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Nicotine addiction – a health problem in adolescents in a neurobiological context

Abstract

Smoking is one of the leading causes of death which can be prevented in the developed countries. Smoking begins mainly in adolescence. Smoking in early adolescence is known to be associated with an increased risk of later addiction. Also the growing popularity of e-cigarettes, which attract young people with a variety of flavors, and are still little associated with harmful effects on health, unlike regular cigarettes. Exposure to nicotine in young people can affect learning, memory and attention, and lead to increased impulsivity, mood disorders and drug dependence. Nicotine and its derivatives are harmful to the human body, causing a significant increase in blood pressure, deterioration of blood supply to the vessels and acceleration of atherosclerotic processes, it has a detrimental effect on the gastric mucosa, causing gastric disorders. In addition, smoking is associated with the risk of many cancers: oral cavity, larynx, esophagus, lung, pancreas, kidney, liver and bladder. Nicotine addiction causes many health, social and financial consequences for the individual and the community as a whole. Multiple nicotine addiction risk SNPs were found in the *CHRNA5/A3/B4* gene cluster, with the best reported results for the risk allele derived from the non-synonymous SNP, rs16969968, in *CHRNA5*. Therefore, in the problem of addiction, including nicotine addiction, it seems important to know the neurobiological factors, including genetic ones, involved in these processes. This could lead to the development of new pharmacological and behavioral treatment strategies in the future.

Keywords: nicotine addiction, health problem, *CHRNA5* gene, adolescents.

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INTRODUCTION

Smoking is one of the leading causes of death which can be prevented in the United States and other developed countries. Annually, according to the US Centers for Disease Control and Prevention (www.cdc.gov), almost 6 million people die from smoking, and the current trend is that by 2030 this number will have increased to 8 million. In the United States, more than 5 million Americans under the age of 18 are projected to die from smoking-related disease. This number is much higher than the deaths from HIV, drug abuse, suicide, murder and motor vehicle accidents combined. Smoking begins mainly in adolescence, about 90% of US smokers reported having smoked their first cigarette before the age of 18. In the USA alone, 3,800 teenagers smoke their first cigarette every day, and 2,100 start smoking every day. It is known that smoking early in adolescence is associated with an increased risk of later addiction, therefore the presented statistics are particularly worrying [1,2]. Moreover, even a small amount of cigarettes smoked, e.g. two to four cigarettes a week, increase the risk of nicotine addiction in early adulthood [2,3]. In adolescence, there is a significant development of the brain [4,5]. There is

a hypothesis that nicotine use during adolescence, the critical period for brain development, causes neurobiological changes that promote nicotine addiction later in life [6]. Investigating the neurobiological consequences of smoking, including those associated with early use, may reveal the mechanisms that explain the basis of the transition from initial use to nicotine addiction. Despite the extensive literature on adult smokers, there is still very little research into adolescents.

The scientific reports presented so far show the growing popularity of e-cigarettes, which are attracting young people with a variety of flavors, and are still little associated with harmful effect on health, unlike regular cigarettes [7].

The 2018 National Youth Tobacco Survey showed e-cigarette use among middle and high schoolers increased 48% and 78%, respectively, in just 1 year [8]. This coincided with rapid increases in market share of JUUL, the e-cigarette product used mostly by young people [9]. More than 3.6 million youth currently use e-cigarettes, with 28% of high school e-cigarette users vaping on 20 days or more in the past month [10].

Exposure to nicotine in young people can affect learning, memory, and attention, and lead to increased impulsivity, mood disorders, and addiction to other drugs [11]. Many young

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people begin using e-cigarettes because of their popularity among peers and their appealing flavors, not recognizing they contain nicotine and risk addiction and other adverse impacts [12,13].

The impact of rising e-cigarette use in children merits special attention because neurodevelopmental changes during adolescence confer particular vulnerability to substance abuse. Inhalational injury is also a concern given case reports of adverse effects on the lung, including increased school absence due to asthma [14], hypersensitivity pneumonitis [15], eosinophilic pneumonia [16], lipoid pneumonia [17], and diffuse alveolar hemorrhage [18,19].

In a cohort study by Rao et al. of adolescents diagnosed with EVALI, we found that the clinical severity was variable, with some patients requiring no supplemental oxygen to one patient requiring invasive mechanical ventilation and extracorporeal membrane oxygenation. All patients who followed-up in the pulmonary clinic reported cessation of e-cigarette use, so it remains to be seen whether the improvement in pulmonary function seen in our patients will also persist in adolescents who choose to resume e-cigarette use. The long-term effects of the other components of e-cigarette liquid on the lung remain unknown and is an area for future study [20].

Health effects of nicotine

Nicotine and its derivatives are harmful to the human body, causing a significant increase in blood pressure, deterioration of blood supply to the vessels, and accelerate atherosclerotic processes. As a result of smoking, there are often changes in the vessels that cause a heart attack or angina. Memory deterioration, lack of energy and general exhaustion of the body are also observed. There are also digestive system disorders, because nicotine has a harmful effect on the gastric mucosa, causing gastric disorders. Nicotine enhances the activity of highly irritating gastric factors and weakens the effect of the protective factors.

Among the effects of nicotine, very dangerous and harmful effects are described in the literature – such as a significant increase in pepsin or hydrochloric acid secretion, increased motor function in the stomach, the risk of infection (e.g. *Helicobacter pylori*), an increase in the concentration of free radicals, vasopressin secretion or an increase in the concentration of the activating factor platelets. The substance called nicotine also leads to increased, spastic contraction of smooth muscles in the intestines and bile ducts [21].

In 1975, the World Health Organization reported another negative effect of smoking. Namely, smoking leads to the organism becoming addicted to nicotine [22]. Addiction to nicotine causes many health, social and financial consequences for the individual and the entire community. According to the International Classification of Diseases and Related Health Problems ICD 10, smoking is a physical and mental addiction (World Health Organization, 2012).

Passive contact with tobacco smoke also causes systemic effects in the body. Passive smokers run the risk of increased incidence of cardiovascular and respiratory diseases and malignant neoplasms. Passive smoking also often causes chronic obstructive pulmonary disease or lung cancer [21].

It has been proven that smoking is associated with the risk of many types of cancer: mouth, larynx, esophagus, lungs, pancreas, kidneys, liver and bladder. Nitrosamines, PAHs, carbon monoxide and other compounds contained in tobacco

and cigarette smoke are responsible for the occurrence of cancers of the oral cavity and bladder [23]. The most important risk factor for lung cancer is smoking. In developed countries, smoking can be attributed to as much as 87% of all deaths from lung cancer [24].

Benzopyrene is a strong chemical mutagen. It occurs in tobacco smoke during incomplete combustion. It belongs to the group of polycyclic aromatic hydrocarbons. Benzopyrene increases the risk of neoplasms, including gastrointestinal, liver, colon, bladder, skin and, above all, lung cancer [25].

Nicotine slows down and inactivates the ability to divide and migrate fibroblasts to the wound site during the wound healing process [26]. In smokers, the number of micro-injuries increases significantly because the skin becomes more sensitive to the harmful effects of external environmental factors [27].

The negative impact of smoking on health is obvious, but it is also worth paying attention to its negative effects in the area of the oral cavity. Thiocyanins contained in cigarette smoke are responsible for lowering the buffering capacity of saliva by lowering the pH in the oral cavity and promoting the development of cariogenic bacteria, such as *Lactobacillus spp.* or *Streptococcus mutans*. The consumption of tobacco products contributes to periodontal disease, candidiasis and cancer. Nicotinism contributes to the formation of discoloration on the teeth and causes an unpleasant smell of breath. It also affects the taste and smell disorders and impairs wound healing, which is due to the vasoconstrictive influence and suppression of neutrophils. Periodontal disease, alveolar bone loss or acute necrotizing gingivitis are more common in nicotine addicts. Failure of the implantation procedure is also observed more often compared to non-addicted persons. As much as 80% of oral cancers are caused by smoking.

Halitosis is another consequence of smoking. It is a foul odor from the mouth that is caused by the volatile sulfur compounds present in cigarette smoke. Nicotine addiction causes changes in the sense of smell and taste, especially bitter and salty. It does not affect the perception of a sweet taste [28].

A common condition accompanying tobacco addiction is xerostomia. It is a dry mouth caused by reduced saliva production. The symptoms include: burning, pain, redness, a tendency to ulceration, disturbances in the sense of taste and unpleasant smell from the mouth - stench ex ore. Xerostomia has a positive effect on the development of Candida yeasts, which leads to the development of inflammation, keratosis and the growth of filamentous papillae of the tongue, which, as a result of discoloration, give the image of a disease called black hairy tongue. The reduction of saliva secretion is cariogenic [29-32].

In contrast to common dictum, depression does not seem to be an antecedent to heavy cigarette use among teens. However, current cigarette use is a powerful determinant of developing high depressive symptoms [33].

Nicotine addiction in the neurobiological context

Smoking is the process of self-delivery of nicotine using a clever but harmful method. Most likely, smoking is the best way to get the maximum pleasure out of using nicotine. Unfortunately, pulsatile administration of nicotine doses has an effect on the reward circuits, which carries the risk of addiction. When smoking, carcinogens and other toxic substances are delivered to the body that harm the heart, lungs and other tissues. Taking into account the psychopharmacological mechanisms

of action of nicotine, it acts directly on nicotinic cholinergic receptors in the reward system. Smoking presynaptic nicotinic receptors on dopaminergic receptors is activated, thanks to which dopamine is released in the nucleus accumbens and presynaptic receptors on neurons are activated – glutamatergic, which leads to the release of glutamate and then dopamine in the nucleus accumbens [34].

Nicotine acts on many nicotinic receptors in different areas of the brain. For example, the effect of nicotine on the postsynaptic alpha 7 nicotinic receptors in the prefrontal cortex may be related to the pro-cognitive and psychologically stimulating effects of nicotine, without being related to its addictive effect. However, the primary target of the action associated with the enhancing properties of nicotine was found to be alpha 4 beta 2 receptors on DA neurons in the VTA. These receptors get used to the long-term, intermittent, pulsatile administration of nicotine in a way that leads to addiction.

Alpha 4 beta 2 receptors are in a resting state before nicotine is administered. When considering getting a further reward, you may stop smoking at this point. It takes as long as it takes to smoke one standard cigarette to desensitize nicotinic receptors. Therefore, the average length of a cigarette is not accidental. Shorter cigarettes would not provide maximum pleasure, and longer ones do not make sense because all receptors would be desensitized beforehand [34].

Administration of nicotine releases dopamine in the nucleus accumbens by attaching it to the postsynaptic alpha 4 2 nicotinic receptors on DA neurons in the VTA. In addition, nicotine attaches to presynaptic alpha 7 nicotinic receptors on glutamatergic neurons in the VTA, which leads to the release of dopamine in the nucleus accumbens. Additionally, nicotine is responsible for the desensitization of postsynaptic alpha 4 beta 2 receptors on GABAergic interneurons in VTA. Reducing the intensity of GABAergic neurotransmission disinhibits mesolimbic dopaminergic neurons, which is the third mechanism of increasing dopamine release in the nucleus accumbens [34].

In 2007, in the first study on the contribution of variants in the *CHRNA5/A3/B4* cluster to nicotine addiction [35]. Saccone et al examined 879 light smokers, without symptoms of addiction, with a score of 0 in the Fagerström test and 1050 heavy smokers with a score above 4.0 in the Fagerström test. They focused on the transition from smoking to addiction. They tested 3,713 SNPs on over 300 candidate genes. Many risk SNPs were found in the *CHRNA5/A3/B4* gene cluster, with the best-reported results for the risk allele derived from the non-synonymous SNP, rs16969968, in *CHRNA5*.

Such a discovery could push us towards formulating the thesis that not only smoking affects our health, but our health, which is recorded in genes, may be burdened by the tendency to become addicted.

NACHRs are primary targets of nicotine, nicotine exerts direct and indirect effects on other receptor systems (e.g., opioid, serotonergic, glutamatergic) that also mediate nicotine-induced behavioral and neural changes in humans. Variation in the genes that code for the drug receptor proteins or that code for metabolic and catabolic enzymes that influence neurotransmitter levels, also represent the candidate genes for nicotine dependence and treatment [36].

The *CYP2A6* genotype confers a slow nicotine metabolism increasing the risk of nicotine dependence [37]. *CYP2A6*, is a genetically variable hepatic enzyme that is responsible for

the majority of the metabolic inactivation of nicotine to cotinine. This enzyme mediates over 90% of the conversion of nicotine to cotinine, which is a major route of elimination of nicotine and therefore *CYP2A6* activity is an important indicator of nicotine metabolism. A slow rate of nicotine conversion into cotinine results in a prolonged presence of higher nicotine concentrations in the bloodstream, thus increasing the exposure of nicotinic acetylcholine receptors in the brain to nicotine. Variant alleles of the *CYP2A6* gene are associated with slower nicotine metabolism [36,38].

CONCLUSIONS

Therefore, in the problem of addiction, including nicotine addiction, it seems important to know the neurobiological factors, including genetic ones, involved in these processes. This could lead to the development of new pharmacological and behavioral treatment strategies in the future.

REFERENCES

1. Kendler KS, Myers J, Damaj MI, Chen, X. Early smoking onset and risk for subsequent nicotine dependence: A co-twin control study. *Am J Psychiatry*. 2013;170:408, doi:10.1176/APPI.AJP.2012.12030321.
2. Lydon DM, Wilson SJ, Child A, Geier CF. Adolescent brain maturation and smoking: What we know and where we're headed. *Neurosci Biobehav Rev*. 2014;45:323-42. doi:10.1016/J.NEUBIOREV.2014.07.003.
3. Riggs NR, Chou CP, Li C, Pentz MA. Adolescent to emerging adulthood smoking trajectories: When do smoking trajectories diverge, and do they predict early adulthood nicotine dependence? *Nicotine Tob Res*. 2007;9:1147-54.
4. Miguel-Hidalgo JJ. Brain structural and functional changes in adolescents with psychiatric disorders. *Int J Adolesc Med Health*. 2013;25:245-56.
5. Paus T, Keshavan M, Giedd JN. Why do many psychiatric disorders emerge during adolescence? *Nat Rev Neurosci*. 2008;9:947-57.
6. de Bry SC, Tiffany ST. Tobacco-induced neurotoxicity of adolescent cognitive development (TINACD): A proposed model for the development of impulsivity in nicotine dependence. *Nicotine Tob Res*. 2008;10:11-25.
7. Rao DR, Maple KL, Dettori A, et al. Clinical features of e-cigarette, or vaping, product use-associated lung injury in teenagers. *Pediatrics*. 2020;146(1):20194104.
8. Graham AL, Jacobs MA, Amato MS. Engagement and 3-month outcomes from a digital e-cigarette cessation program in a cohort of 27 000 teens and young adults. *Nicotine and Tobacco Research*. 2020;22(5):859-60.
9. Cullen KA, Gentzke AS, Sawdey MD, et al. E-cigarette use among youth in the United States, 2019. *JAMA*. 2019;322:2095-103.
10. Wang TW, Neff LJ, Park-Lee E, et al. E-cigarette use among middle and high school students – United States, 2020. *Morbidity and Mortality Weekly Report*. 2020;69(37):1310.
11. U.S. Department of Health and Human Services. E-Cigarette Use Among Youth and Young Adults. A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2016.
12. Willett JG, Bennett M, Hair EC, et al. Recognition, use and perceptions of JUUL among youth and young adults. *Tob Control*. 2019;28(1):115-6.
13. Graham AL, Jacobs MA, Amato MS. (2020). Engagement and 3-month outcomes from a digital e-cigarette cessation program in a cohort of 27 000 teens and young adults. *Nicotine and Tobacco Research*. 2020;22(5):859-60.
14. Cho JH, Paik SY. Association between electronic cigarette use and asthma among high school students in South Korea. *PLoS One*. 2016;11(3):e0151022.
15. Sommerfeld CG, Weiner DJ, Nowalk A, Larkin A. Hypersensitivity pneumonitis and acute respiratory distress syndrome from e-cigarette use. *Pediatrics*. 2018;141(6):e20163927.
16. Arter ZL, Wiggins A, Hudspath C, Kisling A, Hostler DC, Hostler JM. Acute eosinophilic pneumonia following electronic cigarette use. *Respir Med Case Rep*. 2019;27:100825.

17. Dicipinigaitis PV, Trachuk P, Fakier F, Teka M, Suhrlund MJ. Vaping-associated acute respiratory failure due to acute lipoid pneumonia. *Lung*. 2020;198(1):31-3.
18. Agustin M, Yamamoto M, Cabrera F, Eusebio R. Diffuse alveolar hemorrhage induced by vaping. *Case Rep Pulmonol*. 2018;2018:9724530.
19. Rao DR, Maple KL, Dettori A, et al. Clinical features of e-cigarette, or vaping, product use-associated lung injury in teenagers. *Pediatrics*. 2020;146(1).
20. Grzywacz A, Suchanecka A, Chmielowiec J, et al. Personality traits or genetic determinants – Which strongly influences e-cigarette users? *Int J Environ Res Public Health*. 2020;17(1)365.
21. Dutkiewicz, T. *Chemia Toksykologiczna : Podręcznik dla studentów Farmacji*. Warszawa: Państw. Zakład Wydawnictw Lekarskich; 1968.
22. Samochowiec J, Rogoziński D, Hajduk A, et al. Diagnostyka, mechanizm uzależnienia i metody leczenia uzależnienia od nikotyny. *Alkoholizm i Narkomania*. 2001;14:323-40.
23. Dreisbach RH. Tytoń i Nikotyna. In *Vademecum zatruc. Zapobieganie, rozpoznanie i postępowanie*. Warszawa: WZWL; 1995.
24. Rang HP, Dale MM, Ritter JM. *Farmakologia Kliniczna*. Lublin: Czelej; 2001.
25. Siemińska A. W poszukiwaniu genów wpływających na palenie tytoniu. *Pneumonol. Alerg Pol*. 2010:432-8.
26. Jaworska-Zaręba M, Domagała J, Łomżyński Ł, Trębicki J. Wpływ palenia tytoniu na proces osteointegracji wszczepów stomatologicznych. *Nowa Stom*. 2007;2:91-4.
27. Czogała J, Goniewicz ML, Czubek A, et al. Wpływ palenia papierosów na wygląd, starzenie się i zmiany patologiczne skóry i błon śluzowych. *Przegl Lek*. 2008;65:732-6.
28. Agnihotri R, Gaur S. Implications of tobacco smoking on the oral health of older adults. *Geriatr Gerontol Int*. 2014;14:526-40.
29. Aniko-Włodarczyk M, Preuss O, Grzywacz A, et al. Zdrowie jamy ustnej pacjentów z nalogiem. *Stomatologia Po Dyplomie*. 2018;5.
30. Michalak E, Halko-Gąsior A, Chomyszyn-Gajewska M. Wpływ tytoniu na stan jamy ustnej – Na podstawie piśmiennictwa. *Przegląd Lekarski*. 2016;73:516-9.
31. Maciąg W, Bachanek T. Wpływ alkoholu i nikotyny na stan zdrowia jamy ustnej. *Magazyn Stomat*. 2006;16:28-9.
32. Miller A, Miller I, Kurnatowska A, Rabe-Jabłońska J. Zaburzenia sekrecji śliny jako efekt uboczny farmakologicznego leczenia zaburzeń psychicznych – Przegląd piśmiennictwa. *Postępy psychiatrii i Neurologii*. 2006;15:29-34.
33. Thorisdottir IE, Asgeirsdottir BB, Kristjansson AL, et al. Depressive symptoms, mental wellbeing, and substance use among adolescents before and during the COVID-19 pandemic in Iceland: a longitudinal, population-based study. *The Lancet Psychiatry*. 2021;8(8):663-72.
34. Stahl SM, Grabowski K, Kunicki M, Rzewuska M. *Podstawy psychofarmakologii : Teoria i praktyka*. Via Medica; 2010.
35. Saccone SF, Hinrichs AL, Saccone NL, et al. Cholinergic nicotinic receptor genes implicated in a nicotine dependence association study targeting 348 candidate genes with 3713 SNPs. *Hum Mol Genet*. 2007;16:36-49.
36. Mahajan SD, Homish GG, Quisenberry A. Multifactorial etiology of adolescent nicotine addiction: A review of the neurobiology of nicotine addiction and its implications for smoking cessation pharmacotherapy. *Front Public Health*. 2021;9:664748.
37. Karp I, O'Loughlin J, Hanley J, et al. Risk factors for tobacco dependence in adolescent smokers. *Tob Control*. 2006;15:199-204.
38. Benowitz NL, Swan GE, Jacob P III, et al. CYP2A6 genotype and the metabolism and disposition kinetics of nicotine. *Clin Pharmacol Ther*. 2006;80:457-67.

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