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## Nicotine addiction and its Pharmacological effects: A Review

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### ABSTRACT

Despite the known health risks of nicotine addiction, numerous people still smoke cigarettes and use other forms of tobacco, and many have difficulty quitting. Nicotine is readily absorbed from tobacco, resulting in an almost immediate response from the chemical epinephrine released from the adrenal cortex and from the chemical dopamine and other chemicals released in the brain's pleasure and reward systems. Creating a strong desire to repeat the pleasurable feelings nicotine drives the person to use more and more of it. One major step in treatment development occurred when researchers determined that the chemical nicotine is the key addictive component of tobacco. Based on this finding, scientists developed nicotine replacement strategies including the nicotine patch, the nicotine inhaler, and nicotine gum.

**Key words:** Nicotine, Smoking, Blood, Addiction.

### INTRODUCTION

The seeking of various abuses is an inherent human behavior. Nicotine consumption fulfills this need. About 20% to 30% of population in all countries are affected by nicotine use (Brunton et. al., 2006). Nicotine is derived from the leaves of tobacco belonging to the family Solanaceae and has been in use for centuries. It can be smoked, chewed, or sniffed. Although tobacco contains thousands of chemicals, the most active ingredient that acts in the brain and produces addiction is nicotine. Posselt and Reimanbasic isolated nicotine from tobacco leaves in 1828. Since then scientists began studying its effects in the brain and body. Nicotine is an alkaloid. Addiction produced by nicotine is extremely powerful and is almost similar to the addiction of heroin and cocaine (Collins et al., 1994; Picciotto et al., 2000). Nausea occurs in new smokers of nicotine. In larger dosages nicotine may cause tremors, quick breath, and a decrease in the production of urine. When smoke enters the body, it attacks the tissues of the mouth, tongue, throat, esophagus, air passages, and lungs. In the lungs, most of the inhaled compounds are retained. Just after nicotine absorption into the lungs, it affects the brain within 6 seconds, twice as fast as main lining heroin." ([gopher:Hminerva.acc.Virginia:70/00/p...ubstance/facts/substance/drug/tobaccotxt](http://gopher:Hminerva.acc.Virginia:70/00/p...ubstance/facts/substance/drug/tobaccotxt)). Nicotine causes a short term increase in blood pressure, heart rate by 2- 3 beats per minute, and flow of blood from the heart , reducing the flow of blood to the feet and legs. It also causes the arteries to narrow. Amount of oxygen that blood can carry is reduced by carbon monoxide. This combined with the effects of nicotine creates an imbalance in the demand for oxygen by the cells and the amount of oxygen the blood is able to supply. ([www.amhrt.org](http://www.amhrt.org)).

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## HISTORY

Nicotine is named from the tobacco plant *Nicotiana tabacum*, which in turn is named after Jean Nicot de Villemain, French ambassador in Portugal, who sent tobacco and seeds from Brazil to Paris in 1560 and promoted their medicinal use. Nicotine was first isolated from the tobacco plant in 1828 by German chemists Posselt & Reimann, who considered it a poison (Henningfield et al., 2006). Its chemical empirical formula was described by Melsens in 1843 (Melsens et al., 1844). Its structure was discovered by Adolf Pinner and Richard Wolfenstein in 1893, and it was first synthesized by A. Pictet and Crepieux in 1904 (Comptes et al., 1903).

## PHARMACOLOGICAL SPECIFICATIONS

### Effect of nicotine on brain

In comparison to non-smokers, smokers brain cell receptors have fewer dopamine receptors. A specific cell receptor found in the brain that is believed to play a role in addiction (Dagher et al., 2001). Dopamine is normally released naturally while engaging in certain behaviors like eating, drinking and copulation (Di Chiara et al., 1992; Pfau et al., 1990). The release of dopamine is believed to give one a sense of reward. The initial increase in dopamine activity from nicotine results initially in pleasant feelings for the smoker. But the subsequent decrease in dopamine, leaves the smoker craving more cigarettes (Gamberino et al., 1999; Shadel et al., 2000). New animal studies have shown that brain chemistry and receptors may be altered early in the smoking process (Trauth et al., 2000).

### Effect of nicotine on cardiovascular system

Lipids, a form of fat, are a source of energy for the body. High density lipoprotein is the beneficial form of fat. Some forms of fat, such as low-density lipoproteins (LDLs, triglycerides and cholesterol) can be harmful to the body. These harmful forms have their greatest effects on blood vessels. Low density lipoprotein accumulated and stick to blood vessel walls and cause narrowing. Such narrowing can impair blood flow to the heart, brain and other organs, causing them to fail. Nicotine increases the amount of bad fats (LDL, triglycerides, cholesterol) circulating in the blood vessels and decreases the amount of good fat (HDL) available (Mitchell et al., 1999). These silent effects begin immediately and greatly increase the risk for heart disease and stroke (HHS U.S 1994). Nicotine and other toxic substances from tobacco smoke are absorbed through the lungs into the blood stream and are circulated throughout the body. These substances damage the blood vessel walls, which allow plaques to form at a faster rate than they would in a non-smoker (Mitchell et al., 1999). In this way, smoking increases the risk of heart disease by hastening atherosclerosis.

### Effect of nicotine on circulatory system

The effects of tobacco smoke on the circulatory system include:

1. Raised blood pressure and heart rate

2. Constriction (tightening) of blood vessels in the skin, resulting in a drop in skin temperature
3. Less oxygen carried by the blood
4. Stickier blood, which is more prone to clotting
5. Damage to the lining of the arteries, which is thought to be a contributing factor to atherosclerosis (the build-up of fatty deposits on the artery walls)
6. Reduced blood flow to extremities like fingers and toes
7. Increased risk of stroke and heart attack due to blockages of the blood supply.

### Effect of nicotine on immune system

The effects of tobacco smoke on the immune system include:

1. The immune system doesn't work as well
2. The person is more prone to infections such as pneumonia and influenza
3. Illnesses are more severe and it takes longer to get over them.
4. Lower levels of protective antioxidants, for example Vitamin C, in the blood.

### Effect of nicotine on musculoskeletal system

The effects of tobacco smoke on the musculoskeletal system include:

1. Tightening of certain muscles
2. Reduced bone density. ([www.betterhealth.vic.gov.au](http://www.betterhealth.vic.gov.au))

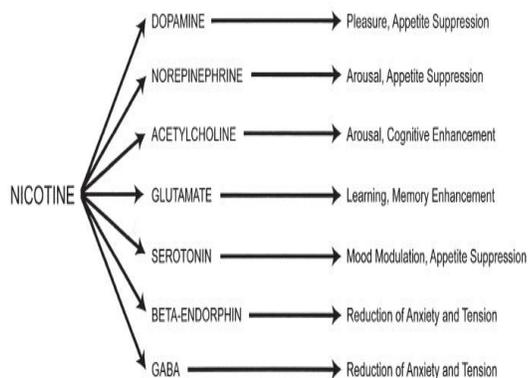
## MECHANISM OF NICOTINIC ADDICTION

When a person inhales smoke from a cigarette, nicotine is distilled from the tobacco and carried in the smoke particles into the lungs, where it is absorbed rapidly into the pulmonary venous circulation. It then enters the arterial circulation and moves quickly to the brain. Nicotine diffuses readily into brain tissue, where it binds to nicotinic acetylcholine receptors (nAChRs), which are ligand-gated ion channels. Stimulation of central nAChRs by nicotine results in the release of a variety of neurotransmitters in the brain, most importantly dopamine. Nicotine causes the release of dopamine in the mesolimbic area, the corpus striatum, and the frontal cortex. Particularly important are the dopaminergic neurons in the ventral tegmental area of the midbrain and the release of dopamine in the shell of the nucleus accumbens, as this pathway appears to be critical in drug-induced reward (Dani et al., 2001; Nestler et al., 2005). Dopamine release signals a pleasurable experience and is critical to the reinforcing effects of nicotine and other drugs of abuse (Nestler et al., 2005). Other neurotransmitters, including norepinephrine, acetylcholine, serotonin, gamma-aminobutyric acid (GABA), glutamate, and endorphins, are released as well, mediating various behaviors of nicotine (Figure 1) (Benowitz et al., 1999).

## MANAGEMENT OF NICOTINE ABUSE

### Nicotine replacement therapy

The most widely studied and used pharmacotherapy for managing nicotine dependence and withdrawal is therapeutic use of nicotine-



**Fig1.** Nicotine receptor activation promotes the release of neurotransmitters, which may then mediate various effects of nicotine use. GABA, gamma -aminobutyric acid. (Adapted with permission from Prim Care) (Benowitz et al.,1999).

containing medications (Fiore et al., 2000; Henningfield et al., 1995; Am J Psychiatry 1996). Nicotine medications make it easier to abstain from tobacco by replacing, at least partially, the nicotine formerly obtained from tobacco and thereby providing nicotine-mediated neuropharmacologic effects (Henningfield et al., 1995; Benowitz et al., 1993). There are six types of nicotine replacement products on the market. These include several brands and types of nicotine transdermal patch systems that deliver nicotine through the skin, nicotine nasal spray, and several products that deliver nicotine through the oral mucosa: gum, lozenge, sublingual tablet, and vapor inhaler (Fiore et al., 2000; Sweeney et al.2001; Fagerstrom et al., 1994).

#### *Transdermal Nicotine Patches*

Nicotine patches are applied to the skin and deliver nicotine through the skin at a relatively steady rate. There are currently four patch formulations on the market that vary widely in their design, pharmacokinetics, and duration of wear (Benowitz et al., 1995; Gorsline et al., 1993). These formulations are NicoDerm CQ patch (marketed in the United States by GlaxoSmithKline Consumer HealthCare), Nicotrol patch (marketed in the United States by Pfizer), Habitrol patch (marketed in the United States by Novartis) (Shiffman et al.,2000).

#### *Gum*

The first Nicotine replacement therapy that was made available to consumers was transmucosal-delivered nicotine polacrilex (nicotine gum), which has been available since the early 1980s in Europe and 1984 in the United States. In many countries, including the United States, nicotine gum is available without a prescription, which has made the products much more widely available to consumers (Shiffman et al., 2002; (Shiffman et al., 1997). The gum is available in two doses: 2 mg and 4 mg, delivering approximately 1 mg and 2 mg, respectively (Benowitz et al., 1987). Users are instructed to use a piece of gum every 1 to 2 hours for the first 6 weeks, then to reduce use to one piece every 2 to 4 hours for 3 weeks, and one piece every 4 to 8 hours for 3 weeks ( Herrera et al.,1995 ; Tonnesen et al.,1988).

#### *Lozenge*

Nicotine lozenge, available in 2- and 4-mg formulations since 2002, is the most recent NRT to receive approval in the United States for smoking cessation (Shiffman et al., 2002). Nicotine from the lozenge is absorbed slowly through the buccal mucosa and delivered into systemic circulation. The lozenge should not be chewed and this is considered a benefit by some patient. The amount of nicotine absorbed per lozenge is somewhat higher than that delivered by gum (Choi et al., 2003).

#### **Medications**

##### *Bupropion*

Bupropion (Zyban) is a smoking cessation aid that was originally marketed as an antidepressant (Wellbutrin). Bupropion is chemically unrelated to tricyclic antidepressants or selective serotonin reuptake inhibitors (SSRIs). The mechanism of action is unknown; however, it is presumed that the action is mediated by noradrenergic and/or dopaminergic mechanisms (Lerman et al., 2004).

##### *Nortriptyline*

Nortriptyline has been listed by the Agency for Health Research Quality as a second-line therapy for nicotine abuse (Fiore et al., 2000). Nortriptyline in combination with transdermal nicotine also shown to enhance the cessation rates above levels seen with transdermal nicotine alone (Prochazka et al., 2004). The tricyclic antidepressant doxepin has also been shown in a small human study to improve cessation rates (Edwards et al., 1989).

##### *Clonidine*

Clonidine is an alpha-2-noradrenergic agonist used in the treatment of hypertension. Clonidine has been shown to diminish symptoms of both opiate and alcohol withdrawal symptoms (Gossop et al., 1988; Mayo-Smith et al., 1998). One study of heavy smokers who had failed in previous quit attempts found that those treated with clonidine had twice the rate of abstinence as those treated with placebo at the end of the 4-week treatment (Glassman et al., 1988). The most common side effects of clonidine are constipation, dizziness, and drowsiness, dryness of mouth, and unusual tiredness or weakness.

##### *Rimonabant*

The cannabinoid receptor system plays a role in the regulation of appetitive behavior (eg, food and water consumption, drug self-administration) (Black SC et al., 2004). In an extensive evaluation of its motivational effects, rimonabant decreased nicotine self-administration even though it was not functioning as a "substitute" with respect to physiological and other behavioral effects (Cohen et al.,2002). The results suggest that activation of the cannabinoid receptor system may participate in the motivational and dopamine-releasing effects of nicotine (Anthenelli et al., 2004).

### Varenicline

Varenicline is a partial agonist of nicotinic receptors. Varenicline selectively binds to the alpha-4 beta-2 (nicotinic) receptor type. Phase II clinical trials of varenicline suggest that the medication is efficacious for smoking cessation ([www.pfizer.com/2005](http://www.pfizer.com/2005)).

### Nicotine Vaccines

There are at least three companies in early clinical development of an antinicotine vaccine: Xenova (TA-NIC), Nabi (NicVAX), and Cytos (Nicotine-Qbeta) (Cerny et al., 2005). A vaccine against nicotine induces antibodies against the nicotine molecule that prevents the drug from reaching neural receptors that produce the effects normally associated with smoking (Pentel et al., 2000).

### CONCLUSION

Nicotine addiction is one of the hardest drug addictions to break. People trying to quit using tobacco products can experience physical withdrawal symptoms that may include restlessness, irritability, problems sleeping and headaches. These withdrawal symptoms are usually short term. Continued use of tobacco products can cause many different types of cancers, such as lung, oral, esophageal, mouth and kidney cancers. In addition, there is a higher risk for heart disease and stroke. Nicotine replacement therapy supplies nicotine to the body in a different way that a tobacco user normally gets it. Nicotine replacement therapy comes in the form of patches, lozenges, gum and inhalers. People should not use tobacco products with nicotine replacement therapy because they will put themselves at risk for nicotine overdose.

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