

INVITED REVIEW

Use of Tobacco Products as a Substance Addiction Entry Tool

Cemal Onur Noyan¹, Nesrin Dilbaz¹, Ceyda Şişman Ünlü²

¹Faculty of Medicine, Üsküdar University, İstanbul, Türkiye

²Addiction Counseling and Rehabilitation, Üsküdar University, İstanbul, Türkiye

ORCID iDs of the authors: N.D. 0000-0003-0724-3489, C.O.N 0000-0002-4819-1032, C.Ş.Ü. 0000-0002-4603-8173.

Main Points

- The fact that the age of substance use is decreasing day by day in the world and in our country raises concern. The National Drug Use and Health Survey Report 2019 data showed that the rate of substance use among individuals over the age of 12 was 60.1%, while the rate of smoking was 21.1%.
- According to the gateway hypothesis, individuals who smoke cigarettes may also use cannabis and other addictive substances in the future.
- The increasing use of e-cigarettes today shows that those who start using e-cigarettes to quit smoking start using cigarettes and other tobacco products. Studies show that individuals who only use e-cigarettes start using cigarettes or tobacco products in the future.
- It is worrisome that individuals are interested in cigarettes and other recreational substances, especially in early adolescence. It is thought that the environment of friends and family attitudes affect individuals during adolescence. According to the gateway hypothesis, it is thought that preventive studies on the use of cigarettes and other tobacco products can prevent substance use and addiction in the future.

Abstract

Research conducted over many years suggests that the process leading to the use of illegal substances and addiction often starts with tobacco use. This process, which progresses from tobacco use to marijuana use and further to the use of other substances, is explained by the “gateway hypothesis,” where tobacco and tobacco products are considered as gateway substances that lead to illegal substance use. Especially, the increasing use of hookah and e-cigarettes is noted to pose a significant risk for transitioning from smoking to illegal substances like marijuana. Weak perceptions of harm associated with smoking and marijuana use, particularly among teenagers, can lead to an increase in the use of these substances. Experiencing the expected negative side effects of the substances can further reduce the perceived harm and encourage teenagers to try other illegal substances. Therefore, raising awareness of the negative effects of tobacco and tobacco products on health and developing preventive programs against new-generation nicotine products is of great importance. Implementing legal regulations that restrict access to tobacco and tobacco products, especially during early adolescence, is also considered beneficial in preventing substance addiction development. In this review article, the effects of tobacco and tobacco product use, studies, psychosocial and neurobiological explanations, and the relationship between tobacco product use and substance use are mentioned.

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Corresponding Author:

Cemal Onur Noyan

E-mail:

cemal.noyan@uskudar.edu.tr

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Introduction

Addiction is defined as the misuse of a substance, an increase in the amount of substance use following tolerance to substance use, continued use despite causing problems in the person’s social life, and

withdrawal symptoms that occur when the amount of substance taken decreases or is stopped (Dilbaz, 2013). Substance addiction has become a public health problem worldwide, affecting individuals psychologically, physiologically, and sociologically (Özbay & Gültekin, 2023). Despite the negative

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social, financial, and physiological consequences of substance use, individuals continue to use substances, highlighting the severity of the problem. Looking at historical records, it is evident that substances have been used in different places and for different purposes (Nalbantoğlu & Tuncay, 2023). Despite the severe consequences of using substances, individuals often want to continue using substances to experience the pleasure they initially obtained, and this can lead to substance use disorder (Özbay & Gültekin, 2023).

Research conducted over many years suggests that the process leading to illegal substance use and addiction often begins with tobacco use (Kandel & Kandel, 2014; Kandel, 1975; Lai et al., 2000; Lindsay & Rainey, 1997). The gateway hypothesis, which describes the process of initiation and continuation of substance use, posits that specific substances serve as a gateway to the use of other substances (Kandel & Kandel, 2014). As the process progresses from tobacco use to marijuana use, and then to the use of other substances, it is explained by the “gateway hypothesis,” and tobacco and tobacco products are considered as gateway substances that facilitate the transition to illegal substance use (Kandel & Kandel, 2015; Yuan et al., 2015). Kandel, in a study that involved tracking 6,453 high school students, explained Kandel’s gateway hypothesis and stated that the process of substance use during adolescence occurs in four stages and in a gradual order. The first stage involves the use of low-alcohol content beverages, followed by the use of cigarettes and high-alcohol drinks in the next stage. The third stage includes marijuana use, and the fourth stage includes the use of other illegal substances (Kandel, 1975). Legal substances like tobacco and alcohol can facilitate the use of other potentially addictive substances such as marijuana, cocaine, or opioids, primarily marijuana, and later, cocaine or opioids (Kandel & Kandel, 2014; Lynskey & Agrawal, 2018).

Theory

Since the use of tobacco and tobacco products is thought to be a gateway to other substances, PubMed, Google Scholar, Ulakbim search engines were used for the study. Keywords were determined for the study, and these keywords, as well as closely related terms, were scanned. Searches were conducted using Turkish keywords, including “Tütün ürünleri,” “adolesan dönemde tütün ve tütün ürünleri kullanımı,” “sigara kullanımı,” and “geçiş kapısı hipotezi.” Searches were conducted using the following English keywords: “Tobacco products,” “Tobacco and tobacco product use in adolescence,” “Cigarette use,” and “Gateway hypothesis”. Review articles, research papers, and meta-analysis studies were included in the search. Both Turkish and English sources were examined, and those consistent with the keywords were included in the study. In this review article, the effects of tobacco and tobacco product use, studies, psychosocial and neurobiological explanations, and the relationship between tobacco product use and substance use are mentioned.

Psychosocial Explanation

The diversity in the age of initiation for different substances and the cause-and-effect relationship of the hierarchical substance use process form the basis of the gateway hypothesis. The age at which smoking and alcohol use starts is lower than the age at which marijuana use begins, and the age at which volatile and

stimulant substances are used is lower than the age at which marijuana use starts. These substances act as gateways to the use of other substances ((Badiani et al., 2015; Coffey et al., 2003; Lai et al., 2000; Lynskey et al., 2003). Although the transition from one substance to another is a multi-step process, it is generally accepted that it starts with tobacco use and progresses to marijuana use and other illegal substances. Weak perceptions of harm associated with smoking and marijuana use, particularly among teenagers, can lead to an increase in the use of these substances. This is especially important because the perceived harm associated with smoking has significantly decreased among teenagers over time, which may further facilitate the transition from smoking to illegal substances. When adolescents start smoking, they develop various behavioral habits such as preparing cigarettes, holding cigarettes in their hands, inhaling and exhaling cigarette smoke. These habits can make it easier for young people to use substances such as tobacco, especially cannabis. Adolescents who quickly overcome the negative experiences of smoking their first cigarette, such as nausea, coughing, and lung irritation, may continue smoking. During this process, the body gets used to smoking and the lungs become desensitized. This highlights the importance of perceived harm and the role it plays in the use of tobacco products and the subsequent transition to illegal substances (Lindsay & Rainey, 1997).

Neurobiological Explanation

In addition to studies attempting to explain the gateway hypothesis through a psychosocial model, recent years have seen research on the biological effects of this gateway phenomenon. Adolescence is a period of preparation for adulthood, marked by hormonal, psychosocial, and biological changes. However, it is also a period characterized by increased stress sensitivity, heightened novelty-seeking, and risk-taking behaviors, making individuals more susceptible to various risky behaviors. Risky behaviors specific to adolescence are closely associated with the incomplete development of the brain (Dilbaz, 2013). Particularly during this vulnerable developmental period, there is heightened sensitivity to the adverse effects of psychoactive substances such as nicotine. The limbic system plays a crucial role in reward processing functions closely related to learning, memory, and adolescent behaviors (novelty seeking, risk-taking, and impulsivity).

Nicotine, the most fundamental psychoactive component of tobacco products, binds to nicotinic acetylcholine receptors (nAChRs), which are pentameric ligand-gated ion channels consisting of α and β subunits ($\alpha 1 - 7, 9 - 10; \beta 1 - 4$). Particularly during adolescence, several significant differences in nAChR function and numbers have been reported. Exposure to nicotine during the critical developmental period of adolescence is reported to lead to long-lasting neurochemical and behavioral changes that facilitate the initiation of substance use through nAChRs (Galván, 2010; Yuan et al., 2015). nAChRs are crucially important in neuromuscular junctions, neurotransmitter release, brain maturation, reward processing, and cognitive processes. They are activated either endogenously by acetylcholine or exogenously by nicotine and are expressed by dopaminergic neurons associated with substance use.

The addictive effects of psychoactive substances occur through dopamine release in the mesolimbic pathway extending from the

ventral tegmental area, also known as the reward center, to the nucleus accumbens. One of the key factors regulating dopamine release in the reward center is the binding of nicotine to nAChRs. The foundation of the associative relationship between nicotine and substance use is based on nicotine consumed in early adolescence, causing changes in the brain's reward center, resulting in enhanced rewarding effects of possible substance use in subsequent periods (De Biasi & Dani, 2011; Levine et al., 2011). Experiments conducted on mice by Kandel and colleagues (Kandel & Kandel, 2014; Ramo, Delucchi, Hall, Liu and Prochaska, 2013) to test the gateway hypothesis showed that nicotine increased the rewarding effect of later cocaine use. Animal experiments measuring the effects of nicotine on the locomotor system have shown that chronic nicotine exposure attenuated the locomotor suppression induced by tetrahydrocannabinol (THC) in adult male mice but increased it in adolescent mice. Nicotine exposure has also been shown to produce lasting effects on the cannabinoid-mediated signals in the brain by enhancing c-Fos expression in the basal ganglia and limbic system, similar to the effects of THC (Miladinovic et al., 2020). Based on all these studies, it has been demonstrated that exposure to nicotine during the ongoing developmental process in adolescence has an impact on brain pathways and neurotransmitters associated with reward, influencing responses to rewards and behaviors. In particular, adolescents exposed to nicotine during adolescence are both more sensitive and more prone to substance use compared to adolescents who have never been exposed to nicotine (Ren & Lotfipour, 2019).

Relationship Between Tobacco Use and Substance Use Disorder Tobacco

The primary psychoactive component of traditional cigarettes, and THC, the primary psychoactive component of marijuana, can affect the brain's reward center, influencing pleasure and reward pathways in similar ways. This interaction can lead to the development of substance-seeking behaviors in adulthood (Galván, 2010). Numerous cross-sectional and longitudinal studies have shown that adolescent smokers have higher rates of marijuana use compared to their non-smoking peers (Badiani et al., 2015; Goodwin et al., 2018; Zuckermann et al., 2020). Moreover, there are studies suggesting that cigarette use leads to marijuana use and, conversely, marijuana use increases cigarette use (Lynskey & Agrawal, 2018; Mayet et al., 2011). It is also noted that the transition from marijuana use to addiction occurs more rapidly in non-smoking adolescents and that using both marijuana and tobacco makes addiction more likely and makes the quitting process more challenging (Peters et al., 2012; Ramo, Liu, and Prochaska, 2012; Ream et al., 2008).

Many cross-sectional, cohort, and meta-analytic studies have been conducted on the relationship between cigarette smoking and illicit drug use. A study conducted in 1993 found that daily smoking in adolescents was associated with a four-fold increase in the likelihood of alcohol use and a 10- to 30-fold increase in the likelihood of using illicit drugs compared to non-smokers (Torabi et al., 1993). In a study on health economics in 2002, it was observed that when cigarette prices were low, smoking rates were high, and the age of starting to smoke was low. During this period, it was reported that individuals who started smoking began using marijuana more frequently and at an earlier age, in

line with the gateway hypothesis. With an increase in cigarette prices, both cigarette and marijuana use rates decreased, supporting the gateway hypothesis (Beenstock & Rahav, 2002).

Based on data from a cohort study from New Zealand, adolescents who smoked cigarettes had a 5 times higher likelihood of using marijuana than adolescents who had never smoked cigarettes (Badiani et al., 2015). In a 14-year-long follow-up study conducted in Germany, early initiation of cigarette smoking was found to increase the risk of marijuana use disorder by 1.8 times, with regular adolescent smokers having a 2.5 times higher risk. This study emphasizes that early initiation of smoking in adolescence is the most critical precursor to the development of marijuana use disorder (Prince van Leeuwen et al., 2014). These findings support the relationship between cigarette smoking and marijuana use, suggesting a gateway effect between these two substances.

Relationship Between Tobacco Products and Substance Use Disorder

Many smokers have reported using e-cigarettes to quit smoking, and it is known that some individuals start using e-cigarettes alongside smoking (Khouja et al., 2020). However, scientific research has provided evidence that e-cigarette use can have negative health effects, lead to secondhand exposure, produce inconsistent effects on smoking cessation, and normalize smoking behavior. There are also concerns that e-cigarette use among young people may facilitate the transition to smoking (Khouja et al., 2020). Khouja et al. (2020) meta-analysis found that there is a consistent and strong association between non-smokers who use e-cigarettes and subsequent smoking. Due to these concerns, restrictions have been imposed on e-cigarette use and sales (Bals et al., 2019; Food and Drug Administration, 2020; 2009a; 2009b).

Recent studies have shown that traditional cigarettes have been replaced as the first substance tried by young individuals by alternative tobacco products like smokeless tobacco, hookah, and cigarillos, including e-cigarettes (Etter, 2018; Park et al., 2020; Primack et al., 2015; Singh et al., 2020). E-cigarette users often cite various flavors, easy access, and the belief that they are less harmful as reasons for their preference (Roditis & Halpern-Felsher, 2015).

There are studies that indicate e-cigarette use is less harmful than traditional cigarettes and that e-cigarettes can be used in smoking cessation treatments (Borelli and O'Connor, 2019; Hajek et al., 2019). Additionally, there are studies suggesting that e-cigarette use may serve as a gateway to the initiation of traditional cigarette smoking (Barrington-Trimis et al., 2016; Etter, 2018; Khouja et al., 2020; Soneji et al., 2017). According to Etter (2018), although it is not known for certain that electronic cigarettes show a transition feature to the use of tobacco products, the widespread use of electronic cigarettes in the future or the differentiation of e-cigarette models may lead adolescents to first use cigarettes instead of using e-cigarettes as combustible. This situation is thought to increase the risk of adolescents becoming addicted.

In a meta-analysis study conducted by Khouja and colleagues (Khouja et al., 2020) in 2020, it was demonstrated that individuals

who had never smoked cigarettes but used e-cigarettes were 4.5 times more likely to start smoking cigarettes in subsequent periods compared to non-users. Despite the limitations on e-cigarette sales to youth and despite declining cigarette smoking rates in countries with high e-cigarette use, an increase in cigarette smoking rates has been observed. This suggests that the relationship between e-cigarettes and traditional cigarettes may be explained by a common liability theory rather than the gateway hypothesis. Some studies have suggested that characteristics involving genetic predisposition, personality traits, comorbidity with psychiatric illnesses, peer influence, and legal restrictions play a role in concurrent use of e-cigarettes and cigarettes (Etter, 2018; Khouja et al., 2020). A 2-year follow-up study conducted by The results of a 4-year follow-up study conducted by Ksinan and colleagues in 2020 (Ksinan et al., 2020) are in line with previous studies, showing that e-cigarette use increases the likelihood of initiating marijuana use. Theories regarding the simultaneous use of e-cigarettes and marijuana have emphasized the importance of e-cigarette devices being used for consuming marijuana and the potential for these two substances to enhance each other's pleasurable effects (Miladinovic et al., 2020; Spindle et al., 2019). In conclusion, various studies have shown that the use of tobacco and tobacco products during adolescence can have a gateway effect on the use of illicit substances. It is believed that the increased use of nicotine delivery systems plays a significant role in this gateway effect. Therefore, raising awareness about the adverse effects of tobacco and tobacco products on health and developing preventive programs against new-generation nicotine products is of great importance. Particularly, implementing legal regulations that restrict access to tobacco and tobacco products during early adolescence is considered beneficial for preventing the development of substance addiction. Such preventive measures can contribute to guiding young individuals toward healthier lifestyles and helping prevent harmful addictions.

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