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The Impact of E-cigarette Use on Seizure Frequency in Vapers with and Without a History of Epilepsy

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ABSTRACT: E-cigarettes/electronic nicotine delivery systems (ENDS), though initially introduced as possible smoking cessation devices for preexisting smokers, have rapidly increased in use over the last few years, attracting youth with aggressive market tactics. Vaping is becoming an increasingly prevalent phenomenon, particularly among younger populations. Though cigarette use has somewhat declined in the United States in the last few years because of awareness and education campaigns, the teen vaping crisis has become more burdensome, especially as teenagers lack insight into the detrimental effects. E-cigarettes mimic regular cigarettes and usually contain nicotine with various flavors, and are used through inhalation. Despite the absence of carcinogenic tars, the use of e-cigarettes still has detrimental effects on several organ systems, such as the lungs and the heart, contributing to various short- and long-term side effects, which are still poorly understood. While using e-cigarettes, nicotine can disperse more quickly than in a regular cigarette due to bypassing first-pass metabolism, which is a phenomenon where a drug is metabolized at a certain location before entering circulation. Bypassing first-pass metabolism leads to higher concentrations of nicotine being delivered. This could lead to acute poisoning with nicotine inhalation toxicity, causing neuronal excitability and, in turn, lowering the seizure threshold. This secondary literature review investigates the effects of vaping on various organ systems, but especially the brain, and its potential for reducing the seizure threshold. This review suggests that e-cigarettes may be related to seizures in someone who has epilepsy. Since vaping is rapidly becoming a public health concern, this information underscores the importance of providing education to adolescents and cautioning them regarding the effects of e-cigarette use. Awareness campaigns and bans on promotions for e-cigarettes could help address the problem of consumption, shedding light on its possible detriments.

KEYWORDS: Vaping, Nicotine Toxicity, Epilepsy, Seizure Threshold, Adolescent Health.

Introduction

The days of regular cigarettes are declining, and many young individuals are drifting toward the trendy electronic cigarettes, also known as vapes or e-cigarettes. In 2020, the Centers for Disease Control and Prevention (CDC) reported that over 480,000 Americans and over 7,000,000 people worldwide had died from various smoking-related illnesses.[1] E-cigarettes were first made in 1965, in China, and patented in 2003.[2] According to the US Food and Drug Administration (FDA), e-cigarettes use a substance called "e-liquid," which is composed of nicotine "derived from tobacco, as well as flavorings, propylene glycol, vegetable glycerin, etc."[3] In addition to nicotine, e-cigarettes may also have ingredients like tetrahydrocannabinol (THC), cannabidiol, and butane hash oil, known as dabs,[4] along with some toxic components, such as formaldehyde, acetaldehyde, acetone, and metals, and volatile organic compounds (VOCs).[5] Each device consists of a rechargeable lithium-ion battery, an electrical heating coil, and liquid in a disposable cartridge or refillable tank, which have undergone modifications over the years. The electric heating coil in the device turns the e-liquid into an aerosol that is inhaled or 'vaped' through the mouthpiece.[6] Nicotine concentration ranges widely, anywhere from 0mg/mL (0%) to 59 mg/mL (5%), and may be more than that of a regular cigarette.[7] The most popular small disposable E-liquid cartridge system is a single JUUL, which contains 5% nicotine in each one, equivalent to one pack of cigarettes, which can give peak nicotine concentration rapidly with sweet flavors, making it even more addictive.[7]

Rapid delivery of the aerosolized nicotine and lack of the usual tobacco aroma made this an attractive option among American adolescents, in addition to fancy delivery systems with various additives. In 2020, the FDA banned cartridge-based e-cigarettes from the market.[8] This did not deter most vapers, as they were still able to acquire them, and many types of e-cigarettes evaded this category.[8] Seizures, as explained by the Mayo Clinic, are when the brain has abrupt and unrestrained outbursts of "electrical activity."[13] Epilepsy is a chronic disease in which people have recurring seizures of various causes. It has been observed that the use of cigarettes is connected to higher breakthrough seizure rates in people with epilepsy.[14] Due to cigarettes increasing seizure frequency, there is the question of whether e-cigarettes do the same. Though the underlying pathophysiology is not completely understood, researchers believe that nicotine modulates acetylcholine receptors and, in turn, contributes to the release of the excitatory neurotransmitter, glutamate.[14] Through the activation of nicotinic acetylcholine receptors (nAChRs) by nicotine, it is thought that there is a large, spontaneous release of glutamate.[15]

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In 2024, 1.63 million students in the United States used e-cigarettes.[32] Between November 2016 and August 2019, it was noted that the total ENDS sales increased by nearly 300 percent,[9] especially among middle and high school students. In the United States, 7.7% of students participate in vaping.[10] By education level, 4.6% of middle school students and 10% of high school students use e-cigarettes.[10] These numbers may be underestimating the true percentage of students who vape due to many students' unwillingness to report the truth. As seen in Figure 1, the prevalence of nicotine-based e-cigarettes in 2017 for those in 8th, 10th, and 12th grade was between 3.5% and 11%. In 2018 (Figure 2), the prevalence of nicotine-based e-cigarette use in grades 8, 10, and 12 almost doubled, as it was reported between 6.1% and 20.9%. There has been a steep increase in the percentage of teenagers who are using nicotine-based e-cigarettes, with the prevalence almost doubling from 2017 to 2018. Many people, especially teenagers, believe that vaping is a healthy alternative to smoking, but this is an incorrect assumption. Smoking cigarettes contributes to most cases of lung cancer and COPD, as stated by the American Lung Association. This does not imply that vaping is without physiological effects; flavors in e-cigarettes can lead to "unknown inflammation"[11] in the lungs, and the development of the brain can be affected, in addition to several other multi-system symptoms.[11]

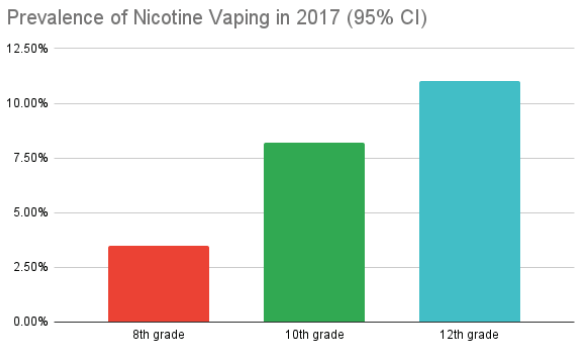

Figure 1: Prevalence of Nicotine Vaping in 2017. The prevalence of nicotine vaping in 2017 in grades 8, 10, and 12 ranged from 3.5% to 11%. Most students who vaped nicotine were in high school, 10th and 11th grade; 8.2% and 11% of students, respectively. Data gathered from Miech *et al.*, 2019.12 Created using Google Sheets.

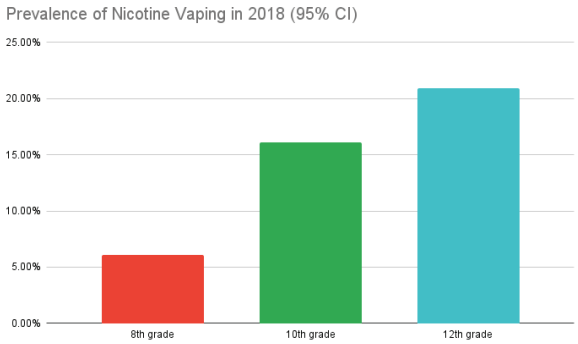

Figure 2: Prevalence of Nicotine Vaping in 2018. The prevalence of nicotine vaping in 2018 in grades 8, 10, and 12 ranged from 6.1% to 20.9%. Most students who vaped nicotine were in high school, 10th and 11th grade; 16.1% and 20.9% of students, respectively. The percentage of students who engaged in the practice nearly doubled from 2017. Data gathered from Miech *et al.*, 2019.12 Created using Google Sheets.

Through this paper, the effects of e-cigarette use on the brain, and more specifically on seizures, will be explored. The findings from this will possibly aid efforts for more education on the consequences of vaping.

Methodology

The key objective of this research paper is to determine the repercussions of e-cigarette use, specifically on seizure potentiation, its frequency, and the proximity to the use of vaping products. This paper is a secondary literature review, which is being conducted through the analysis of many case reports, journal articles, and review studies. To conduct this review, many articles from credible sources, including peer-reviewed original research articles on the health effects of e-cigarettes, e-cigarette use data, effects of vaping on the brain, and the frequency of seizures, were analyzed. A majority of these articles were found through PubMed, Google Scholar, and the Mayo Clinic. Studies published between 2015 and 2024 were considered for inclusion. Overall, a total of 17 peer-reviewed studies and sources were analyzed. A qualitative style of review was used to determine whether vaping increases seizure frequency in those who use e-cigarettes. After this detailed review of various studies, conclusions were made regarding the effect of vaping on the number of seizures, along with other physiologic harmful effects. The following search terms were used: "e-cigarettes," "vaping," "seizures," "epilepsy," "nicotine and brain activity," "nicotine-induced seizures," "neurological effects of vaping," "e-cigarettes and neurological health," and "adolescent vaping and seizures." Through this process of literature review, the ways nicotine affects the brain, and in turn, seizures were researched. Due to this being a literature review, the only materials used were online; no physical resources were used, resulting in no ethical considerations to be observed. Many articles and sources from various parts of the world were used, reducing the risk of research bias.

Discussion

Types of Seizures:

Seizures can be triggered or spontaneous. Spontaneous seizures without any clear identifiable metabolic, or toxic cause, may be related to an underlying genetic cause or structural abnormality. The 2017 International League against epilepsy (ILAE) proposed etiology-specific syndromes contributing to seizures and epilepsy.[16] According to the ILAE report, epilepsy or an epileptic seizure is a neurological disorder that can be associated with abnormal, excessive, or synchronous electrical activity of the brain, causing recurrence of seizures. This can present either as a focal or generalized event, with associated epileptiform abnormalities noted on the EEG. Age of onset can be variable, with a peak noted during the early years of life and another peak again noted in the elderly. Focal seizures are usually related to a focal lesion of the brain, like a stroke, a tumor, an intrinsic brain malformation, or a genetic disorder like tuberous sclerosis. An uncontrolled ongoing seizure lasting longer than 5 minutes is termed "Status epilepticus." This is a neurological emergency. In cases of "Status epilepticus,"

either a prolonged seizure or recurrent seizures without return to the neurologic baseline between seizures may occur.

Although on several occasions, one may not find a clear etiology on imaging studies for the seizure, there may be underlying epileptiform discharges on the EEG. This tendency to have a recurrence of seizures may also be associated with certain triggers. Seizure triggers are causes that can lower the seizure threshold in patients with a tendency to have epilepsy. This can include infections, electrolyte disturbances, metabolic derangements, sleep deprivation, stress, certain medications, and various drugs such as alcohol, cocaine, nicotine, newer synthetic hallucinogens like synthetic cannabinoids and spice. Newer synthetic agents pose challenges for diagnosis, as these are usually not seen in the standard lab testing.

Effects of E-Cigarettes on the Body:

In addition to being a contributor to abuse potential and dependence, nicotine, through vaping, has been seen to have a significant effect on various organ systems, most importantly the lungs. Vapers have differently altered airway epithelia than smokers. It was found that vaping causes significant changes to the airway epithelial proteome that are distinct from the changes seen in smokers, including an altered physical appearance of the airways with erythema and increased friability.[18] Airway epithelial cells play a role in managing the volume and composition of airway surface liquid (ASL), secreting mucins and cytokines, and also providing a barrier against harmful pathogens.[17] The vitamin E acetate with THC in e-liquid was believed to be the cause of the outbreak of acute lung injury related to vaping.[19] Although seeing the exact role of nicotine in this requires more studies, in those who had never smoked and had used an e-cigarette, the gene expression in their lungs changed much more than in those who had used a Propylene Glycol or Vegetable Glycerin (PG/VG) based e-cigarette. The other components of e-cigarettes, including nicotine, have been shown to affect the immune system. This could lead to more susceptibility to pulmonary diseases such as emphysema and bronchiectasis. Nicotine-containing e-liquids are one of the most important contributors to e-cigarette or vaping product use-associated lung injury (EVALI).[17]

Nicotine also has direct effects on the cardiovascular system, via activation of the sympathetic nervous system, given binding of nicotine to α3β4 receptors, triggering release of catecholamines (Epinephrine, Norepinephrine). This, in turn, activates the beta receptors in the heart, causing increased heart rate, workload, and cardiac contractility. In the long term, this over-stimulation of the sympathetic nervous system leads to cardiac remodeling, which promotes the development of heart failure and increases arrhythmogenesis. The use of e-cigarettes could also lead to changes in the heart. Increased arterial stiffness, vascular endothelial dysfunction, increased angiogenesis, cardiorenal fibrosis, and increased atherosclerotic plaque formation were found when observing the effect of chronic exposure to aerosols in animal models.[17] These mechanisms contribute to increased heart rate along with elevated systolic and diastolic blood pressure.

Other components of e-cigarettes have also been observed to cause issues in the body. Flavorings in e-cigarettes, such as sweeteners and chemical flavorants, might account for cardiopulmonary toxicity, asthma, and airway remodeling.

Effects of Nicotine on the Brain:

Nicotine is a key ingredient that is often found in e-cigarettes. The Food and Drug Administration (FDA) received about 117 cases of seizures and other neurological disorders in relation to vaping from April 3, 2019, to June 30, 2019, especially among adolescents.

Inhaled aerosolized nicotine bypasses the first-pass metabolism, allowing it to be quickly absorbed into various organ systems, including the brain. In contrast, only 30% nicotine gets into the systemic circulation through the oral or intraperitoneal route.[20] Nicotine has various complex interactions with neural networks, especially involving mesolimbic reward circuitry in the ventral tegmental area (VTA), striatum, prefrontal cortex, and other limbic pathways. Because of involvement in these reward circuits, substance abuse and addiction problems are primary concerns. Nicotine affects the developing brain of an adolescent more than that of an adult,[21] through specific receptors called nicotinic cholinergic receptors (nAChRs), which are widely distributed in abundance throughout the brain.[22,23] Various animal and human studies have shown that nicotine negatively impacts memory storage and other cognitive functions performed by the hippocampus, thus reducing teen attention, performance, and working memory.[24] Nicotine is reported to increase levels of glutamate in the hippocampus by decreasing glutamate uptake. Additional mechanisms of nicotine induce seizures by attenuation of excitatory amino acid transporter type 3 (EAAT3), thus affecting the clearance of glutamate, which is an excitatory neurotransmitter.[25] As per the Tobacco-Induced Neurotoxicity of Adolescent Cognitive Development (TINACD) theory, which was proposed in 2008 by deBry and Tiffany, smoking nicotine showed aberrant detrimental effects in emotional regulation by reducing the inhibitory control, thus making adolescents more impulsive and inattentive. The amygdala is the primary site in the brain for emotional processing and regulation, along with memory consolidation through its connections with the hippocampus. α7-containing nicotinic acetylcholine receptors (α-nAChRs) are highly expressed in the amygdala, which is an area also involved in seizure generation and epileptogenesis. Nicotine-induced neuronal activation is noted in the amygdala along with other areas involved in the limbic pathways.[26]

Review of Case Reports - Seizures and Vaping:

A case report by Liu-Zarzuela and Sun from the University of Texas focuses on a 20-year-old man who has had recurrent seizures every time he vapes for the past 5 years. The first time he used an e-cigarette, when he was fifteen, he experienced a tonic-clonic (grand mal) seizure.[27] At the age of 19, he used an e-cigarette for the second time, and shortly after, the patient experienced a seizure and had to be hospitalized. This led to him refraining from vaping. Three months later, he used an e-cigarette once again, and within minutes, he experienced a

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generalized tonic-clonic seizure. His labs and scans were all unremarkable and normal, and he was put on levetiracetam (500 mg). The patient quit vaping and started using a nicotine patch. The patches allow for the release of nicotine to be slower, possibly contributing to the lack of seizures after the patient ceases vaping. He had no history of epilepsy, no family history of seizures, nor any risks for them, leading to the conclusion that his seizures were caused by vaping. Nicotine toxicity has been seen in many young people due to e-cigarettes. The authors note that this could lead to interruptions in the neuronal excitability, lowering the "seizure threshold". Exogenous nicotine leads to nAChRs being released into parts of the brain such as the neocortex, amygdala, hippocampus, and thalamus, possibly encouraging seizures.[26] The disruption caused by nicotine leads to overactivity in the brain, encouraging seizures. Nicotine has also been seen to release glutamate, which also excites brain cells, which may trigger seizures. The authors acknowledge that to get a clear link on the relationship between seizures and vaping, more investigation is needed, but it is an important phenomenon to question in terms of public health awareness.[27]

E-cigarettes are popular among youth as the manufacturers make them quite appealing to them with various flavors. These flavorants make adolescents misjudge the nicotine exposure that they are experiencing and their effect on the brain.

One of the case reports by Tatum and Oster follows an eighteen-year-old female without a history of epilepsy. The patient's first seizure occurred in 2019, thirty minutes after she had vaped using a "Juul" e-cigarette, which contains nicotine. During her seizure, she toppled over and hit her head, leading to unconsciousness. She was taken to the emergency room and was quickly discharged with a prescription of levetiracetam (500mg) after her EEG monitoring was reportedly normal without any epileptiform activity. Six weeks later, the patient experienced another seizure one hour after she used a vape with nicotine in it. However, it is important to note that the patient had discontinued levetiracetam by herself two weeks prior to the second seizure episode. The patient endured two more seizures a couple of weeks after the second one, again, within one hour of using the nicotine-based e-cigarette. Her last seizure occurred in early-mid 2020, and she had no other instances of seizures after stopping vaping. In this patient without a prior history of seizure disorder, it was seen that vaping could have been a possible trigger for her seizures, since all of them occurred within an hour of using an e-cigarette.[29]

Based on the case report from Tufts Medical Center in Boston, MA, there is objective evidence of seizure recurrence after adequate control in a young 32-year-old male patient with refractory bitemporal epilepsy in the setting of data available from the responsive neurostimulation (RNS) device (Figure 3). He underwent electroencephalography (EEG) monitoring starting in 2011. By 2017, he was living his life comfortably, was working, and was no longer enduring auras, among other seizure-related advancements. Suddenly, in 2019, there was an increase in ictal and interictal activity that was noted on the RNS recordings, and this was when the patient had started to vape. This report further helps to be aware of the risk associated with the usage of e-cigarettes with tobacco and cannabinoids, resulting in breakthrough seizures.[15]

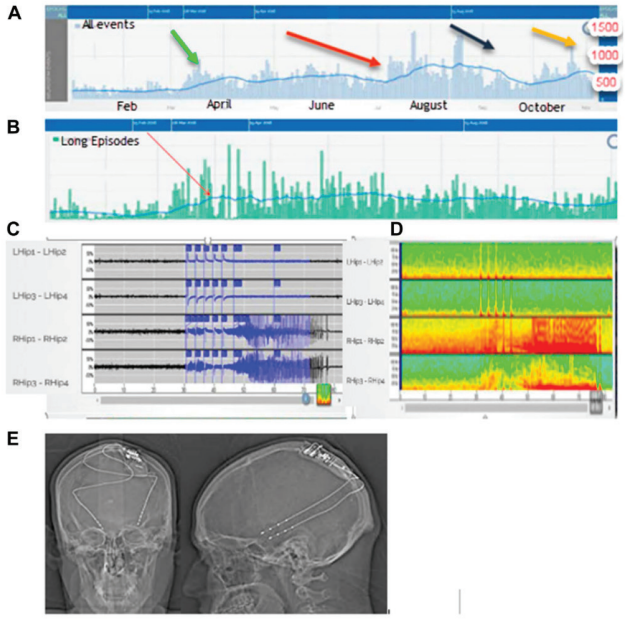

Figure 3: Responsive neurostimulator (Neuropace) Data. RNS device showing the patient's seizure data. Adapted from Oster *et al.* (2021).[15]
A. Data showing interictal discharges and seizures, with worsening especially when associated with vaping (long red arrow)
B. A tally of long episodes of ictal & interictal activity correlating with vaping (thin arrow)
C; D. Recordings of ictal activity; the same data presented in a compressed spectral array.
E. X-ray showing the impulse generator of the RNS device in the posterior head region and the bitemporally placed leads, which record data and stimulate to terminate the electrographic seizure.

In the case report by Tatum and Oster, the focus was on a patient who did not have a history of epilepsy. But in this report by Oster and others, the focus was on a patient with a history of epilepsy. In both works, findings suggest a correlation between vaping and increased seizure frequency.

Lastly, a case was reported regarding a 16-year-old girl with a diagnosis of idiopathic generalized epilepsy at the age of 9. Her semiology included eye rolling, eye fluttering, at times, progressing into generalized tonic-clonic. EEG showing generalized spike and wave discharges, suggesting an underlying generalized epilepsy disorder. Over the years, she tried various anti-seizure regimens, and finally, she was well controlled on lamotrigine monotherapy. After being seizure-free for 7 months, she had recurrent breakthrough seizures over a few days, a total of 5, without any clear trigger. Later, she was found to be vaping in association with these seizures, using a commercial device with nicotine juice. She reported usage of this spearmint, fruit punch, or watermelon flavored vapes, 4 months prior to these breakthrough seizures. She confirmed the usage of e-cigarettes prior to four out of the five reported seizures, but denied any other illicit drug use or alcohol.[29]

E-cigarettes have a plethora of side effects. In the cases observed in the paper, there is seen to be somewhat of a correlation between e-cigarettes and seizure frequency. In most cases, seizures occur within minutes to an hour after vaping.

Through more recognition of the effect of vaping on seizures, the quality of life could be greatly improved. As previously noted, vaping is not healthier than smoking–vaping can lead to various health problems, such as lung disease or heart disease.[31] Inclusion of this repercussion of e-cigarettes could lead to fewer people partaking in the harmful practice, so that they can lead a healthier, more fulfilling life.

Case	Patient Demographics	E-Cigarette Use	Seizure Occurrence	Intervention	Outcome
Case 1	20 year old male, no history of epilepsy	Occasional use of E-cigarette	Seizure experienced minutes after vaping	He was put on levetiracetam and started using a nicotine patch	Did not report to have any more seizures.
Case 2	18 year old female, no history of epilepsy	Used a "Juul" e-cigarette occasionally	Seizures occurred ~30 minutes-1 hour after vaping	She was put on levetiracetam and quit vaping	Did not report to have any more seizures.
Case 3	32 year old male, history of refractory bitemporal epolepsy	Started to use an E-cigarette in 2019	Increase in ictal and interictal activity was noted in RNS activity	Was undergoing EEG monitoring and had an RNS device	N/A
Case 4	16 year old female, history of idiopathic generalized epilepsy	Started to use an E-cigarette with nicotine juice	⅘ of her seizures occured after the use of an E-cigarette	N/A	N/A

Figure 4: Summary of case studies. Overall, a link can be seen between e-cigarette use and seizures.

Conclusion

More research is necessary to establish a definitive causal effect between seizures and vaping. Healthcare professionals also should have a high index of clinical suspicion when an adolescent presents with a new-onset seizure or concerning neurological symptoms, to get a detailed history about vaping products and report these events to the Safety Reporting Portal (SRP). More intense regulatory measures on e-cigarettes should be in place, such as strict law enforcement to curb illegal sales, a promotion ban, a ban on flavoring to be less enticing to teenagers, and possibly increasing the federal ENDS taxes. It is also critical that more education and awareness campaigns be undertaken regarding the consequences of e-cigarettes and their toxic additives.

The purpose of this research was to determine the relation between e-cigarette use and seizures. This was conducted as a secondary literature review through the analysis of multiple primary source articles and studies to conclude. Due to e-cigarettes only recently being popularized, there has not been much exploration of the connection between e-cigarettes and seizure frequency. With the study of long-term impacts of vaping on neurological health, valuable findings would come about. Despite the benefits of using articles, this also poses a limitation: no firsthand studies were conducted for this paper. Through the examination of many articles, a link between e-cigarette use and seizure frequency can be suggested.

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