the young adults to smoke, rather the tobacco smokers will switch to vaping. The FDA notes clearly that their action does not mean that these products are safe or "FDA approved".

Cons

The negative pharmacological responses of e-cig may come from nicotine, the solvent (which is most often glycerol or propylene glycol), and the flavoring agents. Nicotine affects the peripheral and central nervous systems and has been shown to increase heart rate (HR) and blood pressure while constricting cutaneous and coronary blood vessels. The solvents are listed on the FDA's Generally Recognized as Safe (GRAS) list for use as food additives, but their safety in vaping solutions has not been studied. As for the flavors, they range from fruit to candy to alcoholic

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beverages and may be highly attractive to young users. That is why, except for menthol and tobacco, flavored e-cigs have been banned in the U.S. since 2020, due to their appeal to children.

One study, presented at the virtual European Respiratory Society International Congress 2021, showed that e-cigs containing nicotine may cause an immediate increase in blood clot formation as well as a decrease in the elasticity of small blood vessels (6, 7). The study authors hypothesized that this is due to “catecholamine release and activation of the sympathetic nervous system or by increased pulse and blood pressure.” They did a double-blind, randomized, crossover study with 22 healthy adults who reported occasional tobacco use. The subjects were tested before and after they inhaled 30 puffs of an e-cigarette with and without nicotine. There was a gap of 1 week between the two parts - with and without nicotine. Testing included blood test and thrombus formation. They found a significant increase in platelet thrombus formation ($P = .011$) and fibrin-rich thrombus formation ($P = .035$) 15 minutes after vaping with nicotine. They also found a significant decrease in peak endothelial independent microvascular flux ($P = .009$) after vaping with nicotine. However, these effects returned to baseline levels 60 minutes after exposure. As expected, no such effect was found with e-cigarettes without nicotine. These findings support European Respiratory Society recommendations that tobacco smokers use alternate ways for smoking cessation: patches or gum, instead of vaping.

Additionally, it has been demonstrated that variable voltage e-cigs operated at high voltage produce hemiacetal, a formaldehyde-releasing agent. Although the impact of hemiacetal on the respiratory tract is unknown, formaldehyde itself is a potent carcinogen. The authors estimate that vaping only 3 mL of e-cig refill solution per day would correspond to more than double the formaldehyde exposure of a 20 cigarettes per day smoker (7). The long-term safety of e-cigs has not been established.

Vaping cannabinoids

While this article mainly focuses on e-cigs and vaping of nicotine solutions, vaping of tetrahydrocannabinol (THC), the active ingredient in marijuana, is also quite popular. Cannabidiol (CBD) and other cannabinoids can also be used. The major ill effect of any vaping has been described as e-cig and vaping, associated lung injury (EVALI). The cause of EVALI has been described as various flavors and additives (for example, vitamin E acetate), as well as contaminants and adulterants in the nicotine solution or cannabinoid oils. EVALI has been described to significantly increase the risk of death in SARS-CoV-2 infection.

Toxicological analysis of nicotine

Nicotine (Figure A) is metabolized mainly to Cotinine (Figure B) before excretion in urine. Liquid chromatography coupled with mass spectrometry (LCMS) is mainly used to detect cotinine in urine. In addition, screening immunoassays for cotinine are also available. These assays can be run on automated analyzers.

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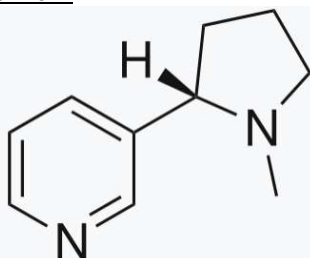


Figure A: Nicotine

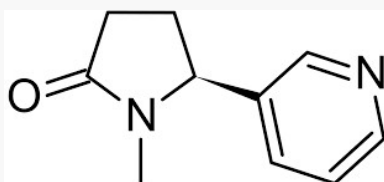


Figure B: Cotinine

Conclusion

e-cig or vaping has gained wide popularity specially among the young population, increasing the various ill effects, like EVALI, on the vapers' health. It is good that FDA is controlling the sale of such products in US, since that will minimize various flavors and additives in the nicotine solution.

Reference:

1. Vaping Devices (Electronic Cigarettes) DrugFacts | National Institute on Drug Abuse (NIDA) accessed Oct 2021.
2. U.S. E-cigarette & Vape Market Size, Share Report 2021-2028 (grandviewresearch.com) accessed Oct 2021.
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4. Flouris AD, Chorti MS, Poulianiti KP, et al. Acute impact of active and passive electronic cigarette smoking on serum cotinine and lung function. Inhal Toxicol 2013;25:91–101.
5. FDA NEWS RELEASE, Oct 12, 2021, FDA Permits Marketing of E-Cigarette Products, Marking First Authorization of Its Kind by the Agency | FDA; accessed Oct 26, 2021.
6. <https://www.healio.com/news/pulmonology/20211001/ecigarettes-with-nicotine-may-affect-thrombotic-activity-impair-microcirculation>, accessed Oct 2021.
7. E-cigarettes containing nicotine cause blood clotting and make small blood vessels less adaptable. <https://www.ersnet.org/news-and-features/news/e-cigarettes-nicotine-blood-clotting-blood-vessels/>. Published Sept. 6, 2021. Accessed Oct. 2021.

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Chair's Corner: Division News

Dear TDM/Toxicology Division Members:

I hope you were able to attend the annual scientific meeting and catch up with colleagues you may not have seen since before the pandemic. Although the Division wasn't able to hold our annual luncheon in Atlanta, we are optimistic that we'll be able to get together at the next annual scientific meeting in Chicago. In the meantime, the Division is considering a fall virtual meeting to introduce the membership to the new divisional officers Paul Jannetto, Christine Snozek, Patrick Kyle, and Fred Strathmann, and to present the division's Best Abstract and Young Investigator awards. Please stay tuned for further communication about this virtual meeting. Until then, I'll see you on the Division Artery page!

Jennifer Colby, Chair.

AACC TDM TOX Award Winners (2021):

- He Sarina Yang (Young Investigator)
- Nicholas Larkey (Outstanding Abstract "Identification of novel macrovancomycin complexes using laboratory developed methods")

AACC TDM TOX Web Resources:

<https://www.aacc.org/community/divisions/tdm-and-toxicology/>

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Announcements:

We need your ideas and article contributions for this newsletter. It is a good opportunity to put authorship in resume. Please contact Dr. Pradip Datta at pradip.datta@siemens-healthineers.com.