THE TURKISH JOURNAL ON ADDICTIONS

www.addicta.com.tr

INVITED REVIEW

Exploring the Impact of Emerging Forms of Nicotine on Adolescent Mental Health

Ayse Rodopman Arman

Child and Adolescent Psychiatrist, Private Practice, Istanbul, Türkiye

ORCID iDs of the authors: A.R.A. 0000-0002-6884-0706.

Main Points

- A significant reorganization of brain regions occurs during adolescence, impacting cognitive and executive functions, working memory, emotional regulation, reward processing, and motivated behavior.
- Nicotine addiction often begins in adolescence, when the brain's reward systems are developing, following even sporadic exposure to tobacco products.
- Nicotine smoke may have a stronger rewarding effect on the adolescent brain, making it more vulnerable.
- Using e-cigarettes may lead to a higher likelihood of tobacco smoking addiction, acting as a "gateway" to stronger substances.
- Preventing adolescent nicotine exposure is critical to reducing smoking prevalence and related health risks.

Abstract

Nicotine, the highly addictive psychoactive component of tobacco, acts on nicotinic acetylcholine receptors, influencing reward, motivation, attention, learning, and memory. Genetic background, sex, age, and environmental factors contribute to individual differences in nicotine addiction. The use of tobacco products is typically initiated and established during adolescence, when the developing brain is most susceptible to nicotine addiction. A significant reorganization of brain regions essential for advanced cognitive and executive functions and motivated behavior characterize the adolescent period. The neuro-inflammatory effects of nicotine have the most damaging impact on the adolescent brain. Many experts suggest that using e-cigarettes may lead to a higher likelihood of tobacco smoking addiction, acting as a "gateway" to stronger substances. The variety of e-cigarette flavors can affect pleasure perception and directly impact the brain reward system of the younger population. Therefore, it is crucial to avoid smoking or using any nicotine-containing products during this time to ensure optimal brain health and development. This article will explore the latest research on nicotine exposure and its impact on adolescent brain development. The review article discusses demographic features, neurophysiological effects of nicotine, contextual and individual differences in addiction, vulnerability to mental disorders, and e-cigarette use in adolescence.

Keywords: Adolescent, behavior, brain, e-cigarette, nicotine, neurobiology

Corresponding author:
Ayse Rodopman Arman
E-mail:
aarman@marmara.edu.tr

Received: November 6, 2023
Accepted: December 13, 2023
Publication Date:
December 29, 2023

Introduction

Nicotine addiction is a prevalent issue that affects many individuals, particularly during their youth and early adulthood (Singh et al., 2016, Yuan et al., 2015). Adolescents are especially vulnerable to developing a dependency on nicotine, as the adolescent brain is susceptible to its neuroplastic effects (Chatterjee et al., 2016, Kandel & Kandel, 2015). Even minimal exposure to nicotine can lead to changes in neuroplasticity, making it crucial to understand the mechanisms underlying nicotine addiction in the younger population (Dinakar et al., 2016).

Throughout preadolescence and adolescence, there is an elevated risk of developing nicotine addiction. According to recent health surveys described by Njie

Cite this article as: Rodopman Arman, A. (2023). Exploring the impact of emerging forms of nicotine on adolescent mental health. *Addicta: The Turkish Journal on Addictions*, 10(3), 222-228.

DOI: 10.5152/ADDICTA.2023.23139

et al., more than 20% of adolescents aged between 12 and 18 are smokers. Among young adults who choose to smoke, the peak age for smoking onset is between 14 and 16 years. More than 70% of adolescents report having smoked a cigarette at least once (Njie et al., 2023). Unfortunately, starting smoking during adolescence can lead to several health consequences. Adolescent smokers are more likely to become heavy smokers, less likely to quit smoking later in life, and are at higher risk of dying from smoking-related illnesses (Callahan-Lyon, 2014). During adolescence, the brain undergoes significant neuropsychological changes that contribute to its development into an adult form. This development is most evident in brain areas crucial for emotional and disinhibitory control mechanisms, such as the limbic and prefrontal regions (Casey & Jones, 2010). Prefrontal inhibitory control is not yet fully developed during adolescence due to sex and growth hormones on the rapidly developing limbic system, resulting in emotional outbursts and impulse control problems (Besson &Forget, 2016). Although sociocultural factors can play a role, research at both preclinical and clinical levels suggests that the heightened sensitivity experienced during adolescence is largely rooted in neurobiology (Counotte et al., 2011; Silveri et al., 2016). While there is some variation in how the adolescence period is defined, it is characterized by a significant reorganization of brain regions essential for advanced cognitive and executive functions, working memory, emotional regulation, reward processing, and motivated behavior (Yuan et al., 2015). However, this unique neurodevelopmental process also puts the brain in a vulnerable state that may increase the risk of drug abuse and the toxic effects of drugs (Besson & Forget, 2016). Thus, nicotine exposure during adolescence may heighten the probability of future addiction to other substances, including cocaine (Korpi et al., 2015). Smoking during adolescence raises the likelihood of developing psychiatric disorders and cognitive impairment later in life (Wellman et al., 2016; Wikipedia, 2023). Furthermore, teenage smokers face attention deficits that worsen with years of smoking (Kandel & Kandel, 2015). Recent research on rodents has uncovered the molecular changes brought about by nicotine exposure during adolescence, which disrupt the functioning of synapses in the prefrontal cortex and lead to long-term effects on cognitive function (Goriounova & Mansvelder, 2012).

This article will explore the latest research on nicotine addiction and its impact on adolescent brain development. The sections are the demographic features, neurophysiological effects of nicotine, individual versus contextual differences in adolescence considering addiction, unique sensitivity to nicotine addiction in adolescence, vulnerability to mental disorders in the presence of addiction, and e-cigarette usage in the adolescent period. Under the criteria of Medical Subject Headings, PubMed, Cochrane, ScienceDirect, and EBSCOhost databases were searched for this review article. The search was carried out in English with the keywords "adolescent," "nicotine," "behavior," "central nervous system," "neurobiology," and "mental health."

Demographic Features of Nicotine Exposure in the Adolescent Period

The first Turkish population-based youth addiction study conducted by Ogel et al. in Türkiye, involving schools nationwide, found that 16.1% of primary school students had tried tobacco at least once. Among secondary school students, the prevalence of tobacco use was 55.9%, while alcohol use was 45.0%, cannabis use was 4.0%, inhalant use was 5.1%, and heroin and ecstasy use was 2.5%. There was a notable difference between males and females in terms of tobacco, alcohol, and other drug use in both primary and secondary schools (Ogel et al., 2004).

In 2003, the Ministry of Health of the Turkish government conducted The Global Youth Tobacco Survey (GYTS) on students aged 13-15 years (Global Youth Tobacco Survey, 2003). The GYTS survey is a school-based survey concerning the prevalence of tobacco use that is conducted multi-nationally and targets students aged between 13 and 15 years. This survey is used to track tobacco use among young people to enable countries to better evaluate their tobacco-prevention programs. Almost 30% of students in Türkiye have tried cigarettes, with boys smoking at higher rates. The rate of exposure to passive smoking was high both in current smokers (89.0%) and never-smokers (79.2%). More than one-third of current smokers intend to quit. Susceptibility to initiate smoking was remarkably high among non-smokers, especially in boys (9.1% versus 5.8%). Considerable proportions of both never and current smokers had positive attitudes toward tobacco use. Half of the students had no school curriculum about the effects of tobacco use (Global Youth Tobacco Survey, 2003). Recently, the same survey analysis involved 34 multinational locations that underwent two rounds of surveys between 2012 and 2020 (Njie et al., 2023). Between 2012 and 2020, the prevalence of self-reported tobacco use among youth remained stable in over 60% of countries that participated in the Global Youth Tobacco Survey. On the other hand, the use of e-cigarettes increased in most countries where comparative data was available.

In another population-based Turkish study, Ertas analyzed survey responses from over 15,000 individuals and found that males and high-school students were more likely to be affected by tobacco exposure than other nonsmokers. The rates of current cigarette smoking were lower compared to those of ever-smokers, with 9% for boys and 4% for girls. Additionally, around 80% of students were exposed to secondhand smoke (SHS). Shockingly, despite laws prohibiting the behavior, almost half of the current smokers still purchased their tobacco from a shop (Ertas, 2007).

According to the recent Türkiye Health Survey, the distribution of individuals aged 15 and above who use tobacco products every day by gender has been outlined from 2010 to 2022. The percentage range for men is 38% to 41%, while for women it is 10.2% to 15.5% over 12 years (Türkiye Sağlık Araştırması, 2022). Recent data from the multinational GYTS show that progress in reducing youth tobacco use has paused between 2012 and 2020, while e-cigarette use has increased in some locations with available data (Njie et al., 2023). The World Health Organization (WHO) has created the MPOWER technical package to assist countries in implementing demand-reduction measures outlined in the WHO Framework Convention on Tobacco Control (World Health Organization and MPOWER, 2023). The report indicates that although many countries are making progress in the fight against tobacco, there is a need to accelerate efforts to protect young people from the harms of tobacco and SHS.

As a conclusion, the prevalence of smoking among adolescents in Türkiye is a serious concern, particularly as the gender gap is narrowing. It is essential to implement effective prevention

and cessation programs alongside relevant legislation to control tobacco use effectively (Erguder et al., 2006, 2008).

The Receptor-Level Neurophysiological Effects of Nicotine in Adolescent Brain

Nicotine, the main pharmacologic component of tobacco, is highly addictive and causes significant withdrawal effects, making it challenging to quit smoking, particularly in adolescents (Mahajan et al., 2021). Nicotine disrupts the blood-brain barrier function, which significantly increases the risk of brain edema and neuroinflammation (Pogun & Rodopman Arman, 2021). A review article by Kandel & Kandel revealed that nicotine can lead to addiction and may serve as a gateway drug for other substances, regardless of the source of exposure, including smoking tobacco, passive tobacco smoke, or e-cigarettes (Kandel & Kandel, 2015).

Upon entering the brain, nicotine stimulates dopaminergic neurons in the ventral tegmental area and pars compacta (Subramaniyan & Dani, 2015). As a psychostimulant, nicotine binds to and activates nicotinic acetylcholine receptors (nAChRs) in the brain, causing the release of neurotransmitters such as dopamine, acetylcholine, and glutamate (Yuan et al., 2015). Nicotine addiction following random exposure to tobacco products often begins in adolescence. The fact still stands that nicotine's neuro-inflammatory effects have the most damaging impact on the adolescent brain (Mahajan et al., 2021). During adolescence, nAChRs signaling in rodent models shows dynamic changes, with higher expression and functional neuronal activity of nAChRs in the forebrain compared to adults (Dineley et al., 2015). It is becoming clear from studies on the rodent brain that adolescent nicotine exposure increases nAChR expression in the medial prefrontal cortex (PFC) (Goriounova & Mansvelder, 2012; Wallace & Bertrand, 2013). This reaction results in higher nicotine-induced GABAergic synaptic transmission compared to adults.

According to the recent glutamatergic hypothesis, levels of Metabotropic glutamate receptor 2 (mGluR2) on the presynaptic glutamatergic terminals located in the PFC are elevated, leading to a decrease in the strength of glutamatergic synapses. After nicotine levels have subsided in the adult rodent brain, nAChR levels in the PFC return to baseline levels, indicating their reversibility. On the contrary, mGluR2 levels significantly and irreversibly decrease below the baseline, even after the cessation of nicotine exposure. This alteration impedes short-term plasticity and disrupts the flow of information processing in PFC (Cross et al., 2018; Goriounova & Mansvelder, 2012). Adolescent nicotine exposure can alter mGluR2 receptors, affecting inhibitory tonus and excitatory transmission, with unexpected short-term and long-term effects on neuronal plasticity.

Recently, microglial activation as a process of neuroinflammation resulting from tobacco exposure has been described by Mahajan and his colleagues (Mahajan et al., 2021). The characteristic of neuroinflammation is the activation of microglia by nicotine during adolescent development, which can lead to long-term nicotine addiction. Several studies have shown that nicotine exposure can lead to the release of dopamine induced by ghrelin (Ayman et al., 2023, Hu et al., 2018). This release occurs due to the activation of the cholinergic-dopaminergic reward link in the ventral tegmental area of the brain, which is a critical part of the reward system that is associated with behavioral reinforcement. Ghrelin signaling may affect the dependency effects of smoking in adolescents during the critical period of reward-seeking, which is unique to this age group.

Individual Versus Contextual Differences in Nicotine Dependency

Long-term population-based studies of the young generation suggest that neurobehavioral characteristics such as sensation seeking, rebelliousness, susceptibility to smoking, and plans to smoke may predict tobacco use (Wellman et al., 2016) Among the Turkish youth, those who attributed positive remarks to smokers were more likely to be tobacco users. Exposure to smoking by parents, teachers, and peers, and perceived ease of access to tobacco products, were all significant predictors of susceptibility to future smoking behavior (Ertas, 2007; Erguder et al., 2008). Adolescents are more likely to start smoking if they have friends and family members who smoke or are exposed to tobacco promotion through commercials (Holz et al., 2015; Sylvestre et al., 2018). This process of developing and modifying pre-smoking beliefs can significantly impact an individual's decision to continue smoking or quit. Therefore, it is crucial to realize the factors that impact the formation of smoking attitudes in adolescents to create successful prevention and cessation methods (Kaya & Unalan 2010).

Why Adolescents Are More Vulnerable to Addiction

During adolescence, individuals often become more sensitive to nicotine due to various factors. Neurobiology is a major contributor to this phenomenon. The changes in brain structure reorganization and function influence emotional reactivity and response to stimuli in this crucial adolescent period (Counotte et al., 2011; Pogun & Rodopman Arman, 2011; Yuan et al., 2015). The adolescent tendency to seek out rewards increases the likelihood of experimenting with nicotine products. From a behavioral psychology perspective, engaging in repetitive behavior can increase the likelihood of addiction to nicotine. Prefrontal inhibitory control is relatively weak and develops much later than the limbic areas. Additionally, sociocultural factors such as peer pressure and societal expectations may also play a role in shaping adolescent behavior and heightened sensitivity to nicotine products (Kaya & Unalan, 2010). Table 1 outlines the stages of nicotine exposure in the adolescent period (Table 1).

The WHO has launched a new global anti-tobacco campaign called "Tobacco Exposed" which will mainly focus on protecting young children from exposure to nicotine products before adolescence (The Lancet Child Adolescent Health, 2020). The tobacco industry employs different strategies to sway young individuals, such as producing appealing tobacco items like bubble gum, candy, and e-cigarettes (Dagli, 2019; Kurtuluş & Can, 2022; Mahajan et al., 2021). According to the WHO, these companies use other tactics such as giving away free cigarettes at open-air concerts, providing soluble nicotine products such as e-cigarettes in an unregulated manner, and selling cigarettes in school neighborhoods in low- and middle-income countries (The Lancet Child Adolescent Health, 2020).

Table 1.
Stages of Nicotine Exposure in Adolescent Period

Stage 1	Heightened interest in smoking behavior During the preparatory stage of smoking, which is often experienced during adolescence, individuals tend to develop various attitudes and beliefs about smoking before trying it. These pre-smoking beliefs can then be modified based on the individual's experiences with smoking, either reinforcing their initial beliefs or leading to a shift in their attitudes toward smoking.
Stage 2	Initiation of nicotine products Before trying smoking, adolescents form attitudes and ideas about what it involves. This includes their perceptions of its potential functions and an increasing awareness of the social pressures to smoke. This stage is crucial in shaping their understanding of smoking. Adolescents try nicotine products for a variety of reasons, such as boosting their social status, gaining approval from their peers, and managing their difficult emotions.
Stage 3	Experimentation with smoking At this exposure stage with nicotine products, peer influences tend to be stronger than family influences. Trying to improve one's self-image may lead to experimentation with smoking and could result in poor academic performance and seeking approval from certain peer groups. Unregulated easy access to e-cigarettes heightens the risk of smoking.
Stage 4	Regular smoking During the fourth stage, individuals gradually increase their frequency of smoking and expand the range of situations in which they smoke. At this point, they have not made a definite decision about smoking and are still contemplating whether it is right for them. As teenagers become regular smokers, the harsh sensations that come with their first few cigarettes, such as burning, roughness, and heat, may start to diminish as they begin to realize the perceived benefits of smoking. During this period, youngsters may start to identify themselves as smokers. Exposure to family members who smoke regularly can significantly increase the chances of obtaining nicotine products during this period.
Stage 5	Daily smoking Adolescents tend to move from occasional smoking to becoming regular smokers, but still with low frequency. Some students smoke at weekend parties, while others tend to smoke on their way to or from school during the week.

New Zealand has banned the sale of cigarettes to individuals born in 2009 or later and prospectively plans to increase the legal smoking age each year. Starting from 2023, the minimum age required to purchase cigarettes will be 15 years or above (Quartz.com, 2022). In 2024, they will have to be 16—and so on, until in 2050 the minimum legal age will be 42. This is the world's second toughest anti-smoking law, following Bhutan's complete tobacco ban in 2010. It shows a determination to curb cigarette smoking in a country that already has one of the lowest rates of smokers anywhere. On the other hand, the focus on creating a smoke-free generation overlooks the fact that cigarettes are already losing popularity as a tobacco product. Smoking alternatives like vapes and e-cigarettes may create nicotine addiction (Quartz.com, 2022).

Research findings have demonstrated that smoking even a few times in childhood and adolescence dramatically raises the probability of becoming a habitual smoker not only in early adulthood but also in middle age (Goriounova & Mansvelder, 2012; Holz et al., 2015). Overall, understanding the complex interplay between biology and culture can help us better support and navigate the unique challenges of nicotine dependency in this developmental stage.

Nicotine Exposure in Adolescence and Mental Disorders

Even occasional nicotine use can cause dependence in adolescents. Prolonged exposure to nicotine leads to the upregulation of receptors in the prefrontal cortex, which is responsible for executive functions and is not fully developed until the mid-20s.

Such disruption of neural circuit development can lead to persistent cognitive and behavioral deficits and has been associated with the development of depression and anxiety (Jenssen & Boykan 2019) Research has established a significant correlation between neuroinflammation in a particular region and major psychiatric and addictive behaviors. This linkage is particularly concerning as it could potentially exacerbate substance use and addiction in younger populations (Jude et al., 2020, Moshensky et al., 2022).

Uygun et al. investigated the impact of high-risk personality traits on adolescent smoking behavior and intention using the Substance Use Risk Profile Scale. Preliminary evidence suggests that feeling dissatisfied with oneself may contribute to current smoking behavior, while traits of impulsivity may affect the intention to smoke in the future by creating nicotine dependence (Uygun et al., 2022).

It is commonly observed that smoking habits often begin several years before the onset of mental illness. Based on statistical analysis, the average age at which individuals commence smoking is approximately 17 years old. Nevertheless, it is typically not until after the age of 30 that individuals are admitted to the hospital for the treatment of a mental disorder.

There exist certain genetic variations that can be classified as "smoking-related genes" (Arinami et al., 2000; Li, 2003). According to a recent study conducted by Balbueana et al., 2023 using a UK Biobank data set with 337,140 participants, individuals with specific genetic variations who refrain from smoking demonstrate a decreased likelihood of developing mental disorders compared to those who smoke. The researchers conclude that the genetic liabilities for smoking and neuroticism are fixed at conception and smoking initiation generally starts before age 20 (Balbuena et al., 2023). It is possible to speculate that preventing smoking in adolescents could help prevent the development of mental disorders. Raising the age limit for purchasing cigarettes could help prevent mental health issues in younger generations.

Adolescent Brain and E-Cigarettes

The tobacco industry is attempting to keep the younger generation dependent on their products by introducing new ones, such as liquid nicotine preparations in soluble form. One such product is the Electronic Nicotine Delivery System (ENDS), also known as e-cigarettes. These e-cigarettes contain nicotine, which can lead to addiction (Kurtuluş & Can, 2022). E-cigarette cartridges contain propylene glycol, glycerol, nicotine, and various flavors (such as menthol, apple, and cinnamon) (Engel & Jerlhag 2014; King et al., 2013). E-cigarettes are marketed as a tool to quit or reduce smoking conventional cigarettes. Aggressive marketing of ENDS on social media poses a major risk for adolescent exposure to e-cigarettes (Njie et al., 2023). According to a multinational screening study conducted in 28 European Union countries by Farsalinos et al., the main reason young people start using e-cigarettes is the belief that it can help them quit or cut back on smoking (Farsalinos et al., 2016). However, these products make it more difficult to quit tobacco usage by creating a vicious cycle since they mimic the act of smoking (Callahan-Lyon, 2014; Dagli, 2019).

Many experts suggest that using e-cigarettes may lead to a higher likelihood of tobacco smoking addiction, acting as a "gateway" to stronger substances. This is because e-cigarettes often contain toxic substances, such as nicotine, which can be particularly harmful to the developing brains of teenagers. A marker of neuroinflammation is microglial activation, which can be triggered by nicotine during adolescence and may result in long-term addiction to nicotine (Mahajan et al., 2021). Nicotine smoke may have a stronger rewarding effect on the adolescent brain, making it more vulnerable. The variety of e-cigarette flavors can affect pleasure perception and directly impact the CNS reward system (Moshensky et al., 2022). Even limited exposure to nicotine can likely induce rewarding effects in adolescents, leading to their persistent use. According to animal studies, nicotine smoke had the most significant impact on the brain, elevating several inflammatory markers, particularly in adolescent rodents (Moshensky et al., 2022, Jude et al., 2020). Additional changes in neuroinflammatory gene expression were noted in the nucleus accumbens, a brain region critical for motivation and reward processing. The youth study by Xie et al. found that students who began vaping between the ages of 8 and 13 reported difficulty with concentration, memory, and decision-making compared to those who started at 14 or older (Xie et al., 2020). Recent research suggests that the various chemicals found in e-cigarettes, such as heavy metals, glass fibers, and flavorings, may contribute to the development of respiratory tract symptoms and asthma in adolescents that may alter the neuroinflammatory reactions in the whole-body system (Dagli, 2019; Kurtuluş & Can, 2022). Regular monitoring of e-cigarettes among youth could help policymakers balance adult cessation benefits in contrast to youth harms (Njie et al., 2023).

Conclusion

Adolescent behavior and heightened nicotine sensitivity may result from sociocultural factors such as peer pressure and societal expectations. Neurodevelopmental features such as reward-seeking and immature inhibitory control mechanisms in the adolescent period make youngsters vulnerable to the addictive effects of nicotine. Adolescent smokers are more likely to become heavy smokers, less likely to quit smoking later in life, and are at higher risk of dying from smoking-related illnesses. Smoking habits often start years before mental illness onset. Preventing adolescent nicotine exposure is critical in reducing smoking prevalence and related mental health risks. The tobacco industry is promoting heated tobacco products with potentially reduced risks as the future replacement for conventional tobacco products. However, the World Health Organization has stated that there is no evidence supporting this claim. Smoking nicotine may have a stronger rewarding effect on the adolescent limbic system, making it more vulnerable to future addiction. Implementing effective prevention and cessation programs, along with relevant legislation, is essential to control tobacco use. From Türkiye's perspective, the prohibition of the promotion and marketing of heated tobacco products should be considered strongly, as it is inconsistent with its constitution and the Framework Convention on Tobacco Control. As clinicians who have direct contact with adolescents such as child and adolescent psychiatrists, pediatricians, and other health workers, we hold the responsibility of increasing awareness about the health hazards and addictive risks associated with new emerging soluble nicotine products among the young population.

Peer-review: Externally peer-reviewed.

Declaration of Interests: The author has no conflicts of interest to declare.

Funding: The author declared that this study has received no financial support.

References

Arinami, T., Ishiguro, H., & Onaivi, E. S. (2000). Polymorphisms in genes involved in neurotransmission in relation to smoking. *European Journal of Pharmacology*, *410*(2 – 3), 215 – 226. [CrossRef]

Ayman, J., Palotai, M., Dochnal,R., & Bagosi, Z. (2023). Ghrelin amplifies the nicotine-induced release of dopamine in the bed nucleus of stria terminalis (BNST). *Biomedicines*, *11*(9), 2456. [CrossRef]

Balbuena, L., Peters, E., & Speed, D. (2023). Using polygenic risk scores to investigate the evolution of smoking and mental health outcomes

in UK Biobank participants. *Acta Psychiatrica Scandinavica*, *148*(5), 447 – 456. [CrossRef]

Besson, M., & Forget, B. (2016). Cognitive dysfunction, affective states, and vulnerability to nicotine addiction: A multifactorial perspective. *Frontiers in Psychiatry*, *7*, 160. [CrossRef]

Callahan-Lyon, P. (2014). Electronic cigarettes: Human health effects. *Tobacco Control*, *23* (Suppl. 2), ii36 – ii40. [CrossRef]

Casey, B. J., & Jones, R. M. (2010). Neurobiology of the adolescent brain and behavior: Implications for substance use disorders. *Journal of the American Academy of Child and Adolescent Psychiatry*, *49*(12), 1189 – 201; quiz 1285. [CrossRef]

Chatterjee, K., Aghoul, B., Innabi, A., & Nikhil, M. (2016). Is vaping a gateway to smoking: A review of the longitudinal studies. *International Journal of Adolescent Medicine and Health*, *30*(3). [CrossRef]

Counotte, D. S., Smit, A. B., Pattij, T., & Spijker, S. (2011). Development of the motivational system during adolescence, and its sensitivity to disruption by nicotine. *Developmental Cognitive Neuroscience*, *1*(4), 430 – 443. [CrossRef]

Cross, A. J., Anthenelli, R., & Li, X. (2018). Metabotropic glutamate Receptors 2 and 3 as targets for treating nicotine addiction. *Biological Psychiatry*, *83*(11), 947 – 954. [CrossRef]

Dagli, E. (2019). "New" Tobacco Products and Struggle Methods in 2019. *Journal of The Continuing Medical Education Publication of Turkish Medical Association*, *28*, 2 – 6.

Dinakar, C., Longo, D. L., & O'Connor, G. T. (2016). The health effects of electronic cigarettes. *New England Journal of Medicine*, *375* (14), 1372 – 1381. [CrossRef]

Dineley, K. T., Pandya, A. A., & Yakel, J. L. (2015). Nicotinic ACh receptors as therapeutic targets in CNS disorders. *Trends in Pharmacological Sciences*, *36* (2), 96 – 108. [CrossRef]

Engel, J. A., & Jerlhag, E. (2014). Role of appetite-regulating peptides in the pathophysiology of addiction: Implications for pharmacotherapy. *CNS Drugs*, *28* (10), 875 – 886. [CrossRef]

Erguder, T., Cakir, B., Aslan, D., Warren, C. W., Jones, N. R., & Asma, S. (2008). Evaluation of the use of Global Youth Tobacco Survey (GYTS) data for developing evidence-based tobacco control policies in Turkey. *BMC Public Health*, *8* (Suppl. 1), S4. [CrossRef]

Ergüder, T., Soydal, T., Uğurlu, M., Cakir, B., & Warren, C. W. (2006). Tobacco use among youth and related characteristics, Turkey. *Sozial- und Praventivmedizin*, *51*(2), 91 – 98. [CrossRef]

Ertas, N. (2007). Factors associated with stages of cigarette smoking among Turkish youth. *European Journal of Public Health*, *17*(2), 155 – 161. [CrossRef]

Farsalinos, K. E., Poulas, K., Voudris, V., & Le Houezec, J. (2016). Electronic cigarette use in the European Union: Analysis of a representative sample of 27 460 Europeans from 28 countries. *Addiction*, *111*(11), 2032 – 2040. [CrossRef]

Goriounova, N. A., & Mansvelder, H. D. (2012). Nicotine exposure during adolescence alters the rules for prefrontal cortical synaptic plasticity during adulthood. *Frontiers in Synaptic Neuroscience*, *4*, 3. [CrossRef]

Türkiye sağlık Araştırması (TÜİK) (2022). https://data.tuik.gov.tr/Bulten/Index?p=Turkiye-Saglik-Arastirmasi-2022-49747

Holz, N. E., Laucht, M., & Meyer-Lindenberg, A. (2015). Recent advances in understanding the neurobiology of childhood socioeconomic disadvantage. *Current Opinion in Psychiatry*, *28*(5), 365 – 370. [CrossRef]

Hu, T., Yang, Z., & Li, M. D. (2018). Pharmacological effects and regulatory mechanisms of tobacco smoking effects on food intake and weight control. *Journal of Neuroimmune Pharmacology*, *13*(4), 453 – 466. [CrossRef]

Jenssen, B. P., & Boykan, R. (2019). Electronic Cigarettes and Youth in the United States: A Call to Action (at the Local, National and Global Levels). *Children*, *6*(2), 30. [CrossRef]

Jude, A. F., Underhill, J., Zhao, B., Giordano, G., Tyndale, R. F., & Khokhar, J. Y. (2020). OpenVape: An open-source E-cigarette vapor exposure device for rodents. *European Neurology*, *7*(5), ENEURO. 0279-20.2020.

Kandel, D., & Kandel, E. (2015). The Gateway Hypothesis of substance abuse: Developmental, biological and societal perspectives. *Acta Paediatrica*, *104* (2), 130 – 137. [CrossRef]

Kaya, C. A.,& Unalan, P. C. (2010). Factors associated with adolescents' smoking experience and staying tobacco free. *Mental Health in Family Medicine*, *7*(3), 145 – 153.

King, B. A., Alam, S., Promoff, G., Arrazola, R., & Dube, S. R. (2013). Awareness and ever-use of electronic cigarettes among US adults, 2010 – 2011. *Nicotine and Tobacco Research*, *15*(9), 1623 – 1627. [CrossRef]

Korpi, E. R., den Hollander, B., Farooq, U., Vashchinkina, E., Rajkumar, R., Nutt, D. J., Hyytiä, P., & Dawe, G. S. (2015). Mechanisms of Action and persistent neuroplasticity by drugs of abuse. *Pharmacological Reviews*, *67*(4), 872 – 1004. [CrossRef]

Kurtuluş, Ş., & Can, R. (2022). Use of e-cigarettes and tobacco products among youth in Turkey. *Eurasian Journal of Medicine*, *54*(2), 127 – 132. [CrossRef]

Li, M. D. (2003). The genetics of smoking related behavior: A brief review. *American Journal of the Medical Sciences*, *326*(4), 168 – 173. [CrossRef]

Mahajan, S. D., Homish, G. G., & Quisenberry, A. (2021). Multifactorial etiology of adolescent nicotine addiction: A review of the neurobiology of nicotine addiction and its implications for Smoking Cessation pharmacotherapy. *Frontiers in Public Health*, *9*(9), 664748. [CrossRef]

Moshensky, A., Brand, C. S., Alhaddad, H., Shin, J., Masso-Silva, J. A., Advani, I., Gunge, D., Sharma, A., Mehta, S., Jahan, A., Nilaad, S., Olay, J., Gu, W., Simonson, T., Almarghalani, D., Pham, J., Perera, S., Park, K., Al-Kolla, R., Moon, H., et al. (2022). Effects of mango and mint pod-based e-cigarette aerosol inhalation on inflammatory states of the brain, lung, heart, and colon in mice. *eLife*, *11*, e67621. [CrossRef]

Njie, G. J., Kirksey Jones, C., Jacques, N., Adetokun, A., Ross, J., Owens, A., Anton, L., Michelle, J., & Pan, L. (2023). Changes in tobacco product use among students aged 13 to 15 years in 34 countries, global youth tobacco survey, 2012 – 2020. *Preventing Chronic Disease*, *20*, 220410.

Ogel, K., Çorapçoğlu, A., Sir, A, Tamar, M., Dogan, O., Uguz, S., Yenilmez, C., Bilici, M., Tamar, D., & Liman, O. (2004). Tobacco, alcohol and substance use prevalence among elementary and secondary school students in nine cities of Turkey. *Turkish Journal of Psychiatry*, *15*, 112 – 118.

Pogun, S., & Rodopman Arman, A. (2021). Understanding nicotine addiction and the health effects of nicotine use. In S. Belo Ravara, E. Dağli, P. Katsaounou, et al. (Eds.). *Supporting tobacco cessation (ERS monograph)* (pp. 18 – 32). European Respiratory Society. [CrossRef]

Quartz.com (2022). https://qz.com/new-zealands-new-cigarette-law-is-fighting-the-wrong-wa-1849893616

Silveri, M. M., Dager, A. D., Cohen-Gilbert, J. E., & Sneider, J. T. (2016). Neurobiological signatures associated with alcohol and drug use in the human adolescent brain. *Neuroscience and Biobehavioral Reviews*, *70*, 244 – 259. [CrossRef]

Singh, T., Arrazola, R. A., Corey, C. G., Husten, C. G., Neff, L. J., Homa, D. M., & King, B. A. (2016). Tobacco use among middle and high school students — United States, 2011 – 2015. *Morbidity and Mortality Weekly Report*, *65*(14), 361 – 367. [CrossRef]

Subramaniyan, M., & Dani, J. A. (2015). Dopaminergic and cholinergic learning mechanisms in nicotine addiction. *Annals of the New York Academy of Sciences*, *1349*(1), 46 – 63. [CrossRef]

Sylvestre, M. P., Hanusaik, N., Berger, D., Dugas, E., Pbert, L., Winickoff, J.,& O'Loughlin, J. L. (2018). A tool to identify adolescents at risk of cigarette smoking initiation. *Pediatrics*, *142*(5), e20173701. [CrossRef]

The Lancet Child Adolescent Health (2020). #TobaccoExposed. *Lancet. Child and Adolescent Health*, *4*(6), 407. [CrossRef]

Uygun, S. D., Arı, D. A., Ünlü, H. K., & Çetinkaya, S. (2022). The role of self-discontentment and impulsivity for youth smoking behavior, nicotine dependence and future smoking intention in a clinical sample of Turkish adolescents. *Turkish Journal of Pediatrics*, *64*(4), 694 – 707. [CrossRef]

Wallace, T. L., & Bertrand, D. (2013). Importance of the nicotinic acetylcholine receptor system in the prefrontal cortex. *Biochemical Pharmacology*, *85*(12), 1713 – 1720. [CrossRef]

Wellman, R. J., Dugas, E. N., Dutczak, H., O'Loughlin, E. K., Datta, G. D., Lauzon, B., & O'Loughlin, J. (2016). Predictors of the onset of cigarette smoking: A systematic review of longitudinal population-based studies in youth. *American Journal of Preventive Medicine*, *51*(5), 767 – 778. [CrossRef]

Wikipedia.com. (2023). *Effects of nicotine on human brain development*. https://en.wikipedia.org/wiki/Effects_of_nicotine_on_human_brain_development#:~:text=Nicotine%20exposure%20during%20adolescence%20adversely,e%2Dcigarettes%2C%20is%20unsafe

World Health Organization, & MPOWER (2023). https://www.who.int/publications/i/item/9789240077164

Xie, C., Xie, Z., & Li, D. (2020). Association of electronic cigarette use with self-reported difficulty concentrating, remembering, or making decisions in US youth. *Tob. Induc Dis*, *18*, 106.

Yuan, M., Cross, S. J., Loughlin, S. E., & Frances, L. M. (2015). Nicotine and adolescent brain. *Journal of Physiology*, *593*(16), 3397 – 3412.

Yuan, M., Cross, S. J., Loughlin, S. E., & Leslie, F. M. (2015). Nicotine and the adolescent brain. *Journal of Physiology*, *593* (16), 3397 – 3412. [CrossRef]