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Updated review on successful control with nicotine replacement therapy for nicotine withdrawal symptoms

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Abstract

Nicotine use as a tool for quitting smoking has a good safety history. Animal studies suggest that nicotine may adversely affect cognitive development in adolescence, but the relevance of these findings to human brain development is disputed. At low amounts, it has a mild analgesic effect. According to the International Agency for Research on Cancer, "nicotine is not generally considered to be a carcinogen." The Surgeon General of the United States indicates that evidence is inadequate to infer the presence or absence of a causal relationship between exposure to nicotine and risk for cancer. Tobacco is dangerous. According to one study trusted source, smoking-related diseases are responsible for about 4,35,000 deaths per year in the United States. That's about 1 in every 5 deaths in the United States. Stopping smoking, no matter how long you have smoked, can greatly benefit your health.

Nicotine creates pleasant feelings in the body and mind. When you use tobacco, your brain releases neurotransmitters such dopamine, the feel-good chemical. This creates a brief feeling of contentment and pleasure. In humans, nicotine from tobacco induces stimulation and pleasure, and reduces stress and anxiety. Smokers come to use nicotine to modulate their level of arousal and for mood control in daily life. Smoking may improve concentration, reaction time, and performance of certain tasks. When a person stops smoking, nicotine withdrawal symptoms emerge. These include irritability, depressed mood, restlessness, anxiety, problems getting along with friends and family, difficulty concentrating, increased hunger and eating, insomnia, and craving for tobacco. Nicotine withdrawal in untreated smokers produces mood disturbances comparable in intensity to those seen in psychiatric out patients. Generally it has been found that nicotine replacement therapies actually give you small amounts of nicotine through a product like gum or a skin patch. While you'll continue to get some nicotine in your system, you won't be exposed to any of the other harmful chemicals that are found in tobacco.

Keyword: Nicotine; Nicotine addiction; Neuropharmocology; Nicotine replacement therapy

1. Introduction

Nicotine is a naturally produced alkaloid in the night shade family of plants (most predominantly in tobacco and Duboisia hopwoodii) and is widely used recreationally as a stimulant and anxiolytic. As a pharmaceutical drug, it is used for smoking cessation to relieve withdrawal symptoms. Nicotine acts as a receptor agonist at most nicotinic acetylcholine receptors (nAChRs), except at two nicotinic receptor subunits (nAChRα9 and nAChRα10) where it acts as a receptor antagonist. Nicotine constitutes approximately 0.6–3.0% of the dry weight of tobacco. Nicotine is also present at ppb-concentrations in edible plants in the family Solanaceae, including potatoes, tomatoes, and eggplants, though sources disagree on whether this has any biological significance to human consumers. It functions as an antiherbivore

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chemical; consequently, nicotine was widely used as an insecticide in the past, and neonicotinoids, such as imidacloprid, are some of the most effective and widely used insecticides. Nicotine use as a tool for quitting smoking has a good safety history. Animal studies suggest that nicotine may adversely affect cognitive development in adolescence, but the relevance of these findings to human brain development is disputed. At low amounts, it has a mild analgesic effect. According to the International Agency for Research on Cancer, "nicotine is not generally considered to be a carcinogen." The Surgeon General of the United States indicates that evidence is inadequate to infer the presence or absence of a causal relationship between exposure to nicotine and risk for cancer. Nicotine has been shown to produce birth defects in some animal species, but not others. It is considered a teratogen in humans. The median lethal dose of nicotine in humans is unknown, but high doses are known to cause nicotine poisoning [1].

2. Nicotine addiction

Nicotine is a highly addictive chemical found in the tobacco plant. The addiction is physical, meaning habitual users come to crave the chemical, and also mental, meaning users consciously desire nicotine's effects. Nicotine addiction is also behavioral. People become dependent on actions involved with using tobacco. They also become accustomed to using tobacco in certain situations, such as after meals or when under stress.

Nicotine is primarily consumed by inhaling the smoke of tobacco cigarettes. Other ways to smoke tobacco include pipes and cigars. Smokeless tobacco is inhaled through the nose as a powder or held in the mouth.

Tobacco is dangerous. According to one study trusted source, smoking-related diseases are responsible for about 435,000 deaths per year in the United States. That's about 1 in every 5 deaths in the United States. Stopping smoking, no matter how long you have smoked, can greatly benefit your health.

Nicotine creates pleasant feelings in the body and mind. When you use tobacco, your brain releases neurotransmitters such dopamine, the feel-good chemical. This creates a brief feeling of contentment and pleasure [2].

But besides nicotine, tobacco cigarettes and smokeless tobacco contain many cancer-causing agents and other harmful chemicals. The nearly 4,000 chemicals found in tobacco have physical, mental, and psychological effects. Using tobacco leads to grave health complications, including:

- Lung cancer
- Emphysema
- Chronic bronchitis
- Cancer, especially in the respiratory system
- Leukemia
- Heart disease
- Stroke
- Diabetes
- Eye issues, such as cataracts and macular degeneration
- Infertility
- Impotence
- Miscarriage and pregnancy complications
- Weakened immune system
- Cold, flu, and respiratory infections
- Loss of sense of taste or smell
- Gum disease and dental issues
- The appearance of premature aging
- Peptic ulcer disease
- Osteoporosis
- Secondhand smoke also increases the risk of lung cancer and heart disease among people close to smokers. According to the Centers for Disease Control and Prevention Trusted Source
- Trusted Source
- Centers for Disease Control and Prevention (CDC)
- Governmental authority
- Go to source
- Children living in homes with secondhand smoke are more likely to have:

- Sudden infant death syndrome
- Asthma
- Respiratory infections
- Ear infections
- Smoking cigarettes or using other tobacco products causes nicotine addiction. Nicotine is very addictive, so even infrequent use can lead to dependence.
- It's possible for smoking cessation products, such as nicotine gum, lozenges, or patches, to cause nicotine addiction. However, the risk is low. This is because the amount of nicotine in these products is lower and delivered more slowly than the nicotine in tobacco
- Anyone who uses tobacco is at risk of developing an addiction. The best way to prevent an addiction is to avoid tobacco.
- Some factors may increase the risk of addiction. For example, people with a family history of nicotine addiction and people who grow up in homes with tobacco users are more likely to start smoking and develop an addiction.
- Also, people who start smoking when they are young are more likely to smoke into adulthood. One study Trusted Source notes that 80% of smokers began smoking by age 18 years. Starting smoking young tends to increase dependence later on in life. It's less common for adults to start smoking or develop an addiction, according to the American Society of Addiction Medicine.
- People who abuse alcohol or drugs or who have a mental illness also have an increased risk of nicotine dependence [3].

3. Mechanisms of action of nicotine addiction neuropharmacology

Nicotine is a tertiary amine consisting of a pyridine and a pyrrolidine ring. (S)-nicotine, found in tobacco, binds stereo selectively to nicotinic cholinergic receptors (nAChRs). (R)-nicotine, found in small quantities in cigarette smoke owing to racemization during the pyrolysis process, is a weak agonist at nAChRs.

When a person inhales smoke from a cigarette, nicotine is distilled from the tobacco and is carried in 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 nAChRs, which are ligand-gated ion channels. When a cholinergic agonist binds to the outside of the channel, the channel opens, allowing the entry of cations, including sodium and calcium. These cations further activate voltage-dependent calcium channels, allowing further calcium entry.

The nAChR complex is composed of five subunits and is found in both the peripheral and central nervous systems. In the mammalian brain, there are as many as nine α subunits (α2 to α10) and three β subunits (β2 to β4). The most abundant receptor subtypes in the brains of humans are α4β2, α3β4, and α7 (homomeric). The α4β2* (asterisk indicates possible presence of other subunits in the receptor) receptor subtype is predominant in the human brain and is believed to be the main receptor mediating nicotine dependence. In mice, knocking out the β2 subunit gene eliminates the behavioral effects of nicotine, such that nicotine no longer releases dopamine in the brain or maintains self-administration. Reinserting the β2 subunit gene into the ventral tegmental area of a β2 knockout mouse restores behavioral responses to nicotine. The α4 subunit appears to be an important determinant of sensitivity to nicotine. In mice, a single nucleotide point mutation in the pore-forming region results in a receptor that is hypersensitive to the effects of nicotine. This mutation makes mice much more sensitive to nicotine- induced reward behaviors, as well as to effects on tolerance and sensitization. The α3β4 nAChR is believed to mediate the cardiovascular effects of nicotine. The homomeric α7 nAChR is thought to be involved in rapid synaptic transmission and may play a role in learning and sensory gating. The α4 β2* receptor may include α5, α6, and/or β3 subunits, which may modulate the sensitivity and function of the receptor. For example, α5 knockout mice are less sensitive to nicotine-induced seizures and hypolocomotion.

Brain imaging studies demonstrate that nicotine acutely increases activity in the prefrontal cortex, thalamus, and visual system, consistent with activation of corticobasal ganglia-thalamic brain circuits. 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. of particular importance 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. Other neurotransmitters, including norepinephrine, acetylcholine, serotonin, γ-aminobutyric acid (GABA), glutamate, and endorphins, are released as well, mediating various behaviors of nicotine.

Most of the nicotine-mediated release of neurotransmitters occurs via modulation by presynaptic nAChRs, although direct release of neurotransmitters also occurs. Dopamine release is facilitated by nicotine-mediated augmentation of glutamate release and, with long-term treatment, by inhibition of GABA release. In addition to direct and indirect stimulation of neurotransmitter release, chronic cigarette smoking (but not nicotine administration) reduces brain monoamine oxidase A and B(MAOA and MAOB)activity, which would be expected to increase monoaminergic neurotransmitter levels such as dopamine and norepinephrine in synapses, thus augmenting the effects of nicotine and contributing to addiction. Inhibition of MAO facilitates acquisition of nicotine self-administration in rats; supporting the idea that MAO inhibition interacts with nicotine to reinforce tobacco dependence.

Dopamine release signals a pleasurable experience, and is critical to the reinforcing effects of nicotine and other drugs of abuse. Chemically or anatomically lessoning dopamine neurons in the brain prevents nicotine self-administration in rats. When intracranial self-stimulation is used as a model for brain reward in rats, nicotine acutely lowers the threshold for self-stimulation. Thus, through its effects on dopamine release, acute nicotine administration increases brain reward function. Likewise, nicotine withdrawal is associated with significant increases in intracranial self-stimulation reward threshold, consistent with deficient dopamine release and reduced reward. The decrease in brain reward function experienced during nicotine withdrawal is an essential component of nicotine addiction and a key barrier to abstinence.

With repeated exposure to nicotine, tolerance (neuroadaptation) develops to some, but not all, of the effects of nicotine. Concurrent with this neuroadaptation is an increase in the number of nAChR binding sites in the brain. This increase is believed to represent upregulation in response to nicotine- mediated desensitization of receptors. This desensitization may play a role in nicotine tolerance and dependence. It has been suggested that craving and withdrawal symptoms begin in chronic smokers when previously desensitized α4β2* nAChRs become unoccupied and recover to a responsive state during periods of abstinence such as during nighttime sleep. Thus, nicotine binding and desensitization of these receptors during smoking may alleviate craving and withdrawal. The idea that desensitization of nAChRs occurs in the usual smoker is supported by a brain imaging study showing that cigarette smoking in amounts used by typical daily smokers maintains near-complete saturation-and thus Desensitization of brain nAChRs. It is speculated that smokers maintain α4β2* nAChRs in a desensitized state to avoid withdrawal. Another theory is that conditioned smoking cues maintain smoking behavior during periods of saturation and desensitization of brain nAChRs. In actuality, these two theories may be complementary: Smokers may continue to smoke throughout the day to maintain plasma nicotine levels that prevent the occurrence of withdrawal symptoms, and may also continue to derive some rewarding effects from the conditioned reinforces associated with smoking such as the taste and feel of the smoke. Conditioning as a component of addiction is discussed in more detail below [4, 5].

Nicotine withdrawal is associated with a negative emotional state, including anxiety and the perception of increased stress, which may represent powerful stimuli to relapse to tobacco use. There is evidence that the activation of the extra hypothalamic corticotropin-releasing factor (CRF)-CRF1 receptor system contributes to negative affect during nicotine withdrawal. During precipitated nicotine withdrawal in rats, which is associated with anxiety-like behavior, CRF is released in the central nucleus of the amygdala. CRF activation produces anxiety behavior, and pharmacologic blockade of CRF1 receptors inhibits the anxiogenic effects of nicotine withdrawal. Blocking the CRF1 nicotine receptor also has been shown to prevent the increase in nicotine self-administration that occurs during abstinence from forced nicotine administration in rats.

Withdrawal from other drugs of abuse such as alcohol, cocaine, opiates, and cannabinoids is also associated with activation of the extra hypothalamic CRF system, suggesting that this is a common mechanism of affective manifestations of drug withdrawal. Thus, both the hypoactivity of the dopaminergic system and the activation of the CRF system appear to mediate nicotine withdrawal symptoms that often precipitate relapse to smoking.

4. Psychoactive effects of nicotine and nicotine withdrawal

In humans, nicotine from tobacco induces stimulation and pleasure, and reduces stress and anxiety. Smokers come to use nicotine to modulate their level of arousal and for mood control in daily life. Smoking may improve concentration, reaction time, and performance of certain tasks. When a person stops smoking, nicotine withdrawal symptoms emerge. These include irritability, depressed mood, restlessness, anxiety, problems getting along with friends and family, difficulty concentrating, increased hunger and eating, insomnia, and craving for tobacco. Nicotine withdrawal in untreated smokers produces mood disturbances comparable in intensity to those seen in psychiatric out patients. Hedonic dysregulation, the feeling that there is little pleasure in life and that activities that were once rewarding are no longer enjoyable, is seen with withdrawal from nicotine and from other drugs of abuse. It is

hypothesized that a relative deficiency in dopamine release following long-standing nicotine exposure accounts for many of the mood disorders and the anhedonia, as well as the tobacco craving, that may persist in smokers for a long time after they have quit.

Thus, the pharmacologic bases of nicotine addiction can be seen as a combination of positive reinforcements, such as enhancement of mood or functioning, as well as avoidance of the negative consequences of prior drug use—that is, the relief of withdrawal symptoms-in situations when nicotine is not available. In addition to these direct pharmacologic mechanisms, there is an important role for conditioning in the development of tobacco addiction [6, 7].

5. Conditioned behaviour and nicotine addiction

All drug-taking behavior is learned, a result of conditioning. Drug-taking behavior is made more probable, or reinforced, by the consequences of the pharmacologic actions of the drug, as discussed for nicotine above. At the same time, the user begins to associate specific moods, situations, or environmental factors with the rewarding effects of the drug. Respiratory tract sensory cues associated with tobacco smoking represent a type of conditioned reinforcer that has been shown to play an important role in the regulation of smoke intake and the craving to smoke, as well as the rewarding effects of smoking.

The association between such cues and anticipated drug effects, and the resulting urge to use the drug, is a type of conditioning. Animal studies find that nicotine exposure increases the behavioral control of conditioned stimuli, which may contribute to the compulsivity of smoking behavior. Furthermore, experimental studies in nicotine-dependent rats show that nicotine withdrawal–associated conditioned stimuli potentiate the magnitude of nicotine withdrawal, including an elevation of brain reward threshold. Thus, cues associated with nicotine withdrawal have the ability to decrease brain reward function.

Cigarette smoking is maintained, in part, by such conditioning. People habitually smoke cigarettes in specific situations such as after a meal, with a cup of coffee or an alcoholic drink, or with friends who smoke. The association between smoking and these other events repeated many times causes the environmental situations to become powerful cues for the urge to smoke. Likewise, aspects of the drug- taking process, such as the manipulation of smoking materials, or the taste, smell, or feel of smoke in the throat, become associated with the pleasurable effects of smoking. Even unpleasant moods can become conditioned cues for smoking. For example, a smoker may learn that not having a cigarette provokes irritability (a common symptom of the nicotine abstinence syndrome) and smoking a cigarette provides relief. After repeated experiences of this sort, a smoker may come to regard irritability from any source such as stress or frustration as a cue for smoking. Functioning imaging studies indicate that exposure to drug-associated cues activates cortical regions of the brain, including the insula. Smokers who acquire damage to the insula (for example, due to brain trauma) are more likely to quit smoking soon after the injury, are more likely to remain abstinent, and are less likely to experience conscious urges to smoke compared with smokers with brain injury that does not affect the insula [8,9].

Although conditioning becomes an important element of drug addiction, conditioning develops only because of a pairing of the pharmacologic actions of the drug with behaviors. It has been suggested that conditioning serves to maintain nicotine use during periods of desensitization of α4β2* nAChRs, in which there is a loss or decrease in the biologic response to nicotine. Therefore, conditioned reinforcers could be the primary motivation to smoke during periods when desensitization prevents the reinforcing effects of nicotine obtained from smoking. This relationship is renewed on a cyclic basis: After a period of abstinence, when α4β2* nAChRs are once again sensitive, the rewarding effects of smoking are re- established and once again paired with the sensory stimuli of tobacco smoking, and the association of these two factors (stimuli and reward) is again strengthened. Conditioning is a major factor that causes relapse to drug use after a period of cessation. It must be addressed as a component of counseling and behavioral therapy for drug addiction [10].

6. Nicotine pharmacokinetics and metabolism

Nicotine is a weak base (pKa = 8.0). Absorption through mucous membranes depends on pH. Chewing tobacco, snuff, and nicotine gum are buffered with an alkaline pH to facilitate absorption through buccal mucosa. Smoking is a highly efficient form of drug administration, as the drug enters the circulation rapidly through the lungs and moves into the brain within seconds. Inhaled drugs escape first-pass intestinal and hepatic metabolism. The more rapid the rate of absorption and entry of a drug into the brain, the greater the rush, and the more reinforcing the drug. Smoking produces high concentrations of a drug in the brain that are comparable to those seen after intravenous administration. A number

of substances of abuse, including marijuana, cocaine, opiates, phencyclidine, and organic solvents, are abused by the inhalational route because access to the brain is so rapid. The smoking process also allows precise dose titration, so a smoker may obtain desired affects.

Nicotine is rapidly and extensively metabolized by the liver, primarily by the liver enzyme CYP2A6 (and to a lesser extent by CYP2B6 and CYP2E1) to cotinine. The metabolite cotinine is widely used as a quantitative marker for exposures to nicotine, and is useful as a diagnostic test for the use of tobacco and as a measure of compliance with treatments for smoking cessation. Cotinine is subsequently metabolized to trans-3′-hydroxycotinine (3HC) exclusively or nearly exclusively by CYP2A6. The ratio of 3HC to cotinine can be used as a phenotypic marker for CYP2A6 activity and for the rate of nicotine metabolism. The half-life of nicotine averages ~2 h, while the half-life of cotinine averages ~16 h.

Cotinine levels are fairly stable throughout the day in smokers; because the levels of 3HC are formation- limited, the ratio of 3HC to cotinine is also fairly stable. This ratio can be measured in the blood, saliva, or urine of people while they are using tobacco, based on their intake of nicotine from tobacco. Nicotine and cotinine are also metabolized by glucuronidation, primarily, it is thought, via UGT 1A4, 1A9, and 2B10. Although glucuronidation is usually a minor pathway of nicotine metabolism, in people who have low CYP2A6 activity, glucuronidation can be a major determinant of nicotine clearance [11]. Considerable genetic polymorphism in CYP2A6 and UGT activity is associated with wide individual variability and racial differences in the rate of nicotine metabolism. Asians and African Americans metabolize nicotine on average more slowly than do Caucasians or Hispanics. Sex hormones also substantially affect CYP2A6 activity. The rate of nicotine metabolism is faster in women than men. Among women, nicotine metabolism is faster in women taking estrogen-containing oral contraceptives, and is even faster during pregnancy, compared with other women.

There is considerable peak to trough oscillation in blood levels from cigarette to cigarette. However, consistent with the half-life of two hours, nicotine accumulates in the body over six to nine hours of regular smoking. Thus, smoking results not in intermittent and transient exposure to nicotine, but in an exposure that lasts 24 hours per day. Arterio-venous differences in nicotine concentration during cigarette smoking are substantial, with arterial levels exceeding venous levels up to tenfold. The persistence of nicotine in the brain throughout the day and night results in changes in the structure and function of nicotinic receptors and in intracellular processes of neuroadaptation, as mentioned previously [12, 13].

7. Nicotine metabolism as a determinant of tobacco use and disease risk

Insofar as smokers regulate their intake of nicotine to maintain particular levels of nicotine in the body throughout the day, people who metabolize nicotine more quickly would be expected to take in more cigarette smoke per day compared with slower metabolizers. This appears to be the case. Genetically poor metabolizers (e.g., people with variant CYP2A6 genes associated with substantially reduced enzyme activity) smoke on average fewer cigarettes per day and tend to have higher carbon monoxide levels than do normal metabolizers. In addition, genetically slow metabolizers appear to be less dependent, based on the observation that the fraction of slow metabolizers in the population of smokers decreases with increasing age of the smoker cohort, suggesting that slow metabolizers are more likely to quit. In a population of Asian and white smokers, the clearance of nicotine assessed by intravenous infusion of deuterium-labeled nicotine was positively correlated with the number of cigarettes smoked per day and the nicotine intake per cigarette, supporting the idea that clearance influences smoking behavior.

Genetic variation of CYP2A6 may influence the risk of smoking-induced cancer by a mechanism in addition to its effects on smoking behavior. The tobacco-specific nitrosamine 4-(methylnitrosamino)-1- (3-pyridyl)-1-butanone (NNK) is believed to contribute to lung and possibly pancreatic cancer. This nitrosamine is activated to a carcinogen in part by CYP2A6. Therefore, a smoker who is a slow metabolizer would be expected both to take in less smoke per cigarette and to bioactivate less of the NNK taken in compared with a normal metabolizer. A few studies support this hypothesis, showing that slow metabolizers have a lower risk of lung cancer compared with normal metabolizers, although some studies do not confirm this association. Genetic variation of CYP2A6 activity may also explain some racial differences in lung cancer risk, such as the lower risk in Asians, who have lower CYP2A6 activity and slower nicotine clearance on average compared with whites. However, this mechanism does not seem to hold for African-American smokers, who are also more likely to be CYP2A6 slow metabolizers, but who have a higher cancer risk compared with whites [14, 15].

8. Genetics of nicotine addiction

Twin studies indicate a high degree of heritability (~50%) in the prevalence of cigarette smoking and the ability to quit smoking (dependence) and in the number of cigarettes smoked per day. Twin studies even demonstrate heritability in the nature of particular symptoms experienced when a smoker stopped smoking.

Numerous studies have attempted to identify genes underlying nicotine addiction, as summarized in a recent review. Studies of the genetics of nicotine dependence and smoking behavior are problematic because complex behaviors such as smoking are determined by multiple genes, as well as environmental factors, and because there are many different dependence phenotypes that may be examined, which may have different genetic underpinnings. Family linkage studies and candidate gene association studies have suggested a number of loci or particular genes that are associated with smoking behavior, although smoking phenotypes vary considerably from study to study. Candidate genes coding for nicotine receptor subtypes, dopamine receptors or transporters, GABA receptors, and others have been identified in various studies as being associated with different aspects of smoking behavior. However, subsequent research has not replicated many of these earlier findings.

Recent genome-wide association studies point to several genes that are promising signals for genetic determinants of nicotine dependence. Bierut, Saccone, and coworkers examined a phenotype that is thought to reflect a vulnerability to becoming dependent on nicotine. All subjects had to have smoked 100 cigarettes lifetime, and the comparison groups were those who became dependent on nicotine versus those who did not become dependent. Genotype signals from the genome-wide association studies were used to guide a second-phase candidate gene association study, which resulted in several strong genetic associations. Most prominent were the α-5, α-3, and β-4 nicotinic receptor gene complex, neurexin 1, VPS13A (vacuolar sorting protein), KCNJ6 (a potassium channel), and the GABA A4 receptor gene. Of interest is that some of these genes, such as the neurexin 1 gene, are genes related to cell communication. Other genome-wide association studies have identified a number of genes affecting cell adhesion and extracellular matrix molecules that are common among various addictions, consistent with the idea that neural plasticity and learning are key determinants of individual differences in vulnerability to nicotine, as well as other drug addictions [16, 17].

9. Nicotine addiction and psychiatric comorbidity

Tobacco addiction is much more prevalent with people with mental illness and substance abuse disorders. These individuals consume 44% of all cigarettes sold in the U.S., despite representing only 22% of the population. More than 40% of smokers report having a mental health disorder in the past month and 60% have experienced a mental health disorder in their lifetimes. The prevalence of smoking is higher in patients with a diagnosis of schizophrenia, major depression, bipolar disorder, anxiety disorder, panic attacks, attention deficit hyperactivity disorder, posttraumatic stress disorder, alcohol abuse, and illicit drug abuse than in the general population. Patients with more severe psychiatric symptoms are more likely to be smokers. Smokers with a history of major depression are at increased risk for experiencing depression after cessation of smoking.

Several mechanisms are believed to underlie comorbid nicotine addiction with mental health disorders. There appears to be a shared genetic susceptibility to tobacco addiction with alcohol abuse and major depression. Nicotine may also serve to medicate some psychiatric symptoms. For example, the serotonin and norepinephrine released in the brain by nicotine are similar to the neurochemical effects of some antidepressant medications. Nicotine acting on α7 nAChRs may improve sensory gating, which is abnormal in schizophrenics. Improved sensory gating, secondary to nicotine intake, might be expected to enhance the ability to sort out extraneous stimuli and therefore to improve attention. As mentioned earlier, cigarette smoking inhibits MAOA and MAOB. MAO inhibitors are used to treat depression, suggesting that cigarette smoking might provide benefit to depressed patients in the same way. There is evidence that excessive cholinergic activity contributes to depression. As described earlier, regular nicotine exposure may result in desensitization of nAChRs. It is postulated that desensitization of these receptors results in stabilization of mood and amelioration of depression. Finally, nicotine, by its stimulant effects, may reduce unpleasant sedative side effects of psychiatric medications and sedation from alcohol, providing another motivation for tobacco use [18, 19, 20].

The adverse health consequences of tobacco use in people with mental illness and drug abuse are substantial. People with chronic mental illness die on average 25 years earlier than individuals without those disorders, primarily due to cardiovascular disease and diabetes. A substantial number of the premature deaths are undoubtedly caused by smoking. In chronic alcoholics, half of the premature deaths are attributable to cigarette smoking. Smoking cessation treatment is difficult in patients with psychiatric comorbidities; but given the high prevalence of smoking in this population and

the enormous burden of disease due to smoking, developing effective treatments for this population is an important public health priority [21, 22].

10. Pharmacodynamics of nicotine: contributions to smoking-related disease

Because nicotine underlies addiction and sustains cigarette smoking, it is logical to consider nicotine maintenance as a potential alternative to tobacco use for smokers who cannot quit. The administration of nicotine replacement therapy in smokers has been shown to reduce smoking rates, and among those who reduce their smoking, to promote smoking cessation. However, the currently available nicotine delivery systems deliver nicotine into the blood stream much more slowly than does cigarette smoking, so for most smokers nicotine medications are not satisfactory substitutes for smoking. The development of a consumer-acceptable inhaled nicotine delivery system with absorption kinetics similar to those of a cigarette has been proposed and could be an important advancement in pursuing harm reduction through nicotine maintenance.

An important question in promoting nicotine maintenance is the safety of nicotine per se. Without doubt, nicotine medication is much safer than cigarette smoking, with the latter delivering not only as much or more nicotine but also thousands of toxic combustion products to the smoker. However, there are some concerns involving the safety of long-term exposure to nicotine, including cardiovascular disease, cancer, reproductive disorders, and delayed wound healing.

Nicotine is a sympathomimetic drug that releases catecholamines, increases heart rate and cardiac contractility, constricts cutaneous and coronary blood vessels, and transiently increases blood pressure. Nicotine also reduces sensitivity to insulin and may aggravate or precipitate diabetes, and nicotine may contribute to endothelial dysfunction. These various effects of nicotine on the cardiovascular system could, in theory, promote atherogenesis and precipitate acute ischemic events in people who have coronary artery disease. This has been of particular concern in smokers who use nicotine medication while they are still smoking. However, increased cardiovascular risk due to nicotine medication does not appear to be a problem. The dose-response curve for cardiovascular effects such as heart rate acceleration or the release of catecholamines is flat, such that adding nicotine medication to smoking produces no further effect. Clinical trials of nicotine patches in smokers with cardiovascular disease showed no increased risk of cardiovascular events compared with placebo. Furthermore, the experience of men in Sweden with a long history of snuff use, which delivers nicotine without combustion products, suggests little or no increase of cardiovascular risk.

Nicotine is not a direct carcinogen, but there are concerns that it may be a tumor promoter. In animal studies, nicotine can inhibit apoptosis, resulting in impaired killing of cancer cells. Nicotine also promotes angiogenesis in animals, an effect which could lead to greater tumor invasion and metastasis. Whether nicotine is a cancer promoter in people has not been established, but one report that suggests that smokers who switch to smokeless tobacco may have an increased risk of lung cancer compared with smokers who quit entirely raises concern about this possibility. Exposure to nitrosamines from smokeless tobacco could also explain or contribute to such an increase in lung cancer risk. Against the proposition that nicotine promotes cancer are data from Scandinavia, where the use of low nitrosamine oral snuff (snus) is very common among men. Epidemiology studies indicate that snus use is associated with an increased risk only of pancreatic cancer, which would be unlikely in a general population if nicotine exerted a general tumor-promoting action [23, 24, 25].

Suspected adverse reproductive effects of nicotine include most prominently fetal neuroteratogenic effects. In general, it is not desirable to use nicotine during pregnancy, but if the alternative is cigarette smoking, then nicotine medication is undoubtedly less hazardous. The use of snus by pregnant women in Scandanavia has been associated with an increased risk of pre-eclampsia. This is in contrast to a reduced risk of pre-eclampsia in smokers. The discrepancy between snus use and smoking might be due to carbon monoxide in cigarette smoke, which is expected to have vasodilatory effects that could counteract the vasoconstricting effects of nicotine. Nicotine is a potent cutaneous vasoconstrictor and can impair wound healing. However, clinical trials using nicotine replacement medication to aid cessation in surgical patients indicate that the overall outcome is much better in individuals using nicotine therapy who quit smoking compared with continued smoking [26,27].

11. Pharmacotherapy to aid smoking cessation

A complete review of the pharmacology of drugs used to treat tobacco dependence is beyond the scope of this article. The focus here is on mechanisms of action and the prospects for future therapies.

Currently, three classes of medications have been approved for smoking cessation: nicotine replacement products (patch, gum, spray, inhaler, and lozenge), bupropion, and most recently, varenicline. Although not approved by regulatory authorities for smoking cessation, clinical trials have also demonstrated the efficacy of nortriptyline and clonidine, which are considered to be second-line drugs. All of the drugs mentioned above have been shown in controlled clinical trials to be effective, with odds ratios ranging from two to four in comparison with placebo treatment. Absolute smoking cessation rates range from 5 to 35%, depending on the drug and the intensity of concomitant counseling [28,29].

12. Nicotine withdrawal

Nicotine withdrawal involves physical, mental, and emotional symptoms. The first week, especially days 3 through 5, is always the worst. That's when the nicotine has finally cleared out of your body and you'll start getting headaches, cravings, and insomnia. Depending on how long you've smoked and how many cigarettes you have a day, symptoms of nicotine withdrawal can last anywhere from several days to several weeks.

Most relapses happen within the first two weeks of quitting. If you can get over that hump, the physical symptoms will start to go away but you'll still be dealing with mental and emotional challenges such as anxiety, depression, and irritability. Those will also taper off after a few weeks.

13. Main symptoms of nicotine withdrawal

13.1. Physical Withdrawal Symptoms

Everybody is different, and symptoms of withdrawal depend on many things, like how long and how many packs a day you've smoked. But for the most part, you can expect to have these common physical issues when you quit:

- Appetite. Within a day or so of your last cigarette, your appetite will shoot up for a while. Cigarettes bind to receptors in the brain which augment the release of the neurotransmitters serotonin and dopamine from the brain. These two chemicals reduce hunger, so when they're out of your system you'll want to eat more. A lot of people also find that they eat to fill the time when they used to be smoking. And unfortunately, you might crave more carbs and sweets. The first 2 weeks are the worst -- most people gain about 5 to 10 pounds as they try to quit smoking.
- Cravings. Nicotine cravings are the symptom you will deal with the longest, and they could start just 30 minutes after your last cigarette. Each craving will last only about 15 to 20 minutes, but they'll keep coming. You'll need to do your best to avoid triggers (like drinking alcohol or being around people who smoke) and find ways to get yourself through each craving.
- Cough. Your respiratory system can't clean itself very well when nicotine is around. As your body works it out, you'll probably have a cough that could last for a few weeks.
- Headaches and dizziness. These are usually on the mild side, and they're often the first withdrawal symptom to show up and first to taper off.
- Fatigue. Nicotine is a stimulant and perks you up, so you'll probably feel tired without it. But you'll also be restless and might have insomnia.
- Constipation. For the first month, constipation can be another unpleasant side effect Mental, Emotional, and Behavioral Symptoms [30,31,32].
- Like physical symptoms, how much you are affected mentally and emotionally when you quit smoking will be different for everybody. But assume you will deal with some or all of the following signs of withdrawal:
- Anxiety. Smoking relieves stress, so your anxiety can skyrocket when you quit. It tends to pop up around 3 days in and can last a couple of weeks.
- Depression. It can start the first day you quit but is generally gone within a month. But if you have a history of anxiety and/or depression, yours could last longer and you might need extra help from your doctor to manage your symptoms.
- Irritability. You might have a short fuse -- even find yourself angry -- from time to time as you deal with the physical symptoms. It's normal and should pass.
- Mental fog. You'll probably have a hard time concentrating as the nicotine wears off and leaves your body [28,29,30].

14. Nicotine withdrawal timeline

Here's what you can expect after finishing your final cigarette:

- 30 minutes to 4 hours: The effects from the nicotine will wear off and you'll start to crave another cigarette.
- 10 hours: You'll be very restless, physically craving a cigarette, and wondering how to fill the time. You may feel sad and hopeless.
- 24 hours: Irritability kicks in and your appetite increases.
- 2 days: You'll have headaches as the nicotine leaves your system.
- 3 days: The nicotine should be gone now. Your cravings taper off but anxiety will start to rise.
- 1 week: You made it a week. Pat yourself on the back; you've made it through the worst. Keep avoiding those triggers.
- 2 to 4 weeks: You still won't have much energy, but the brain fog will be clearing up and your appetite will settle down. Your cough, depression, and anxiety will also improve.
- 5 weeks on: The challenge now is keeping a strong mental game [33,34,35].

Table 1 Nicotine Withdrawal Symptoms Timeline Table

Timeline	Symptoms
30 minutes to 4 hours	The effects from the nicotine will wear off and you'll start to crave another cigarette.
10 hours	You'll be very restless, physically craving a cigarette, and wondering how to fill the time. You may feel sad and hopeless
24 hours	Irritability kicks in and your appetite increases
2 days	You'll have headaches as the nicotine leaves your system
3 days	The nicotine should be gone now. Your cravings taper off but anxiety will start to rise.
1 week	You made it a week. Pat yourself on the back, you've made it through the worst. Keep avoiding those triggers.
2 to 4 weeks	You still won't have much energy, but the brain fog will be clearing up and your appetite will settle down. Your cough, depression, and anxiety will also improve
5 weeks	The challenge now is keeping a strong mental game

15. Nicotine replacement therapy

Whether you're a smoker trying to kick the habit or you know someone who is, you know it's extremely tough. And that's all because nicotine the ingredient in tobacco products like cigarettes is very addictive.

Nicotine actually changes your brain chemistry to make you crave it more. It also makes you feel unpleasant symptoms of withdrawal when you don't get the amount your body's used to.

While withdrawal symptoms usually go away on their own after you quit smoking for a few weeks, some people find that using nicotine replacement therapies can ease the transition and make quitting easier [36,37,38].

15.1. How it works

Nicotine replacement therapies actually give you small amounts of nicotine through a product like gum or a skin patch. While you'll continue to get some nicotine in your system, you won't be exposed to any of the other harmful chemicals that are found in tobacco.

Nicotine replacement won't help with any emotional connection you may have to smoking. But it can help reduce your cravings and the physical symptoms of withdrawal so you can focus on breaking your mental addiction [39,40,41].

15.2. The different options

This is the most common type of treatment used to help people quit smoking. Doctors often recommend it and studies show it's safe and effective.

There are a variety of nicotine replacement therapies on the market today. Some are available without a prescription, but some you'll have to get your doctor to prescribe for you.

Nicotine replacement therapy is generally considered safe for most healthy adults, but it's a good idea to talk to your doctor about the potential risks and benefits for you. Side effects are possible for any treatment option. While some people may experience side effects, others may not [42,43,44].

- Nicotine patch: The over-the-counter patch is placed directly on your skin to release a low, steady amount of nicotine over time. Possible side effects: Irritation or redness on your skin, dizziness, headache, nausea, racing heartbeat, musclepain or stiffness, or problems sleeping.
- Nicotine gum (nicotine polacrilex): You can buy over-the-counter nicotine replacement gum. It comes in 2 mg and 4 mg strengths and you get the nicotine immediately through the mucous membranes in your mouth when you chew it. Possible side effects: Irritation to your mouth or throat, bad aftertaste, problems with existing dental work, nausea, jaw pain, racing heartbeat.
- Nicotine lozenges: Like gum, nicotine lozenges are available over the counter. You suck on them so you get the nicotine slowly. They're meant to dissolve like hard candies. Possible side effects: Coughing, gas, heartburn, trouble sleeping, nausea, hiccups, racing heartbeat.
- Nicotine inhaler: The prescription-only inhaler releases nicotine when you attach the cartridge to a mouthpiece and inhale. They're the nicotine replacement method that's most like smoking a cigarette. Possible side effects: Coughing, irritation to your mouth or throat, runny nose, nausea. Other side effects that can occur include headache, nervousness, and a racing heartbeat. These are related to the nicotine, not the inhaler itself.
- Nicotine nasal spray: This prescription-only nasal spray lets you squirt a quick burst of nicotine into your bloodstream directly through your nose. Possible side effects: Irritation to your nose or throat, coughing, watery eyes, sneezing. These side effects usually get better after 1-2 weeks of treatment. Other side effects that can occur include headache, nervousness, and a racing heartbeat. These are related to the nicotine, not the spray itself [45,46,47].

Although it's rare, nicotine overdose is a possible risk. Follow the instructions on each product carefully. If you have symptoms like a fast heartbeat, nausea and vomiting, dizziness, weakness, or a cold sweat, get medical attention immediately [48,49].

16. Conclusion

Nicotine withdrawal in untreated smokers produces mood disturbances comparable in intensity to those seen in psychiatric out patients. Generally it has been found that nicotine replacement therapies actually give you small amounts of nicotine through a product like gum or a skin patch. While you'll continue to get some nicotine in your system, you won't be exposed to any of the other harmful chemicals that are found in tobacco. According to one study trusted source, smoking-related diseases are responsible for about 435,000 deaths per year in the United States. That's about 1 in every 5 deaths in the United States. Stopping smoking, no matter how long you have smoked, can greatly benefit your health.

Nicotine creates pleasant feelings in the body and mind. When you use tobacco, your brain releases neurotransmitters such dopamine, the feel-good chemical. This creates a brief feeling of contentment and pleasure. In humans, nicotine from tobacco induces stimulation and pleasure, and reduces stress and anxiety. Smokers come to use nicotine to modulate their level of arousal and for mood control in daily life. Smoking may improve concentration, reaction time, and performance of certain tasks. When a person stops smoking, nicotine withdrawal symptoms emerge. These include irritability, depressed mood, restlessness, anxiety, problems getting along with friends and family, difficulty concentrating, increased hunger and eating, insomnia, and craving for tobacco.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors have no conflict of interest.

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