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The Impact of Nicotine Exposure Through E-Cigarettes on Adolescent Brain Development: Implications for Public Health

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ABSTRACT

Over the past few years the use of e-cigarettes among the adolescent global population has exponentially increased. Evidence suggests that e-cigarettes are not a healthy alternative for traditional tobacco cigarettes. Furthermore, the exposure of nicotine and other chemicals in the e-liquid disrupts the neurodevelopment of adolescents, a critical period for neural growth.

METHODS

We conducted a literature review in which we synthesized data and results from peer-reviewed research papers, public health reports, and neuroimaging studies. Key aspects of this paper include the transport of nicotine in the brain, metabolic reactions between nicotine and e-liquid chemicals with brain receptors, and the effect of chemicals on the adolescent brain and their behavioral activity.

RESULTS

Adolescents from the US and other developed countries are getting more drawn towards e-cigarettes because of appealing flavors and insufficient regulation. Nicotine acts as a potent agonist at β2- and α6-containing nicotinic acetylcholine receptors, activating brain reward pathways and conferring a high risk of addiction. Hence, it may cause decreased neural development, mood disorders and long-term addiction. Additionally, adolescent nicotine exposure disrupts neuroplasticity and hippocampal function, increasing the risk of long-term cognitive and neurological harm. Various studies from the US National Institute of Health support the higher likelihood of youth transitioning from e-cigarettes to tobacco cigarettes, as compared to non-e-cigarette smokers.

CONCLUSION

The findings in this review emphasize that e-cigarettes are not a benign alternative to tobacco cigarettes, particularly for adolescents due to their ongoing brain development. The findings underscore the urgent need for targeted public health interventions and policies to curb adolescent access to e-cigarettes.

INTRODUCTION

An electronic cigarette is a device which many people, particularly adolescents, use as an alternative for tobacco cigarettes. They are mainly used for their longer life span and the idea that they are a safer option than tobacco cigarettes. According to the Surgeon General Report (2016), e-cigarettes consist of four main parts: a battery, an atomizer to heat the coil and aerosolize the e-liquid, a cartridge to store the e-liquid, and the mouthpiece. The e-liquid is vaporized when the user inhales through the mouth piece. E-liquids usually contain nicotine dissolved in solvents like propylene glycol and glycerin, along with flavorings. The vapor delivers nicotine and other chemicals into the lungs, mimicking smoking (Health, 2016).

E-cigarettes were developed in 1965 and officially patented in China in 2003. It entered the North American market in 2007. The market includes 400 different brand names and 7,000 various flavors. Despite their popularity, especially among young people, e-cigarettes were largely unregulated until the FDA began oversight in 2016. Use among U.S. adolescents surged, increasing by 900% between 2011 and 2015 (Lichtenberg, 2017).

Since their introduction, e-cigarettes have evolved significantly in terms of engineering and design. Early models, often referred to as "cigalikes," mimicked the appearance of traditional cigarettes. Later generations, such as vape pens, mods, and pod-based systems like JUUL, offered more advanced features, such as adjustable power, refillable cartridges, and higher nicotine delivery efficiency. Modern devices often utilize nicotine salts, a form that allows higher concentrations of nicotine to be inhaled with less throat irritation, making them especially appealing to young, first-time users. (Lopez & Eissenberg, 2015) describe how e-cigarettes rapidly evolved since their introduction. Early models, called cigalikes, resembled traditional cigarettes in size and appearance, using small batteries and prefilled cartridges. These first-generation devices delivered nicotine less efficiently. Second-generation devices introduced larger batteries and refillable tanks, improving battery life and vapor production. This allowed users to customize flavors and nicotine levels. Third- and fourth-generation devices, often called mods, are larger, more powerful, and highly customizable. Users can adjust voltage, wattage, and airflow to control vapor amount and nicotine delivery. These advanced devices also allow modifications to atomizers and heating elements, increasing efficiency but potentially raising health risks due to higher temperatures and chemical exposure. Therefore, regulation has become more challenging.

From a biological standpoint, the e-liquid consists of many chemicals such as heavy metals, formaldehyde, and carcinogens, which are harmful during the critical stage of adolescent brain development. However, nicotine is a substance in the e-liquid that prevents users from quitting smoking due to its addictive characteristics. When nicotine binds with the nicotinic acetylcholine receptors (nAChRs), it enables dopamine to be released and provide the user with pleasurable feelings. (Sansone et al., 2023) states that Nicotine is a plant-derived alkaloid mainly found in *Nicotiana tabacum* and is the primary addictive compound in tobacco. As outlined by, nicotine exerts its effects by binding to nicotinic acetylcholine receptors (nAChRs), particularly the α4β2 subtype in the brain, triggering the release of neurotransmitters like dopamine and glutamate, which contribute to its addictive potential. Nicotine's changes to microRNAs and DNA methylation can disrupt brain cell growth and connections during development. This affects brain areas that control attention, mood, and behavior, increasing long-term risks for ADHD, depression, addiction, and Alzheimer's disease.

The systematic review and meta-analysis by (Salari et al., 2024) reported a 16.8% prevalence of ever e-cigarette use and 4.8% current use among youth. When including both youth and young adults, the prevalence was 15.3% for ever use and 7.7% for current use. The study included data from numerous countries and revealed that e- cigarette use is widespread among young populations worldwide. Additionally, prevalence rates were generally higher in boys than girls, indicating gender differences in usage patterns.

Consequences of adolescent e-cigarette use and onset and/or exacerbation of chronic mental illness:

(Pearson, 2021) emphasizes the complex interplay between youth e-cigarette use, other substance use, and mental health conditions. For example, a 2017 U.S. survey found that over 90% of adolescents who used e-cigarettes in the past 30 days also used at least one other substance, with 87% using alcohol, 76% tobacco, and 66% cannabis concurrently. A systematic review of 40 studies revealed associations between e-cigarette use and internalizing problems (like depression and anxiety), externalizing behaviors (such as conduct disorder and impulsivity), and stress. Furthermore, adolescents who use multiple substances, including e-cigarettes, are at increased risk for the onset or exacerbation of chronic mental illnesses.

A cross-sectional survey among 9th-grade students, average age 14 from 10 public high schools in Los Angeles was conducted to explore psychiatric comorbidities linked to e-cigarette and conventional cigarette use. The study found that 12.4% of adolescents reported using e-cigarettes only, which was more common than the 4.6% who used conventional cigarettes only and the 5.7% who used both (dual users). Compared to non-users, e-cigarette only users showed higher rates of depression and panic disorder but lower levels of internalizing disorders than conventional cigarette users. Additionally, externalizing problems and substance use were lowest among non-users, moderate in single-product users, and highest in dual users, indicating that dual use is associated with the greatest psychiatric comorbidity (Leventhal et al., 2016).

Another study analyzed data from the Population Assessment of Tobacco and Health (PATH) involving adolescents (12-17 years). It was found that mental health problems such as depression and anxiety were associated with an increased risk of initiating both e-cigarette and combustible cigarette use. Adolescents with pre-existing mental health issues had higher odds of starting to use e-cigarettes compared to those without such conditions (Riehm et al., 2019).

Potential respiratory diseases by e-cigarettes to adolescents:

(Chaffee et al., 2021) investigated the association between e-cigarette use and adverse respiratory symptoms using logistic regression models for adolescents and young adults aged 13-21 years (N=10483). This study took data from four United States cohorts in California and Connecticut, spanning from 2018 to 2020. People using e-cigarettes more than 5 times a month were compared with non-users for bronchitis symptoms. People who smoked the e-cigarettes were 1.56 times more likely to have bronchitis symptoms, with a confidence range of 1.37 to 1.77. They were also 1.68 times more likely to experience shortness of breath, with a confidence range of 1.35 to 2.08. However, the link between e-cigarette use and asthma attacks was not clear, as the odds were 1.36 times higher, but the confidence range of 0.95 to 1.95 means this result could be due to chance.

Another study supporting the claim of potential respiratory diseases by e-cigarettes was found, by (McConnell et al., 2017), which investigated the association between e-cigarette use and respiratory symptoms in adolescents using data from the Southern California Children's Health Study (CHS). The researchers conducted a cross-sectional analysis of 2,086 11^{th} and 12^{th} grade students in 2014. Logistic regression models were used to estimate odds ratios (ORs). The results showed that both past and current e-cigarette users had significantly higher odds of reporting bronchitis symptoms compared to never-users. Compared to never users, past users were 1.85 times more likely to report bronchitis symptoms with a confidence interval of 1.37-2.49. And the current users were 2.02 times more likely to report bronchitis symptoms with a confidence interval of 1.42-2.88. In conclusion adolescent e-cigarette users have the tendency to develop bronchitis symptoms at higher rates than non-users.

While these studies mainly focus on respiratory outcomes, their findings are relevant to adolescent brain development. Recurrent bronchitis symptoms and shortness of breath indicate chronic airway inflammation and reduced oxygen exchange, which may limit oxygen delivery to the developing brain. Adolescence is a critical period for neurodevelopment, and prolonged hypoxia and systemic inflammation during this stage can interfere with neuroplasticity, synaptic refinement, and cognitive maturation. In addition, inflammatory responses resulting from e-cigarette related lung injury may contribute to neuro-inflammation by crossing or disrupting the blood–brain barrier. Together, these respiratory effects may increase the neurodevelopmental risks associated with prolonged nicotine exposure in adolescents.

This review aims to synthesize current evidence on how nicotine and e-cigarette toxicants impact adolescent brain development, focusing on neurodevelopmental and cognitive outcomes. It also examines

associated risks of neurodegenerative diseases and potential long term public health implications, highlighting the urgent need for targeted prevention and regulatory strategies.

METHODS

To identify studies for this literature review, a comprehensive search was conducted in databases such as PubMed and Google Scholar. The search keywords included: e-cigarettes and adolescents, composition of e-liquid, e-cigarettes mechanism, e-cigarettes and neurodegenerative diseases. Ninety studies were added to Zotero, a reference management tool. This helped avoid duplicate entries and ensured consistent citation tracking, especially since many articles appeared across multiple databases such as PubMed and ScienceDirect. After reviewing the studies, they were selected based on their relevance, for instance, some studies required scientific theory of human biology explaining the anatomy, physiology, and biochemistry, such as: (Maggi et al., 2004) concludes that nicotine contributed to decreased synaptic activity in the human brain. Older studies, published before 2003, when e-cigarettes were officially introduced in China were only included if they provided essential background information on neurobiology and nicotine's mode of action in organisms. However, the studies relating to e-cigarettes including their mechanism were selected and preference was given to recent studies post 2010, to ensure the data reflected current formulations and use patterns of e-cigarettes among adolescents. Studies from the 20th century were excluded, as only articles published after 2000 were reviewed. Other studies in the exclusion criteria were those that did not include investigations relating to adolescents and young adults, as they solely focused on the older demographic. Non-peer reviewed articles with personal opinions and articles from blog spots were also excluded from this research. These studies included references from my mentor for subtopics in my research by providing me with the names of experts and social media links for their lecture in conferences, so I could better understand their work and use their studies in the right context to the best of my abilities. Most studies were consistent using rats and mice as their test subjects in experiments, for example: concluding the toxicity of a chemical found in e-liquid. This included reaction of ethanol with nicotinic acetylcholine receptors in the two groups of rats: RR and QQ, by (Sanna et al., 2004), and how nicotine travels from the blood to the brain using rats by (Tega et al., 2013). A research outline was made before writing to facilitate systematic organization and synthesis of the selected literature, relevant study details were extracted and compiled into a structured Excel spreadsheet. This spreadsheet included key variables for each article: author(s), year of publication, study design and methodology, participant characteristics (where applicable), and findings or results of the study. These tables were then transferred into Microsoft Word, serving as a summary resource for quick reference during writing. This approach enabled efficient cross-referencing of critical information and improved clarity in understanding each study's contribution before citing or writing it in the narrative. Similarly, prior to the writing process, a comprehensive research outline was collaboratively developed with my mentor. This structured outline served as a strategic framework, defining key sections such as the introduction, methods, results, and discussion. Specific topics and sub-topics within these sections included an overview of e-cigarette mechanisms, nicotine as a biological primer, and the identification of research gaps, particularly concerning the long-term effects of e-cigarette use among adolescents.

Establishing this outline not only facilitated a logical progression of ideas but also ensured that each component of the paper was thoroughly planned and interconnected. This preparatory step proved invaluable to the clarity and depth of the final research paper.

RESULTS

Nicotine pharmacokinetics and blood-brain barrier:

E-cigarettes contain the following components that enable the aerosolization of various chemicals and particles: battery, coil, atomizer, cartridge, and mouthpiece. When the user inhales, the coil heats up and the aerosol is produced. The materials in the e-liquid are nicotine, propylene glycol, vegetable glycerin, and flavors often based on foods (e.g., strawberry ice cake). Many e-cigarettes allow users to vary resistance. Lower coil resistance allows more electrical current flow, which enables the coil to heat more easily; thus the e-liquid is converted to a gaseous/vapor state quickly. Conversely, higher coil resistance allows less electrical current flow, which enables the coil to become less heated; thus the e-liquid is converted to a gaseous/vapor state over a longer time. The higher the number of coils, the more aerosol produced. The nicotine delivered via heated aerosol is not pyrolyzed at temperatures below 600°C. This lack of pyrolyzation causes denser aerosol to be ingested. The low resistance in the coil allows the more heated aerosol to be inhaled easily, with more concentration of aerosol in the rate of puffs and volume. Therefore, the concentration of the aerosol is increased. These inhalations with insufficient e-liquid (i.e., 'dry hits') may produce toxic carbonyls from propylene glycol/glycerol degradation. Furthermore, in the case of custom setups when e-liquid is directly applied to the coils (i.e., ‘dripping’), metal and chemical inhalation may increase (National Academies of Sciences., 2018).

A real-time, high-resolution spectrometer was used to track the evolution of aerosol size and concentration during e-cigarette puffs. The aerosols were delivered directly with minimal dilution, preserving the native particle distribution. E-cigarette vapor usually has two particle sizes, both nanoparticles (11–25 nm) and submicron particles (96–175 nm) present in similar concentrations (10^7–10^8 particles/cm³). When someone vapes without enough liquid (dry puff), only nanoparticles are to be observed. The filters inside captured metals in the aerosol, confirming the presence of harmful compounds. The toxicants included: metals such as chromium (Cr), nickel (Ni), lead (Pb). And carbonyls in the aerosol. In terms of health, the nanoparticles increase bioavailability of toxicants (Mikheev et al., 2016).

For the transportation of nicotine, (Tega et al., 2018) investigated the absorption of nicotine in the brain and determined which type of transport system was involved. Nicotine is absorbed into the bloodstream

via the lungs and then circulated to organs including the liver, kidneys, and brain. Nicotine rapidly crosses the blood-brain barrier with dominant influx over efflux. In other words, as nicotine containing blood flows into the brain more of that nicotine is retained in the brain than flows out with the blood. Nicotine is primarily ionized in physiological pH, which makes passive diffusion difficult and less than the carrier-mediated transport. Nicotine becomes charged and hinders the passive transport system due to the forces of attraction and repulsion that the nicotine ion creates. This ionization causes active transport, which is a carrier-mediated transport system from carrier proteins influenced by hydrophobic cationic drugs. Thus, more transport occurs from lower to higher concentration.

Another study demonstrated how blood enters and is cleared from the brain using a rat model. A special type of rat brain cell, TR-BBB13, was used to test how nicotine crosses the barrier in a controlled environment. Nicotine moves into the brain about twice as fast as it moves out. Pyrilamine is a substance that blocks certain transporters. When Tega et al. used pyrilamine, the amount of nicotine that entered the brain decreased, which demonstrated that specific transporters are involved in moving nicotine into the brain. In conclusion, pyrilamine blocked nicotine from entering the TR-BBB13 cells, which supports the idea that organic cation transporters are responsible for moving nicotine into the brain (Tega et al., 2013).

(Cisternino et al., 2012) investigated how nicotine crosses the blood brain barrier in mice using in situ brain perfusion, allowing precise control of the perfusate composition. Radiolabeled nicotine ([^{3}H]-nicotine) was used to measure its transport. Various mouse models were used, including wild type and transporter knockout mice: organic cation transporters, P-glycoprotein, and breast cancer resistance protein. The study tested for passive diffusion versus carrier-mediated transport, influenced by pH, inhibitors, and ion changes. They also evaluated how different drugs and ion manipulations (e.g. sodium removal and pH shifts) impacted nicotine transport. The transport of nicotine is likely carried out by a proton-coupled antiporter, which also helps move tramadol and diphenhydramine. Nicotine transport was influenced by pH, intracellular acidification, and proton gradients, but not sodium. Blocking this antiporter may reduce nicotine brain entry and offer a target to combat nicotine addiction. Known transporters: Organic cation transporters, P-glycoprotein, Breast cancer resistance protein, multidrug and toxin extrusion protein 1 (MTEP1), organic cation carnitine transporters, Plasma Membrane Monoamine Transporter did not mediate nicotine transport. They concluded that nicotine transport at the blood brain barrier is both passive (21%) and carrier-mediated (79%), which follows Michaelis–Menten kinetics (Km = 2.60 mM, Maximum rate/speed = 37.60 nmol/s/g).

A study was conducted to investigate how quickly nicotine from e-cigarettes reached the brain. Volunteers puffed on e-cigarettes: 9 men and 8 women. The levels of nicotine in blood and brain were measured using functional magnetic resonance imaging (fMRI) and nicotine concentration analysis. It was observed that nicotine rapidly reached the brain after just one puff from an e-cigarette, with half maximal brain nicotine concentration reached in about 27 seconds. The highest nicotine concentration in the brain was 25% more in women compared to men. This fast paced effect of nicotine may explain its highly addictive behavior. They concluded that the total nicotine accumulation in the brain from e-cigarettes was lower than that from combustible cigarettes, 24% in men and 32% in women (Solingapuram Sai et al., 2020).

Nicotinic acetylcholine receptor activation:

The difference between nicotine craving from e-cigarettes and tobacco cigarettes was studied. Seven nicotine users participated in this experiment. Nicotine binding with receptor was measured by neuroimaging via positron emission tomography (PET) using (-)-[18F] Flubatine, which is a radiotracer. Each participant was exposed to nicotine from 0 mg/ml (no nicotine), 8 mg/ml nicotine (low dose), and 36 mg/ml nicotine (high dose). The devices used were electronic cigarettes with 0, 8, or 36 mg/ml nicotine, using 3.3 Volt, and 1.5 Ohm settings, and a standard tobacco cigarette for comparison. The subunit beta-2 (β2) from nicotinic acetylcholine receptors (nAChR) occupied/activated different percentages of nicotine in the brain. In tobacco cigarettes it was 68 ± 18%, in 8 mg/ml e-cigarette it was 64 ± 17%, and in 36 mg/ml e-cigarette it was 84 ± 3%. Over time the blood nicotine level was higher in the cigarette smoking group compared with the 8mg/ml group ($p = 0.03$), and the blood nicotine level was higher in the cigarette smoking group compared with the 36 mg/ml EC ($p = 0.29$). They concluded that nicotine craving after use did not differ between e-cigarettes and cigarettes (Baldassarri et al., 2018).

Furthermore, (Grupe et al., 2015) reviewed the potential of positive allosteric modulator (PAM) drugs to enhance receptor activity without the risks associated with traditional nicotine treatments. It is well established that nicotinic acetylcholine receptors (nAChR) cause smoking addiction by e-cigarettes, and this is a risk factor for central nervous system chronic diseases such as schizophrenia and Alzheimer's disease. Weak malfunctioning and signaling of these receptors may cause these diseases. PAMs (e.g., desformylflustrabromine and the compound NS9283) help the receptor to enhance activity by binding to sites distinct from the main binding site on a protein, thereby boosting neurotransmission without disrupting normal signaling patterns. PAMs do not cause the intense and immediate response of the brain's reward chemical dopamine. Therefore, these drugs help the brain function better without being addictive.

Ethanol content in 56 e-liquid samples was measured. Thirty-five of them contained nicotine only and the remaining 21 comprised of chemicals other than nicotine. Ethanol content was measured by headspace gas chromatography with flame ionization detection. Small electrical signals were produced after the chemicals were separated by chromatography, which indicated how much of each chemical is present. Ethanol was observed in 33 out of the 35 nicotine containing e-liquids. The concentrations ranged from 0.07 to 206 mg/mL, and two samples exceeded 100mg/mL. VapeWell's Cherry flavor was the only sample that mentioned their ethanol content: 56 mg/mL. Among the 21 e-liquids that contained chemicals other than nicotine, 20 of them contained ethanol: concentrations ranged from 0.10 to 194 mg/mL. Ethanol was present in all but one sample. The subunit alpha-6 (α6) releases the hormone dopamine when nicotine and ethanol bind with it. Therefore, having addictive characteristics for both nicotine and alcohol, which are present in most of the e-liquids (Poklis et al., 2017). To assess how the α6 subunit influences alcohol sensitivity, (Sanna et al., 2004) divided Sardinian alcohol non-preferring (sNP) rats into 2 groups, normal (RR) and mutated (QQ), and compared them. They gave the rats chronic ethanol exposure and measured protein levels using western blot analysis to assess levels of the α6 protein in rat brains after

exposure to ethanol. Sanna et al. (2004) showed that in the normal RR rats, the α6 subunit increased after alcohol exposure, while in the mutated QQ rats, it stayed the same. Both rat groups showed a decrease in α1 subunit levels, as this could impact how alcohol affects the brain, potentially making the rats less sensitive to alcohol's calming effects. Therefore, requiring more alcohol to achieve the same effect.

Together, these changes may contribute to tolerance and an increased risk of alcohol addiction.

Moreover, (Jackson et al., 2009) suggests that α6 play a key role in nicotine addiction and blocking these receptors by an antagonist α-conotoxin MII peptide (MII[H9A;L15A]) that reduces nicotine's rewarding effects. This antagonist blocks anxiety-related behavior, but had no effects on physical withdrawal symptoms like somatic signs or enhanced pain including hyperalgesia. Hence α6 receptors are involved in the emotional aspects of withdrawal such as stress and anxiety, rather than physical dependence. The α6 receptor is likely involved in causing those emotional reactions if nicotine craving is not satisfied.

Aerosol Toxicology:

(Olmedo et al., 2018) studied 56 e-cigarettes were used for their experiment which contained e-liquid tank, refilling dispenser, and aerosol. They studied potential transfer of metals from the heating coil to e-liquid and aerosol. The collection method of the aerosol was by droplet deposition via pipette tips. Metal concentrations that were reported as mass fractions (i.e., μg/kg in liquids) were converted to concentrations (i.e., mg/m^3) in aerosols so that human exposure to the metals could be assessed. It was observed that the concentration of metals was higher in the aerosol tank versus the refill dispenser, all $p<0.001$. Olmedo et al. (2018) found the following mass fractions of metals in aerosol and tanks versus in dispensers: aluminum: 16.3/31.2 vs. 10.9 μg/kg, chromium: 8.38/55.4 vs. <0.5 μg/kg, nickel: 68.4/233 vs. 2.03 μg/kg, lead: 14.8/40.2 vs. 0.476 μg/kg, and zinc: 515/426 vs. 13.1 μg/kg. Other metals that were detectable were manganese, iron, copper, tin, and antimony. Cadmium was not present in refill dispensers at all but was present in 30.4% of the aerosols and 55.1% of the tanks. Arsenic was present in 10.7% of the dispenser samples and similar in the aerosol as well. Some metal concentrations exceeded health limits such as: chromium, manganese, nickel, and lead. EPA's maximum contaminant level for chromium in drinking water is 0.1 mg/L, and the FDA's limit for lead in bottled water is 5 parts per billion. Although no specific FDA limits exist for these metals in e-cigarette liquids, their presence at similar or higher concentrations raises concern due to inhalation exposure potentially exceeding safe levels set by the Agency for Toxic Substances and Disease Registry (ATSDR) and Occupational Safety and Health Administration (OSHA). Based on the evidence from this study, greater metal concentration is found in aerosol and tanks compared to refill liquid from the dispenser. Hence, more metals are present inside the e-cigarette, which are then aerosolized by the heating of the e-cigarette components, and are potentially harmful for human health.

Another study analyzed aerosols from 194 e-cigarette devices including MODs, PODs, and disposable PODs (d-PODs), to assess metal exposure from various brands and flavors. Devices were acquired through online purchases and Johns Hopkins EMIT study participants, and aerosols were collected using machine-simulated inhalation protocols (0.25 – 0.5 mL per puff). Twelve metals were quantified using

aerosol samples, including aluminum (Al), arsenic (As), chromium (Cr), lead (Pb), manganese (Mn), and nickel (Ni), with concentrations reported in mg/m³. Metals were detected in the aerosols of all devices tested. MODs generally produced the highest total metal levels, while PODs and d-PODs showed elevated levels of cobalt and nickel. Notably, tobacco-flavored PODs contained up to seven orders of magnitude higher concentrations of certain metals (e.g., Al, Cr, Cu, Fe, Pb, Mn, Ni) compared to mint or mango flavors. Approximately 52% of devices exceeded the Agency for Toxic Substances and Disease Registry (ATSDR) minimal risk level (MRL) for nickel and 14% for manganese, with several samples also surpassing EPA and California EPA limits for lead and arsenic. These emissions were traced to heated internal components, particularly coils and joints made from nichrome alloys (Schmidt, 2024).

The presence of toxic metals in commercially available e-cigarettes was also investigated, by (Neu et al., 2020). Cartridges from MarkTen, VUSE, and Blu devices were purchased in the greater Baltimore area between September 2017 and February 2018. All devices were stored at room temperature: 22 ± 2°C, to simulate how people normally using the e-cigarette would store the device. These cartridges were deconstructed and cleaned, and then their e-liquids were extracted using ZiplocÔ bags, a vice, and a centrifuge. The metals were detected by inductively coupled plasma mass spectrometry. Neu et al. (2020) observed high recovery rates between 98% and 112% for the following metals: lead, copper, chromium, and nickel. The base level of the metals inside the e-liquid is 100% and as mentioned above. Based on the evidence from Neu et al. (2020), it can be concluded that these toxic levels of metals come from heating the coil, and it varies by brand and flavor. This study encourages better regulation, product labelling, and quality control in the e-cigarette industry.

Furthermore, the formation of benzene in e-cigarette aerosols was examined by (Pankow et al., 2017). They tested three types of e-cigarette devices: JUUL™ pod system and two refillable tank devices: EVOD™ and Subtank Nano device, with adjustable power settings. Using gas chromatography/mass spectrometry (GC/MS), they analyzed aerosols produced from e-liquids containing combinations of propylene glycol, glycerol, benzoic acid, benzaldehyde, and nicotine. Benzene was not detected in any JUUL™ aerosols, however it was formed in the two refillable tank systems, For the EVOD device the mean benzene concentration was 1.7 μg/m³ at 6W and 750 μg/m³ at 13W. In contrast, for the Subtank Nano device, benzene was not detected at 6W and was only 1.5 μg/m³ at 25W. The highest benzene concentration observed was 5000 μg/m³. Comparatively in the ambient air in the U.S. it contains approximately 1 μg/m³ of benzene, while traditional cigarette smoke contains around 200,000 μg/m³. The study concluded that even though benzene levels are less in e-cigarettes than tobacco cigarettes, repeated exposure, especially at high power may still pose health risks. The 15th reports on carcinogens from the (National Toxicology Program., 2021) characterizes benzene as a carcinogen. In various studies exposure to benzene increases the risk of developing leukemia, particularly acute myelogenous leukemia. This is the reason that in 2012 the International Agency for Research on Cancer (IARC) classified benzene as a carcinogen. And IARC also found limited evidence that benzene exposure may be linked to certain cancers like lymphocytic leukemia, multiple myeloma, and non-Hodgkin lymphoma.

A review of chemical constituents found in e-cigarette liquids and aerosols by analyzing data from multiple studies was conducted. It was reported that naphthalene, a polycyclic aromatic hydrocarbon was

found in both e-cigarette liquids and aerosols in several studies, although the concentration of naphthalene varied depending on the device and e-liquid formulation (Eshraghian & Al-Delaimy, 2021). (Lewis, 2012) investigated whether naphthalene exposure poses a carcinogenic risk to humans by reviewing data from animal studies and epidemiological records. The study reviewed two long-term National Toxicology Program (NTP) inhalation bioassays which found that rats exposed to naphthalene developed nasal tumors and mice developed lung tumors at concentrations of 10–60 parts per million (ppm). The study concluded that while animal evidence strongly supports naphthalene's carcinogenicity, the relevance to humans is uncertain due to anatomical and metabolic differences between species, and insufficient epidemiological data.

However, regulatory bodies such as the U.S. EPA and IARC have considered naphthalene a potential or possible human carcinogen, extrapolating from the animal data.

The presence of formaldehyde in e-liquid samples (N=16) was investigated. They used chromotropic acid method to detect and quantify the concentration of formaldehyde, as this method is a colorimetric process. Four of the samples contained formaldehyde, among them 2 were flavored and 2 were non-flavored. All of these were pods or disposable e-cigarettes. The 4 e-liquids that tested positive for formaldehyde had an average nicotine concentration of 3.85%, and the 12 e-liquids that did not contain formaldehyde had a slightly higher average nicotine concentration of 4.03%. Suggesting that the presence of formaldehyde is not directly related to nicotine concentration. They conclude that the toxic chemicals are not declared as formaldehyde is present. Hence regulatory bodies need to perform stricter regulation (Ruggiero et al., 2022). Formaldehyde as a carcinogen for humans by experimenting on rats and non-human primates was also examined. The DNA adducts occur when harmful chemicals like formaldehyde stick to the DNA. They were measured by nano-ultra performance liquid chromatography coupled with tandem mass spectrometry (nano-UPLC MS/MS). There were two stages of mass spectrometry so that identifying complex molecular structures are done with more specificity. Rats were exposed to different formaldehyde concentrations: 0.7–15 parts per million (ppm) for up to 6 hours. Whereas non-human primates were exposed to formaldehyde at 1.9 and 6.1 ppm, and DNA adducts were measured in nasal tissues. Formaldehyde exposure induced nasal DNA adducts in rats, at 15 ppm the DNA damage from outside became greater than the natural damage in the body in rats, hence breathing in a lot of formaldehyde can increase the risk of DNA damage and cancer. In non-human primates no formaldehyde induced DNA adducts were detected in distant tissues like bone marrow, and brain, suggesting limited carcinogenic potential outside nasal tissues. This is because non-human primates breathed through both nasal cavity and the mouth, so formaldehyde exposure was not constant like in the case of rats. In both cases formaldehyde exposure led to down-regulation of micro RNAs in lung cells and nasal epithelium, indicating epigenetic changes that could contribute to carcinogenesis (Swenberg et al., 2013). A systematic review to assess the carcinogenic effects of formaldehyde exposure was conducted which analyzed 21 peer-reviewed articles published between 2000 and 2021. The review found weak but consistent associations between formaldehyde exposure and cancers such as nasopharyngeal cancer, leukemia, and non-Hodgkin's lymphoma. These findings support the classification of formaldehyde as a

Group 1 human carcinogen by the International Agency for Research on Cancer (IARC) (Protano et al., 2021).

(Son et al., 2020) investigated carbonyl and carbon monoxide (CO) emissions from various e-cigarette devices, assessing how design and usage influenced emissions. Four e-cigarette types were tested: a cig-a-like (V2), a top-coil clearomizer (eGo CE4), a variable-wattage mod device (ReuLeaux RX200), and a closed pod system (JUUL). Aerosols were generated in a lab using a custom vaping machine, with puff durations ranging from 3.3 to 4.2 seconds and volumes between 80 and 133 mL. Power settings were varied on the mod device, and both flavored and unflavored e-liquids were tested. Carbonyls were collected using 2,4-dinitrophenylhydrazine (DNPH)-coated filters and analyzed via high-performance liquid chromatography (HPLC), while CO levels were measured using a calibrated CO analyzer The top-coil clearomizer produced the highest carbonyl and CO emissions, sometimes above short-term exposure limits. JUUL had the lowest emissions but delivered the most nicotine. Emissions rose with longer puff duration, while puff flow had minimal effect. Flavored e-liquids produced more toxicants than unflavored. A strong link between CO and carbonyls suggested both came from the same heating process in the coil. The study concluded that while e-cigarette emissions are generally lower than those from cigarettes, some devices, especially top-coil models can still emit harmful levels of toxicants.

Though the e International Agency for Research on Cancer (IARC), the National Toxicology Program (NTP), and EPA have not labelled carbon monoxide as a human carcinogen, it can still be damaging towards human health. Because EPA has classified carbon monoxide as a hazardous air pollutant (Wilbur et al., 2012). Neurologic complications of carbon monoxide (CO) poisoning, analyzing clinical, neuropathological, and neuroimaging data from patients exposed to CO were reviewed. The study highlighted that CO binds hemoglobin with high affinity, causing brain hypoxia and damage, especially in the globus pallidus, hippocampus, and white matter. Using neuroimaging and postmortem analysis, they found both acute and delayed brain injuries leading to cognitive deficits, movement disorders, and neuropsychiatric symptoms such as dementia and depression. They emphasized that CO poisoning often presents with nonspecific symptoms, complicating diagnosis. Oxygen therapy remains the primary treatment though outcomes vary widely (Betterman & Patel, 2014).

The studies reviewed suggest the presence of the following chemicals: heavy metals (lead, nickel, chromium), benzene, naphthalene, formaldehyde, carbonyls, and CO. Due to nicotine addiction adolescents are continuously getting exposed to these chemicals. In adolescents, whose brains are still developing, these neurotoxicants can impair synaptic development, alter neurotransmitter systems, and induce DNA or epigenetic changes, potentially affecting cognition, memory, and behavior. This links toxic exposures directly to adolescent neurodevelopment.

Propagation of neurodegenerative diseases:

Decreased synaptic activity in the brain caused by nicotine, by cutting hippocampal slices was tested by (Maggi et al., 2004). They were cut from 1 to 7 day old rats, prepared and maintained in oxygenated artificial cerebrospinal fluid to preserve neuronal activity. Electrical responses from CA1 pyramidal neurons were measured using patch-clamp recordings. Focusing on signals that activate the neurons, which are controlled by AMPA and NMDA receptors. To better isolate these signals, GABAA receptors, which normally quiet down brain activity were blocked, and a toxin called Tetrodotoxin (TTX) was used to reduce unwanted background activity. It was found that exposure to nicotine in the immature rat hippocampus causes a persistent decrease in synaptic efficacy at the Schaffer collateral–CA1 synapses. This reduction in synaptic strength remained even after nicotine was removed, indicating a long-lasting effect.

To evaluate the effects of nicotine on neural stem cells (NSCs) and neural progenitor cells (NPCs), which are essential for neurogenesis, (Brooks & Henderson, 2021) conducted a systematic review. This review examined both in vitro and in vivo studies, particularly targeting two brain regions where human neurogenesis occurs: the subventricular zone (SVZ) and the subgranular zone (SGZ) of the hippocampus. In in vitro studies they used neurosphere cultures derived from embryonic mouse brains. NSCs were treated with different amounts of nicotine: 100 to 800 μM to see how it affected their growth and survival. The results showed that higher nicotine levels led to fewer and smaller cell clusters (neurospheres), meaning that cell growth was reduced. A marker for cell division (PCNA) also went down, showing that the cells weren't dividing as much. However, markers that show the cells were still stem cells like nestin, stayed the same. Nicotine also increased inflammation related proteins like COX-2 and TNF-α and affected certain genes that control how DNA is read: HDAC1 and SIRT1. When HDAC inhibitors were used, some of the harmful effects on cell growth were reduced. In vivo studies revealed that effects were region specific: nicotine enhanced neurogenesis in the SVZ but suppressed it in the SGZ, particularly affecting areas related to memory and learning. This review finds that nicotine disrupts neurogenesis in a complex, brain region dependent manner, which may have lasting consequences during adolescent brain development.

(Grundey et al., 2012) investigated how nicotine affects neuroplasticity in healthy non-smokers by using a rapid-delivery nicotine spray. Participants were randomly given either nicotine or a placebo. To test how the brain adapts, the researchers used two brain stimulation methods: transcranial direct current stimulation (tDCS), which affects broad areas of the brain, and paired associative stimulation (PAS), which targets specific brain connections. The brain activity was measured before and after using transcranial magnetic stimulation (TMS). This technique records the changes in electrical signal: motor-evoked potentials (MEPs), which show how active and responsive brain cells are, hence acting as a marker of neuroplasticity. The results showed that nicotine quickly disrupted the brain's normal plasticity response. Specifically, nicotine abolished inhibitory plasticity regardless of the stimulation method, blocked the formation of non-focal facilitatory plasticity from tDCS, and enhanced focal facilitatory plasticity from PAS. The findings suggest that nicotine disrupts the brain’s ability to adapt by suppressing general forms of plasticity while heightening more targeted, synapse specific changes, highlighting how

even short-term nicotine exposure can alter neural adaptability in non-smokers by reducing general flexibility.

(Meehan et al., 2024) researched by reviewing multiple systematic reviews and surveys from European School Survey Project on Alcohol and Other Drugs (ESPAD), Action on Smoking and Health UK (ASH UK), and The New England Journal of Medicine (NEJM), about vaping of adolescents and young adults. It was a meta-analysis of 69 countries. It states that vaping has increased throughout Ireland among teenagers. In ESPAD 2019 survey nearly 40% of Irish 16-year-olds had tried vaping and 15% of them were current users. Use of disposable vapes has risen dramatically in recent years. Meehan et al. (2024) reviewed from ASH UK survey: From 2021 to 2023, disposable vape use among 11 to 17-year-old vapers increased 9-fold from 7.7% to 69%. Furthermore, (Osibogun et al., 2020) researched the statistics of youth transitioning from e-cigarettes to traditional tobacco cigarettes. The participants were: U.S. youth aged between 12 and 17 years. The timeframe for this analysis was from January 2019 to December 2019. Youth who had used e-cigarettes in the past 30 days were identified and there transitioning progress to tobacco cigarettes was tracked. Their smoking habits were compared to those who did not use e-cigarettes at the beginning of the study. The findings revealed that e-cigarette users had five times higher odds (OR = 5.0; 95% CI = 1.9–12.8) of becoming regular cigarette smokers compared to their non-using peers who were nonsmokers at baseline. A direct linear relationship was observed, where increased frequency of e-cigarette use predicted more frequent cigarette smoking at follow up. These results suggest a strong transition from e-cigarette use to established cigarette smoking among youth, highlighting concerns that e-cigarette use may undermine tobacco harm reduction efforts by facilitating cigarette initiation rather than preventing it.

The studies reviewed suggest that adolescents who vape are more susceptible to tobacco cigarettes, which are proven to decrease neuroplasticity, and synaptic activity as a result of even more nicotine exposure.

(Piao et al., 2009) reviewed how nicotine affects inflammatory neurological disorders such as multiple sclerosis, Parkinson's disease, and Alzheimer's disease. They analyzed evidence from laboratory experiments, animal studies, and clinical research to understand nicotine's influence on inflammation, immune responses, and neurodegeneration. The study highlighted nicotine's interaction with nicotinic acetylcholine receptors, which play a key role in both brain function and immune regulation. While nicotine can activate anti-inflammatory pathways that may be protective in some cases, such as in multiple sclerosis, it can also increase inflammation and oxidative stress that worsen disease progression in disorders like Parkinson's and Alzheimer's. The effects of nicotine were found to depend on the dose, duration of exposure, and type of neurological disease. They concluded that nicotine can contribute to the propagation of neurological diseases by promoting inflammation and damaging neural tissue, especially with chronic use. Furthermore, (Hajdusianek et al., 2021) reviewed studies on how tobacco and nicotine affect the nervous system and also contribute to neurological diseases. Using evidence from human, animal, and cell studies, they found that tobacco increases inflammation, oxidative stress, and nerve cell damage, worsening conditions like Alzheimer's, Parkinson's, and multiple sclerosis. Exposure during prenatal or adolescent stages raises the risk of later brain disorders by weakening immune and repair systems.

The effects of chronic nicotine exposure on Alzheimer's disease progression using a transgenic mouse model known as 3xTg-AD was investigated, which develops both amyloid plaques and tau pathology. The mice received nicotine through their drinking water over an extended period to simulate long-term use. After treatment the researchers analyzed the brains using immunohistochemistry and western blotting, focusing on levels of phosphorylated tau protein in regions associated with memory and cognition, such as the hippocampus and cortex. Ser202 and Thr231 are spots on the tau protein where harmful changes (phosphorylation) happen. The study found that nicotine exposure significantly increased tau phosphorylation at sites linked to neurodegeneration, including Ser202 and Thr231. Interestingly, no significant change was observed in amyloid-beta levels, suggesting that nicotine specifically worsens tau-related pathology. These results indicate that chronic nicotine use may accelerate the progression of Alzheimer's disease by directly enhancing tau damage, particularly in brain areas critical for learning and memory. (Oddo et al., 2005).

The studies reviewed suggest that nicotine and tobacco exposure contribute to the progression of neurological diseases by increasing inflammation, oxidative stress, and neural damage, with chronic use worsening conditions such as Alzheimer's, Parkinson's, and multiple sclerosis, particularly through mechanisms like enhanced tau pathology and impaired immune regulation in the brain.

Author Name	Publication Year	Population/Model	Neurodevelopment Outcome	Key Findings
Laura Maggi	2004	Rat hippocampal slices (postnatal day 1–7)	Reduced Synaptic activity and plasticity	Nicotine caused long lasting reduction in synaptic efficacy at CA1 synapses
Arrin C. Brooks & Brandon J. Henderson	2021	In vitro mouse neural stem cells and in vivo animal models	Region specific effects on neurogenesis: enhanced in SVZ, suppressed in SGZ	Nicotine reduced stem cell proliferation and suppressed hippocampal neurogenesis
Jessica Grundey	2012	Healthy non smoking adults	Disrupted Neuroplasticity	Nicotine disrupted general brain plasticity and altered synapse specific responses
Judith Meehan	2024	Adolescents (69 countries)	Nicotine exposure prevalence	Adolescent vaping rates are high and rising, especially for disposable vapes

Olatokunbo Osibogun	2020	U.S. adolescents aged 12–17 years	Transition to cigarette smoking	E-cigarette users had five times higher odds of becoming regular smokers
Wen-Hua Piao	2009	Animal, cellular, and clinical studies	Neuro inflammation and neurodegeneration	Nicotine increased inflammation and oxidative stress, contributing to neural damage
Wojciech Hajdusianek	2021	Human, animal, and cell studies	Neurological disease risk	Nicotine exposure increased inflammation and neuronal damage, raising later brain disorder risk
Salvatore Oddo	2005	Transgenic Alzheimer's mouse model (3xTg-AD)	Neurodegeneration and tau pathology	Chronic nicotine increased tau phosphorylation in memory related brain regions

Table 1: To summarize the key findings on nicotine exposure and its impact on adolescent brain development, a summary table (Table 1) is provided, highlighting the main studies, models, neurodevelopmental or neurodegenerative outcomes, and their primary results.

DISCUSSION

This review critically examined the neurobiological and toxicological effects of nicotine through e-cigarette use, drawing from various experimental, clinical, and systematic studies. The findings underscore significant health concerns related to both the chemical toxicants generated during vaping and the biological effects of nicotine on the brain, especially in adolescents.

Central Finding 1: Nicotine from e-cigarettes activates similar neurobiological pathways to tobacco cigarettes, with strong addiction potential.

The addictive potential of e-cigarettes appears to be rooted not only in their nicotine content, but in how that nicotine engages the brain's reward and craving circuitry. Despite common perceptions that e-cigarettes may be less harmful or less addictive, the neurobiological response they trigger through β2 and α6 nicotinic acetylcholine receptors suggests otherwise. These receptors are key mediators of dopamine release and craving, and their activation mirrors, or even surpasses, that seen with traditional

cigarette use. Moreover, the presence of ethanol in many e-liquids may amplify this effect by further enhancing dopamine activity. The role of α6 in emotional withdrawal such as anxiety and irritability underscores how e-cigarette dependence can be both physiologically and psychologically. Together, the combination of nicotine and other chemicals creates a reinforcement cycle that promotes continued use and makes cessation more difficult, especially for young or new users.

Central Finding 2: The toxic chemicals including carcinogens in e-cigarettes pose serious health risks for adolescents as many exceed the regulatory bodies guidelines.

Most e-cigarettes contained hazardous amounts of chemicals. The inhalation of heavy metals and volatile inorganic compounds is concerning, though the concentrations may be lower than in traditional cigarettes, but the delivery process of e-cigarettes is more advanced and efficient because the vapor is more easily aerosolized, and passes quickly through the blood-brain barrier. Many of the toxic compounds are also deposited through the heating mechanism of the device, rather than just being a component in the e-liquid. The more modern threat for users is that the person can control the wattage and frequency of inhalation. This customization can enable chemicals to cause harm more rapidly and consequently contribute to the neurodegenerative diseases described in the results.

Central Finding 3: How nicotinic acetylcholine receptor activation increases brain vulnerability and health risks.

These reactions involve complex interactions between different sub-units of the receptors, particularly the β2 and α6 subunits, which play a central role in mediating the addictive properties of nicotine. The α4β2 receptor combination is one of the most abundant in the human brain and has been directly associated with nicotine dependence. Its high affinity for nicotine means that even low exposure levels can lead to strong and lasting receptor engagement. The α6 subunit has been associated with emotional disturbance linking e-cigarette use to anxiety and mood disturbances, especially during periods of withdrawal. The situation is further complicated by the presence of ethanol in many e-liquids, which can interact with the same receptors, effectively compounding the stimulation and deepening the potential for dependency. These overlapping mechanisms not only reinforce addictive behavior but also overlap with neurological pathways.

Central Finding 4: E-cigarettes disrupt brain development, neuroplasticity, and can also contribute to neurodegenerative diseases.

Nicotine’s impact stretches beyond addiction. It interferes with critical processes such as: synaptic activity, neurogenesis, and the ability of the brain to adapt and learn. This interruption at the stage of adolescence is alarming because the brain is still refining cognitive, emotional, and behavioral regulation. The hippocampus, a key region for learning and memory, appears especially vulnerable, with nicotine exposure impairing both its structural and functional plasticity. Nicotine accelerates processes implicated in neurodegenerative disorders such as Alzheimer’s, likely by promoting oxidative stress and abnormal protein accumulation.

Public policy and regulatory implications:

It was emphasized that the need for proactive regulatory oversight when product risks are not fully understood but potential harm exists. Applying this principle, the findings presented here support stronger regulatory intervention by the FDA (Lichtenberg, 2017). The detection of formaldehyde, benzene, and neurotoxic metals across numerous devices demands mandatory ingredient labeling and toxicity disclosures. Furthermore, policy must address flavor regulation as they found certain flavors (e.g., tobacco flavored PODs) emitted disproportionately higher metal concentrations (Schmidt, 2024).

Regulations should also expand to cover coil material standards, e-liquid composition, and youth access restrictions as the sharp rise in adolescent use reflects regulatory gaps. Proper protocols would restrict the five times higher odds (OR = 5.0; 95% CI = 1.9–12.8) of youth becoming regular cigarette smokers compared to the youth who did not use e-cigarettes (Osibogun et al., 2020). Lastly, adoption of positive allosteric modulators (PAMs) as a therapeutic approach to target nicotine receptors without addictive potential, could inform non-addictive cessation therapies supported by FDA regulation (Grupe et al., 2015).

While this synthesis provides information at depth, the limitations would be that many toxicology findings are from animal or in vitro models, which may not fully replicate human metabolism. E-cigarettes being patented in 2003 in China means that even the oldest adolescents have not entered into the older demographic for proper assessments to be made. However, the findings will keep on getting more accurate with time passing.

LIMITATIONS AND FUTURE RESEARCH

This paper contributes to a growing body of literature by consolidating multi-disciplinary findings ranging from neuroimaging and animal models to toxicology and epidemiology to present a holistic picture of e-cigarette risks. While previous studies have separately addressed addiction potential or toxic emissions, this synthesis emphasizes the compound neurotoxic and developmental effects. Additionally, this paper highlights emerging evidence that e-cigarettes may not be the harm-free alternative they are often marketed as, particularly for adolescents.

Future research should prioritize longitudinal human studies that track neurodevelopmental and cognitive outcomes in e-cigarette users from adolescence into adulthood. Standardizing device parameters and chemical testing protocols across studies would improve comparability and regulatory relevance. Investigating PAM-based therapies or other non-dopaminergic nicotine alternatives could also yield safer cessation options. Additionally, better studies are needed on vape flavor chemicals and how they

decompose when heated, so we can create safer products and decide which flavors should be banned. Because flavors are the main factor of variability in e-cigarettes.

CONCLUSION

This review consolidates evidence that e-cigarettes are not a benign alternative to traditional cigarettes. E-cigarettes may also provide a pathway to tobacco cigarettes for adolescents. Chronic nicotine use from vaping impairs brain development, fosters dependence, and may accelerate neurodegenerative disease. In light of these findings, urgent regulatory action, informed public health messaging, and continued scientific investigation are essential to mitigate the escalating health burden posed by e-cigarette use.

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