Review Article
Tobacco Addiction - Blame it on Genes!
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Abstract
Tobacco use, in any form, either smoked or smokeless, is of a major concern to the dentist as it can cause a wide spectrum of oral mucosal lesions. As the multiple oral and systemic health effects of tobacco usage have been extensively explored and reported, the dentists are well aware of them, but have only limited understanding of the complex biological mechanisms of nicotine addiction. Dependence on tobacco, like many other drug dependencies, is a complex behavior with both genetic and environmental factors contributing to it. The purpose of the present article is to familiarize dentists with the current concepts on the mechanisms involved in initiation, maintenance, cessation, relapse and various therapeutic approaches of the habit.

Key words: Tobacco;Addiction;Nicotine;Dopamine;Dopaminergic Receptors;Candidate Genes.

Introduction
Tobacco addiction is reported to be the most common cause of death as more than 5.4 million people dies annually due to this habit\(^1\). Despite the knowledge of its disastrous health effects, one-third of the global population, still use tobacco daily because they are addicted to it\(^2\). Addiction is characterized by compulsive seeking and use of a substance or drug, even in the face of negative health consequences\(^3\). Multiple aspects of using tobacco, including initiation, persistence and cessation are influenced by a complex web of social, environmental and genetic factors\(^4\).

The dentists are well aware of the wide spectrum of oral mucosal alterations or lesions associated with tobacco use, like tooth stains, abrasions, smoker’s melanosis, acute necrotizing ulcerative gingivitis, burns, keratotic patches, black hairy tongue, nicotinic stomatitis, palatal erosions, leukoplakia, epithelial dysplasia and squamous-cell carcinoma, but have limited knowledge on nicotine dependence\(^5\). The purpose of the present article is to discuss the multiple aspects of nicotine addiction, from the tendency to begin smoking, to the chances of quitting; thus aiming to help the dentists in understanding the psychology of the patients addicted to the habit.

History
Tobacco was first introduced into European society by Hernandez de Toledo, who discovered the plant in 1520. Jean Nicot, French ambassador to Portugal received the tobacco plant from Hernandez and eventually sent it to the Queen. For his efforts, the new world species was given the name Nicotiana\(^6\). The Spanish word ‘Tabaco’ is thought to have its origin in Taino language, where it was said to refer either to a roll of tobacco leaves, or to the ‘Tabago’, a kind of Y-shaped pipe for sniffing tobacco smoke. There are many species of tobacco, which are all encompassed by the plant genus ‘Nicotiana’. Apart from smoking, tobacco had a number of uses as medicine. As a pain killer it was used for earache, toothache, as a cure for colds, asthma and tuberculosis. It was believed that the plant was sacred and if one abuses it, it will abuse that person in return, causing sickness. The proper and traditional native way of offering the smoke was said to involve directing it towards the four cardinal points (north, south, east, and west), rather than holding it deeply within the lungs for prolonged periods\(^7\). But as its use spread into Western cultures, it was no longer used primarily for religious purposes\(^8\).

Nicotine and Tobacco Addiction
Nicotine is one of the 4000 chemicals found in the tobacco and it is the primary component responsible for addiction\(^9\). It is the tobacco plant’s natural protection from being eaten by insects. It is a toxin, drop for drop, more lethal than rattle snake venom\(^9\). More recent research has shown that the addiction
produced by nicotine is extremely powerful and is rated ahead of drugs like heroin and cocaine in terms of dependence. This natural insecticide’s chemical signature is so similar to the neurotransmitter Acetylcholine that once inside the brain it fits a host of chemical locks permitting it direct and indirect control over the flow of more than 200 neurochemicals. When tobacco is smoked, nicotine enters the bloodstream through the lungs and reaches the brain faster than the drugs that enter the body directly through the veins. When it is chewed or sniffed, nicotine passes through the mucosal membranes of the mouth and nose to enter the bloodstream. Nicotine can also enter the bloodstream by passing through the skin. Nicotine reaches the brain within seven seconds. This sudden burst of nicotine causes an instant high blood pressure which is caused by the stimulation of the adrenal glands resulting in discharge of epinephrine. The release of adrenaline causes a sudden release of glucose as well as an increase in blood pressure, respiration and heart rate.

Nicotine readily crosses the blood brain barrier and binds to specific nicotinic acetyl choline receptors (nAChR) distributed on the mesolimbic and mesocortical dopaminergic pathways and increase the concentrations of dopamine, which produces pleasure, stimulation and mood modulation. Nicotine also increases serotonin secretion in brain that stimulates enkephalin which in turn inhibits Gamma Amino Butyric acid (GABA) thereby increases the levels of dopamine. Alternatively, it decreases the level of Monoamine oxidase (MAO) which prevents the breakdown of dopamine. All the three pathways increase the level of dopamine, which induce the pleasurable sensation that lasts for few minutes. Once exposed, the brain records the entire dopamine experience and keeps asking for continuous pleasure effect making the person to get addicted to it.

**Predisposing factors for Tobacco Addiction**

Factors that predispose to tobacco addiction involve a complex web of social, environmental and genetic influences (Fig 1). The age of smoking initiation is declining and tobacco use is rising among youth in many countries. The factors that predispose young people to smoke vary among individuals and among different populations. Low prices, easy access, parenteral smoking, family conflicts, peer pressure and positive image of smoking through advertisement are all contributing factors for initiation of tobacco use in adolescence.

![Figure 1: Predisposing factors of tobacco addiction.](image)

Continuation of tobacco consumption is associated with low income, low education and individual factors such as race, gender, use of alcohol or other illicit drugs, depression and personality type.

Hispanics and Asians have lower smoking tendency than Caucasians or African Americans. Gender differences exist in terms of nicotine sensitivity and requirements. In comparison to men, women are less likely to become smokers, have significantly lower nicotine levels after smoking similar cigarettes, and tend to have greater difficulty in quitting.

There is considerable evidence that smoking, alcohol and depression are linked. Compared to non smokers, smokers have more than twice the lifetime prevalence of major depressive disorder. Other predisposing factors include the personality and behavioral traits like neuroticism, attention deficit and hyperactive disorder (ADHD), novelty or stimulation seeking and sensitivity to reward or reinforcement.

In a mixed group of population comprising of adolescents, young adults and elderly, the fact that only some people are more susceptible to get started with the habit and become lifetime users and as well differences observed in the associated difficulty with quitting raised a suspicion, “Is tobacco addiction, totally an environmental and social phenomenon or are there genes specifically responsible for it?” To address these queries, many epidemiological studies, family studies with monozygotic and dizygotic
twin, adoption studies and recently genetic analysis were undertaken12,13.

**Genetics of Tobacco Addiction**

Family, twin and adoption studies provided substantial evidence of a common genetic vulnerability to nicotine addiction and helped in understanding and identifying the etiology of nicotine dependence and functional genetic variants to a certain extent that could help in designing future smoking cessation and treatment approaches14,15. To identify exactly which gene variants are associated with smoking phenotypes, molecular epidemiology has primarily used the candidate gene approach. No single genetic locus was found to be the causal factor for substance abuse, rather, multiple alleles were found at various loci interacting to produce vulnerability at an outcome. Other than the specific gene identification, research also concentrated on detecting single nucleotide polymorphisms and constructing haplotype maps to pinpoint areas of chromosomes for future research2.

Genes for the neurotransmitter dopamine synthesis, degradation, receptors and transporters have become candidate genes16.

At the same time, serotonin, norepinephrine and GABA modify dopamine metabolism and dopamine neurons; so they are also being studied12. It was proposed that individuals with defects in various combinations of the genes for these neurotransmitters results in ‘Reward Deficiency Syndrome’ and such individuals are at risk for substance abuse17.

The candidate genes are2

- **Nicotine**
  - Receptor genes.
  - Metabolizing pathways
- **Dopamine**
  - Receptor gene.
  - Transporter gene
  - Metabolizing pathways
- **Serotonin**
  - Synthesis neurotransmitter
  - (Tryptophan hydroxylase gene)
  - Transporter gene

**Nicotinic receptor genes**

These genes code for nAChRs that are primary targets for nicotine in brain. Reward pathways are initiated when nicotine binds to nAChRs facilitating the neurotransmitter release. Nicotine dependence is highly heritable and studies indicate roles for nicotinic receptor subtypes in development of dependence. Alpha(4) beta(2) nicotinic acetylcholine receptor subtype is the main receptor mediating nicotine dependence. Recent studies have provided evidence that nAChR genes may have a role in mediating early behaviors that are risk factors for nicotine dependence, such as age of initiation and early subjective response to drugs. Polymorphisms in a receptor gene, CHRNA2 (cholinergic receptor, nicotinic beta polypeptide 2 located on chromosome 1q21) have been identified as a functional candidate gene for nicotine dependence15,17,18.

**Nicotine metabolizing pathways**

Individual variation exists in the metabolism of nicotine, which is influenced by genes. It is primarily metabolized to cotinine in liver by the Cytochrome P450 2A6 (CYP 2A6)19. Polymorphisms in CYP 2A6 enzyme cause variability in rate of metabolism, there by influencing the vulnerability to tobacco dependence, amount smoked, response to smoking cessation treatment, and tobacco related cancer20.

**Dopamine receptor gene**

The synaptic levels of dopamine may also be determined by the density of dopamine receptors, which involves the dopamine receptor gene (DRD). Although there are many dopamine receptors (D1-D5), each exhibiting polymorphisms, the D2 dopamine receptor gene has been the focus of research regarding substance abuse. People with reduced D2 receptor density have deficit in the reward system thereby making them prone to nicotine addiction21.

**Dopamine transporter gene**

Released dopamine is taken up by the presynaptic neuron via the dopamine transporter (DAT), which is the primary mechanism for dopamine clearance from the synapse in the midbrain. A defect in the transporter proteins results in decreased clearance of dopamine which decreases the desire for substances like nicotine22.

**Dopamine metabolizers**

MAO is an enzyme that metabolizes dopamine. Polymorphisms of the genes that code for MAO resulting in its deficiency have been linked to smoking behavior23.

**Serotonin synthesis neurotransmitter:**

Tryptophan hydroxylase gene
Tryptophan hydroxylase catalyzes the rate limiting step of serotonin biosynthesis. Two polymorphisms of the genes that code for tryptophan hydroxylase are found to be associated with smoking by influencing the age of initiation and the intensity of smoking.\textsuperscript{24}

**Serotonin transporter gene**

The serotonin transporter gene, on chromosome 17q12, regulates the uptake of serotonin from synaptic junction. Polymorphisms of this gene are linked to increased nicotine intake, dependence and motivations for smoking such as smoking to self medicate mood disturbances.\textsuperscript{25}

**Treatment**

Tobacco addiction is a chronic disease that often requires multiple attempts to quit. Although some smokers are able to quit without help, many others need assistance. Behavioral interventions (counseling) and medication can help smokers quit; the combination of medication with counseling is more effective than either alone.\textsuperscript{26}

Behavioral treatments employ a variety of methods to assist smokers in quitting, ranging from self-help materials to individual counseling. These interventions teach individuals to recognize high-risk situations and develop coping strategies to deal with them. Nicotine replacement therapies (NRTs), such as nicotine gum and the nicotine patch, were the first pharmacological treatments used in smoking cessation therapy. NRTs deliver a controlled dose of nicotine to a smoker in order to relieve withdrawal symptoms during the smoking cessation process. NRT products include nicotine chewing gum, the nicotine transdermal patch, nasal sprays, inhalers, and lozenges and are most successful when used in combination with behavioral treatments.\textsuperscript{28}

Bupropion and varenicline are two non-nicotine medications that increase the rates of long-term abstinence from smoking by targeting nicotine receptors in the brain, easing withdrawal symptoms and blocking the effects of nicotine if people resume smoking. Scientists are currently pursuing many other avenues of research to develop new tobacco cessation therapies. One promising intervention is a vaccine that targets nicotine, blocking the drug’s access to the brain and preventing its reinforcing effects. Preliminary trials of this vaccine have yielded promising results.\textsuperscript{26}

**Conclusion**

Tobacco addiction is a combination of many environmental effects, multiple genes, and a large interaction between these factors. While social and environmental factors are important in smoking initiation, genetic constitution is likely to influence the continuation of the habit, quantity smoked and their ability to quit. Genetic variation in the psychological need for nicotine, the ability to metabolize it, and the pathway to its pleasurable effects, ultimately influences if and how people use tobacco. As population rates of smoking decline in response to social pressures, genetic influences may be particularly strong among the remaining smokers. Nicotine may not be the only psychoactive component in tobacco and role of other components is being investigated. Pharmacological treatment involving NRT and Bupropion has been shown to be effective when provided in combination with behavioral support. However cessation rates remain somewhat modest and one possibility is that success rates may be enhanced by offering treatments tailored to an individual’s genotype. The research on this issue remains in its infancy and the scope for individualized treatment tailored to genotype is promising. Each new addiction gene identified becomes a potential "drug target". Genetic profiles of smokers someday may be used by providers to choose the type, dose and duration of treatment for individual smokers.

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**References**

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