adolescents

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Review

Adolescents and Electronic Vapor Product Use: A Dangerous Unknown

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Abstract: Electronic vapor products (EVPs) are non-conventional tobacco products that use a battery to heat liquid, generating an aerosol to be inhaled by the user. Despite being initially proposed as a harm reduction tool for adults looking to quit conventional tobacco cigarettes, EVP usage has grown significantly in the adolescent population over the past decade. Data from the 2021 Youth Risk Behavior Survey (YRBS) show that currently, in the United States, 36% of adolescents have ever used an EVP, 18% currently use an EVP, and 5% use EVPs daily. Initial studies have raised concerns about the health effects on multiple organ systems (e.g., respiratory, cardiovascular, and neurodevelopmental), and little information is known about the long-term effects, as well as the impacts specific to the still-developing adolescent body. EVP usage in the adolescent population is a public health crisis. The purpose of this narrative review is to address what is known thus far and to advise areas of focus for future research and advocacy.

Keywords: electronic vapor product; electronic cigarette; vaping; adolescence; nicotine

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1. Background

E-cigarettes are non-conventional tobacco products that use a battery to heat liquid, generating an aerosol to be inhaled by the user. The aerosol content may vary depending on the exact product, but most commonly is a combination of propylene glycol, vegetable glycerin, varying flavors, and potentially nicotine [1]. E-cigarettes were initially developed by a Chinese pharmacist in the early 2000s and, over the next few years, were exported worldwide [2]. By 2006, e-cigarettes were available in the United States as a conventional tobacco cigarette substitute [3], and by 2007, they were internationally patented [4].

E-cigarettes can be divided into four groupings or "generations" and are now referred to as electronic vapor products (EVPs). First-generation e-cigarettes looked like conventional tobacco cigarettes with their non-refillable cartridges and were not rechargeable. Second-generation products resembled a pen (with larger batteries), and their tank was refillable. Third-generation products were also refillable and rechargeable, but also had modifiable features and therefore became known as "mods" [5]. Fourth-generation products entered as a group of less standardized pod-based devices that have shown great popularity among the adolescent population [6]. These products (e.g., JUUL) have individual devices and liquid features that allow consumers to choose between liquid nicotine as a salt or free base [7]. The liquid nicotine using salts (containing benzoic or citric acid) rather than the free base, is fast absorbing and is available in the highest nicotine strengths while still providing a satisfying experience for newer users.

EVPs have been advertised as a "healthier" option than conventional tobacco cigarettes, with initial marketing as a smoking cessation tool [8]. A recent randomized control trial showed that EVP use was superior to conventional nicotine replacement therapy, but with several caveats—both groups had regular in-person appointments with clinicians, only 18% achieved smoking abstinence, and 80% continued to use EVPs a year later [9]. Unfortunately,

those seeking a smoking cessation tool were not the only population drawn to EVPs, as use in the adolescent population has risen dramatically over the past decade [10]. The reason for this alarming rise in EVP usage is likely multi-factorial, including youth-targeted advertising, a misunderstanding of product contents and potential harm, appealing flavors, sleek design, social media activity, celebrity endorsements, lower cost, ease of access, and the ability to be used discreetly in public places [11].

Data from the 2021 Youth Risk Behavior Survey (YRBS) show that in the United States, 36% of adolescents have ever used an EVP, 18% currently use an EVP, and 5% use EVPs daily [12]. Trends in usage can be tracked as multiple years of YRBS EVP data are available. Despite an overall decrease in total use from 2015 to 2021 (from 44 to 36%) and no linear change in the current use of EVPs overall (18%), the daily EVP usage increased (from 2 to 5%). The fact that 1 in 20 adolescents are now using EVPs daily is alarming and should be addressed in an urgent manner.

2. Flavoring and Adolescent Appeal

EVPs have unique properties that differ from conventional tobacco cigarettes, including differences in nicotine strength, form (different generations of products), and ability to add flavoring. More than 15,000 flavors exist [13], and recent studies demonstrated that for youth, flavored e-cigarettes were found to be the highest percentage of initial e-cigarettes used [14,15]. A systematic review showed that adolescents were more likely to start vaping using flavored EVPs (especially sweet flavors for prior non-smokers), and several flavors were associated with decreased harm perception [16]. Another study found that for adolescents, flavoring was found to be the second most important factor in starting EVP use (after curiosity) [17]. Using a focus group method, a recent study found that positive perceptions of new EVPs were increased by flavoring [18]. A social media-based study demonstrated that the most frequently discussed flavors include cream, fruit, tobacco, and menthol [19]. A systematic review exploring patterns of EVP flavors showed an apparent trend across studies for preference of sweet and fruity flavors over tobacco or menthol, with multiple studies in the cohort suggesting a positive association of first use of flavored EVPs being associated with continued vaping [20]. There is also some evidence that adolescents and young adults may be attracted to flavors that have names that mimic alcoholic beverages [21]. Individuals using flavored EVPs reported greater self-perceived addiction [22], and despite legislation to block the sale of flavored EVPs, they remain prevalent in their availability to youth [12]. Although there is inconclusive evidence at this time that flavored EVPs are specifically associated with the transition to conventional tobacco cigarettes, experts are concerned that this may have a "gateway" effect (e.g., increased initiation) for conventional tobacco cigarettes.

Based on data demonstrating increased use, the United States Food and Drug Administration (FDA) extended its regulatory authority to include EVPs in 2016 and, since that time, has added warning statements on EVP packaging and blocked the sale of 55,000 flavored products [16,23]. In 2019, Tobacco 21 federal legislation was passed to prohibit the sale of tobacco products to individuals under the age of 21. Unfortunately, adolescents continue to have access to EVPs by obtaining products from friends/family as well as via online retailers' websites [24]. By 2022, the global EVP market reached a multi-billion-dollar value [25], with the highest pooled prevalence of EVP use observed in high-income countries [26].

EVPs were initially publicized as a safer alternative to conventional tobacco cigarettes, as well as an effective manner for smoking cessation [25]. Unfortunately, no preclinical toxicology testing was performed, and no long-term safety trials were conducted prior to the marketing of EVPs [27]. With the rapid dissemination of EVPs in the adolescent population, we are now left with the question—what are the acute and long-term effects on the developing adolescent body? The purpose of this narrative review is to address what is known thus far and to advise areas of focus for future research. The search strategy used for this narrative review included searches of PubMed, Scopus, Web of Science, CINAHL,

PsychInfo, Business Source, Clinical Trials, Open Dissertations, (article) references, and Mednar (to identify grey literature sources). Upon initial search, 3600 documents were retrieved. No language or date limiters were used. Search terms (from PubMed) included vaping OR electronic nicotine delivery systems, OR e-cigarettes, OR electronic cigarettes, OR JUUL or vape devices AND cardiovascular disease OR evali OR e-cigarettes or vape us associated lung injury OR trends OR statistics OR substance-related disorders OR addiction AND adolescent or adolescence or young adult or teenage NOT adult or middle aged or animal* or rats or rodents. Duplicated titles between databases were removed. The authors reviewed the remaining articles to remove clearly irrelevant articles and then selected published articles and reports to include a breadth of high-quality references (93 total articles).

3. Health Consequences of EVPs by System

3.1. Respiratory

Flavoring is not just dangerous for increased appeal/initiation risk in adolescents but can also expose users to toxic compounds. A study of five flavors across multiple types of EVPs showed how flavors affected the in vitro toxicity profile [28]. The Flavor and Extract Manufacturers Association identified more than 1000 flavorings used in EVPs that should be considered a respiratory hazard due to their irritant and volatility characteristics [29]. There are differences even among different flavorings, with fruity and sweet flavors resulting in higher levels of reactive oxygen species [30]. Not only is there concern for higher levels of inflammatory cytokines, [31] but inhaling contaminants can also increase the risk of infections [32].

A recent systematic review and meta-analysis showed that EVP use (both current and ever use) was associated with higher odds of having asthma [27]. This finding confirmed prior literature reviews [33] on the relationship between asthma and e-cigarette use, as well as experimental studies evaluating the biological impacts [34]. Other studies have yielded conflicting results related to asthma [35] but have demonstrated other negative respiratory effects such as chronic bronchitis symptoms [36], shortness of breath [35], and bronchiolitis obliterans [37]. Different models to evaluate EVP usage have shown not only common pathways with conventional tobacco cigarettes causing damage resulting in chronic pulmonary disease [38] but also distinctive respiratory damage due to the additives and metal nanoparticles [33]. The airways of EVP users compared to those of non-users have shown increased erythema and friability [39], and a recent study has shown improvement in airway health status even in short-term cessation for regular EVP users [40].

With EVPs often being obtained by youth from a variety of unregulated sources, other additives, drugs, or psychoactive substances (e.g., tetrahydrocannabinol or THC) can be delivered. In 2019, there was an outbreak of e-cigarette or vaping product use-associated lung injury (EVALI), with over 2800 cases and 68 deaths reported by February 2020 [41]. Patients presented with a range of symptoms, including cough, hypoxia, shortness of breath, chest pain, abdominal pain, nausea, vomiting, headache, lethargy, and confusion [42]. This outbreak was linked to vitamin E acetate, which is an additive found in some EVPs containing THC [43].

3.2. Cardiovascular

E-cigarettes can contain nicotine and toxic heavy metals at higher levels than conventional tobacco cigarettes [44], with concern not only for the development of carcinogenic disease [45] but also coronary events [46]. A cross-sectional analysis demonstrated daily usage was linked to increased odds of myocardial infarction [47], and another study raised concern for increased heart rate, blood pressure, and arterial stiffness [48], although ongoing work has had mixed results for both cardiovascular and pulmonary effects of EVP usage [47]. While there have been very few safety studies in humans and therefore the long-term cardiovascular effects remain largely unknown [26], the European Commission

and its Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) noted in their final report that overall weight of evidence for risks of long-term systemic effects on the cardiovascular system is moderate [49].

3.3. Neurodevelopmental and Mental/Behavioral

Brain development is an ongoing process during adolescence that continues into adulthood [50], and specific concerns have been raised regarding the effect of nicotine on brain white matter [51]. There is critical regulation of brain development by neuronal nicotinic acetylcholine receptors [52,53], which are expressed at higher levels during central nervous system maturation in adolescence; therefore, nicotine has a greater impact on neuronal activity in the adolescent brain than in the adult brain [54]. Research has shown that nicotine exposure in the adolescent brain can lead to the inappropriate activation of nicotinic acetylcholine receptors, causing permanent changes to neuronal signaling that may impact cognition, impulsivity, hyperactivity, attention span, emotional regulation, and addictive concerns [55,56]. The prefrontal cortex, which is crucial to executive functioning and attention, continues to develop during adolescence. Prior work has demonstrated that smoking during adolescent years increases the risk of cognitive decline later in life [57]. Altered neurotransmission is not the only neurotoxic effect of EVP compounds—other concerns, such as calcium dyshomeostasis, impaired autophagy, epigenetic changes, inflammation, and oxidative stress, need to be considered [58]. Similar to conventional tobacco cigarettes, EVP usage increases both oxidative stress and inflammation [59]. Although the levels of oxidative stress triggered may be lower by EVPs than by conventional tobacco cigarettes [60], the human brain is particularly susceptible to damage from oxidative stress [61]. This susceptibility is further exacerbated in the developing brain for several reasons, including a high rate of oxygen consumption, a large number of sensitive immature cells, and poor antioxidant capacity [60].

Initial research has shown that EVP usage may also exacerbate other neurologic conditions, such as the frequency of seizure activity in patients with known epilepsy [62]. In addition to the above-listed neurologic concerns, the role of EVP-induced oxidative stress can be linked to sleep concerns [63], increased levels of psychological distress [64], depression [65,66], and suicide [56,65,67]. Furthermore, whereas EVPs are touted as being safer than conventional tobacco cigarettes, the long-term neurologic impact of EVP aerosol components (especially in a cumulative effect) is largely unknown, and current minimal knowledge is concerning [58].

3.4. Nicotine and Addiction

Prior work has demonstrated that the initiation of tobacco product use during adolescence is associated with not only increased nicotine dependence but also sustained use into adulthood [68]. Multiple studies over the years have shown that an earlier age of nicotine use is directly correlated with greater severity of nicotine dependence [69–71]. In the United States, more than 85% of adult smokers started before the age of 18, and 99.9% started by age 30 [72]. This evidence establishes the concept that nicotine dependence should be considered an adolescent-onset disorder, and despite prior improvements in conventional tobacco cigarette usage, EVPs have opened the gates again for this early nicotine exposure. Furthermore, recent research revealed that EVPs have a greater addiction potential than conventional tobacco cigarettes in educated young adults [73]. With adolescent EVP usage, not only is there concern for increased future risk of conventional tobacco cigarette use, but also increased risk of other addictive substances [1,65,74]. Cross-sectional work carried out by the National Centre for Epidemiology and Population Health in a report for the Australian Department of Health is suggestive that EVP dependence may be associated not only with earlier age of initiation and daily use but also with later generation/more powerful devices [75].

The nicotine content of EVPs may vary significantly between unique products [76], and nicotine has even been detected in products labeled as “nicotine-free” [77]. Although

nicotine is the second most vaped substance for adolescents (after pure flavoring), one in five adolescents thought EVPs had no nicotine or were unsure of the nicotine content [78]. One study demonstrated that almost all e-cigarettes sold in most U.S. retail outlets contained nicotine [79], and another found that from 2013 to 2018, the average nicotine concentration increased by >80% for flavor categories and rechargeable devices [80]. Alarmingly, data from the 2021 National Youth Tobacco Survey show the most common reasons for use were to relieve stress/anxiety/depression and the nicotine use "buzz" (colloquial terminology for the feeling of intense excitement/exhilaration) [81]. Moreover, adolescents who are using EVPs as a coping method for stress or other mental and behavioral health disorders (e.g., anxiety and depression) can create a vicious cycle of nicotine dependence, as symptoms of nicotine withdrawal can include anxiety and depression [68].

4. Discussion

Although some early studies indicated that EVPs were an improved method for quitting conventional tobacco cigarette smoking, reviews of recent evidence show a lack of clear efficacy for this harm reduction tool [48]. Unfortunately, this smoking cessation tool with only low certainty evidence has also reached an entirely different demographic, and we are now left with a myriad of questions about the health impacts on the adolescent population. The World Health Organization (WHO) has stated not only are these products harmful to adolescent health, but they also may serve as a starting point for nicotine addiction [82]. Data from over 15 cohort studies show that for adolescents, EVP users were nearly three times more likely than never users to start smoking cigarettes [83]. Although the rate of conventional tobacco cigarette use in United States high school students has decreased from 36% in 1997 to 6% in 2019 [84], these important strides in public health have been all but erased by the increase in EVP use. Although there was a limited period of decrease in EVP usage from 2019 to 2021 (likely related to the implementation of policies limiting flavored product sales and the social impacts of the COVID-19 pandemic), there has been no linear decrease from 2015 to 2021 [12]. Knowing that these products remain prevalent among adolescents in the United States, much work is needed to better understand the long-term implications as well as effective methods for decreasing usage.

Numerous challenges impede researchers' efforts to study the health impacts of EVP usage in adolescents. These challenges include heterogeneous products, rapid introduction and evolution of new products, dual usage with conventional tobacco cigarettes or other tobacco products, age/ethical considerations, legal issues, and the need for longitudinal studies [1]. Despite these challenges, we must press on with pursuing specific areas of future research related to adolescent EVP usage.

4.1. Future Directions—EVP Usage Health Effects Research

Future research should continue to focus on specific organ systems and the acute as well as long-term health effects of EVP usage. As outlined in a report on the Public Health Consequences of E-Cigarettes by the National Academies of Sciences, Engineering, and Medicines, there has been insufficient time for an appropriate scientific body of evidence to be developed on the health effects of EVPs [83]. A recent systematic review calls out the paucity of evidence about the effects of EVPs on the musculoskeletal system [85]. Both laboratory studies and early human research demonstrate concerns (e.g., consumption of nicotine causing vasoconstriction [86] and impaired healing), but the long-term orthopedic consequences of EVP use remain largely unknown. Another example is that even if EVPs are labeled as "safe" since they are nicotine-free, we do not fully understand the dangers of other EVP components (e-liquid, flavors, vapor, and exposure to toxic metals), [56] as well as the impact of specific device types and vaping techniques. We need to acknowledge that the adolescent body (and particularly the adolescent brain) is not the same as an adult body, so we cannot just extrapolate data from adults. Methodologically sound studies for both the acute and cumulative effects are needed to assess the role of EVP-induced oxidative stress on the neurodevelopmental and mental/behavioral health of adolescents.

4.2. Future Directions—Investigation of Motivation for EVP Usage

In addition to ongoing research about the health impacts of EVP use, we must continue to evaluate and monitor trends in EVP content, and factors that lead to initiation (flavoring and accessibility) to effectively advocate and inform policymakers. EVPs are a widely inconsistent product with varying pharmacokinetics, and future research is needed to accurately describe and measure product use characteristics [87]. Even with improved legislation and regulation of EVPs, we know this will not be enough as they continue to evolve rapidly and remain accessible to adolescents. Data from the 2021 YRBS show that 54% of adolescents who currently use EVPs obtained them from a friend, family member, or someone else [12]. Legislation will never be able to completely remove EVPs from the hands of adolescents, so we need prevention programs that can alert adolescents to the multi-system dangers of EVPs.

4.3. Future Directions—Implementation and Evaluation of Programs to Reduce EVP Usage

Future work should also focus on close monitoring of trends within individual groups to be able to target primary prevention strategies. For example, the 2021 YRBS has added to prior evidence in the literature that EVP usage among sexual minority adolescents varies by sexual orientation [88]. There was also variation in increased rates of usage for specific populations (e.g., Black, Hispanic, White, and multi-racial) [12]. This knowledge can be leveraged to create focused primary prevention strategies that address what specifically motivates these populations. We also should involve the adolescents, their teachers/coaches, and the communities they live in to participate in the research and development of these prevention strategies. We should be screening for EVP use in all adolescents and openly discussing the dangers of these products. For those adolescents who are already using EVPs, healthcare providers should be trained to have real-time discussions as well as readily available resources to assist with cessation. Recognizing the lack of risk perceptions related to EVPs by adolescents is critical to prevention and intervention strategies [89]. Research has demonstrated multiple protective (parental monitoring and support, perceived risks, costs of vaping) and risk factors (other substance use, exposure to advertising, externalizing problems, perception of minimal harm, and sensation seeking) [11] for the initiation of EVP usage, and this knowledge should be leveraged to develop targeted educational programs for adolescents. Cessation resources for those looking to quit EVP usage also need to be tailored to the individual. A recent study in the United States found that 64% of current vapers had made an attempt to quit within the past year, but most of these adolescents did not use any resources to assist them in quitting. Among those who did seek resources, there were varying sources (peer support, help on the internet, mobile app, text messaging, family support, teacher/coach support, and doctor/healthcare provider support), highlighting the need for individualized cessation methods based on the adolescent's preferences [90].

4.4. Future Directions—Advocacy for Improved EVP Policies

In addition to multi-pronged and multi-layered EVP research, there needs to be a convincing push to advocate for stricter policies and regulation of EVPs. There needs to be a strong emphasis in the United States to incorporate smokeless tobacco control into existing tobacco control guidelines [91]. Although adolescents may still obtain EVPs from friends and family, tighter regulation of EVPs sold online (oftentimes with a relaxed age verification process) [24,92] may help decrease the number of products in the hands of adolescents. Additionally, advocacy efforts for the tighter regulation of liquid nicotine for refillable devices should be addressed, as these can be appealing for younger children to ingest based on their coloring and designs. In the United States alone, 4745 children < 5 years of age were treated for liquid nicotine-related poisoning over a 4-year span (2013–2017 [93]. These safety concerns are also recognized internationally, as SCHEER provided in its final report that the weight of evidence for risks related to poisoning and injuries due to burns and explosions is strong [49]. There are reporting systems for adverse events both in the United

States (via the FDA) and the United Kingdom, but there needs to be a transition from solely reporting to advocacy for proactive measures.

5. Conclusions

In the United States, adolescent EVP usage remains prevalent, as well as increasing daily use. Due to a lack of regulation, there is significant heterogeneity of the compounds in EVPs, making them difficult to study. The evidence thus far related to the impacts on the developing adolescent body is alarming and should serve as an ongoing call to action for expanded research into the effects of EVP usage, the most effective cessation programs and ongoing advocacy for improved policies and regulation. Future directions of this crucial research should focus not only on the acute consequences of EVP usage but also on the long-term effects on the adolescent. In a time where there are so many unknowns about the effects of EVP on the developing adolescent body, we should work to have open communication with adolescents and families to provide effective prevention and cessation strategies. In the adult population, EVP usage should be a risk/benefit discussion as a smoking cessation tool. However, for our nicotine-naïve adolescents, the question remains—is there only risk?

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