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Permalink

<https://escholarship.org/uc/item/4hq506cc>

Journal

Journal of Adolescent Health, 66(1)

ISSN

1054-139X

Author

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Publication Date

2020

DOI

10.1016/j.jadohealth.2019.10.016

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Seizures after Vaping Nicotine in Youth: a Canary or a Red Herring?

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Disclaimer: Dr. Benowitz is a consultant to Pfizer and Achieve Life Sciences, companies that market or are developing smoking cessation medications, and has served as a paid expert witness in litigation against tobacco companies.

Acknowledgements:

ABSTRACT

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Key words: seizures; electronic nicotine delivery systems, ENDS; nicotine

COMMENTARY

Electronic nicotine delivery devices (ENDS, referred to for the purposes of this editorial as electronic cigarettes) were developed as a less harmful source of nicotine to help cigarette smokers quit smoking. A recent large controlled clinical trial and epidemiological data support the idea that the use of e-cigarettes in smokers who are motivated to quit can promote quitting and are more acceptable than conventional nicotine replacement medications (1, 2).

However, the U.S. has experienced a recent surge of e-cigarette use among middle and high school students and young adults who are not using them to quit smoking. While most youth vaping is experimental as evidenced by less 10 days or fewer per month, a sizable fraction are vaping more frequently and some are become highly dependent on nicotine (3). Clearly, there is no health benefit for non-smokers who are using e-cigarettes. The question remains as to the nature and magnitude of adverse health consequences of nicotine vaping among non-smoking youth.

To date, the main adverse effects that are documented in youth who vape nicotine are respiratory – cough and worsening of asthma (4). However, Faulcon and colleagues from the Center for Tobacco Products of the FDA, raise another worrisome health concern (5). These authors describe a series of 122 cases of seizures and other neurological symptoms associated with e-cigarette use that were spontaneously reported to FDA or the American Association of Poison Centers between December 2010 and January 2019. The authors suggest that because of its known pro-convulsant effects, nicotine might be responsible for these events. The authors and the FDA appropriately request that healthcare providers assess the use of e-cigarettes in patients who present with seizures and submit reports to FDA when e-cigarettes are involved.

However, the examination of the spontaneous reports, details of which are provided in the supplemental table, raises questions about a causal link, which needs to be considered in assessing the actual health threat of nicotine vaping for youth. A big question is why nicotine inhaled from e-cigarettes should cause seizures, while nicotine from conventional cigarettes does not. The intake of nicotine is typically similar to or lower from e-cigarettes compared to from tobacco cigarettes. One needs to take in a very large dose of nicotine to cause seizures, and such an exposure would be expected to produce other signs of nicotine intoxication. Also, toxicity after inhaling nicotine would be expected to occur quickly, as brain levels peak within minutes of inhalation, and would be expected to resolve within a few hours.

As a first step in interpreting the association between neurological events, one needs to consider what the events actually were. Descriptions of the seizure events were provided by self-report, and are not always clear. In some cases, tonic-clonic seizures are reported, but in other cases shaking or seizure-like activity are reported. In most cases, records of a medical evaluation are not available. Nicotine can cause anxiety attacks and involuntary muscle contractions, but these are not seizures. Of note is that in 54 cases the reporters continued to vape nicotine after the first event, and had recurrent seizure events. Continued use would be surprising if the user had previously experienced a real seizure.

The probability of causation can be analyzed by considering three elements: 1) biological plausibility; 2) timing of the event in relation to the dosing of the product; 3) the presence of alternative explanations (6).

Biological plausibility. With respect to biological plausibility, as mentioned above, a nicotine overdose can cause seizures, and nicotine can cause seizures in some animal models of epilepsy.

(7, 8) Seizures have been observed in adults who were poisoned with nicotine, and in young children who have consumed liquid nicotine, including nicotine-containing e-liquids (7). Severe nicotine poisoning is expected to cause nausea, vomiting, pallor, sweating, abdominal pain, salivation, lacrimation, muscle weakness, confusion and lethargy before one experiences seizures. These symptoms have been reported of oral or dermal exposure; it is possible that inhalation of a high dose of nicotine may produce a different syndrome, but it seems unlikely that seizures would appear without other manifestations of systemic toxicity. While nicotine overdose can cause seizures, lower doses of nicotine may have anticonvulsant activity in people. An anticonvulsant effect of transdermal nicotine has been reported in people with autosomal dominant nocturnal frontal epilepsy (caused by a mutation in nicotinic cholinergic receptor subunits) and in focal epilepsy (9). Cigarette smoking per se is associated with an increased risk of seizures, but this appears to be due to medical complications of smoking rather than acute effects of nicotine (10).

Another biological plausibility issue relates to several spontaneous reports of recurrent seizures in the absence of vaping. As mentioned before, the effects of nicotine are relatively brief, and cannot explain recurrent seizures at a later time. Most likely, these individuals have a seizure disorder. Whether nicotine can trigger a seizure in a person with an underlying seizure disorder is unclear.

Timing of events. The timing of seizures in relation to vaping in the series was quite variable. 62% had a seizure within 30 minutes and a few had seizures immediately after vaping. If inhaled nicotine caused seizures, seizures would be expected to occur within minutes of vaping, when brain levels are highest; however, many of the seizure cases reported a much longer time lag. In eight cases, a seizure was reported after first use, and in some cases after a single puff.

Generally, a novice vaper inhales the e-cigarette aerosol inefficiently and is exposed to less nicotine than an experienced vaper and takes in less nicotine than a person gets from smoking a cigarette. It is hard to imagine that the dose of nicotine in a single puff would be sufficient to cause a seizure.

Alternative explanations. Many of the case reports suggested alternative explanations for seizures. Some had known seizure disorders, some used cannabis and other drugs in addition to nicotine. Some vaping liquids have been reported to be adulterated with synthetic cannabinoids, cocaine and/or caffeine, all of which can produce seizures.

Could a chemical other than nicotine be the cause of seizures with e-cigarette use? The typical e-liquid contains nicotine, propylene glycol, glycerin and flavoring chemicals. Propylene glycol and glycerin are not known to cause seizures, although at high heating temperatures they may be degraded to form toxic chemicals such as formaldehyde, acetaldehyde and acrolein.⁽¹¹⁾ The amount of these chemicals are however usually lower than those found in cigarette smoke, and cigarette smoking does not acutely cause seizures. Some flavoring chemicals are cytotoxic, but there are no reports of these chemicals causing seizures.

Analysis of the case reports in the paper by Faulcon raises many questions about the nature of the seizures and other events, and whether there is a causal link to nicotine vaping. A formal causation analysis, which has not yet been done, would likely indicate possible causation at most. At this point in time I would not consider seizures to be a potential adverse effect that should influence the decision of an adult smoker to use e-cigarettes to try to stop smoking conventional cigarettes.

However, the possibility of neurological events reported by young vapers should not be ignored. The U.S. is currently experiencing an outbreak of cases of acute lung injury in young people from vaping illicit cannabis products and possibly some adulterated nicotine liquids.(12) Similar to the guidance given to healthcare providers regarding acute lung injury, providers should be aware of a possible link between nicotine vaping and neurological events, should carefully evaluate medical causes of such events, including detailed neurological evaluation and biochemical screens for illicit drug use, should collect vaping devices and liquids for later analysis if possible, and should report such cases to the FDA and state health departments.

Of course, the best solution to address the concern about seizures from e-cigarette use is to eliminate vaping by non-smoking youth. Some public health authorities and politicians have urged banning the sale of e-cigarettes completely to reduce e-cigarette use in youth. The public health cost of such a policy would be to deny adult smokers the availability of a cessation aid that may be life-saving. It makes most sense to focus on limiting youth access rather than banning e-cigarettes completely. Policies of banning sales of e-cigarettes in gas stations and convenience stores, but allowing sale in specialty tobacco and vape shops, and over the internet, where age verification of purchases can be enforced, are reasonable. Hopefully, in this way youth can be protected from harm while supporting the potential benefits of ENDS in reducing the devastating harms from smoking in adults.

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