

Pharmacology of Nicotine: Addiction, Smoking-Induced Disease, and Therapeutics

Neal L. Benowitz

Departments of Medicine and Biopharmaceutical Sciences, Division of Clinical Pharmacology and Experimental Therapeutics, Medical Service, San Francisco General Hospital Medical Center, University of California, San Francisco, California 94143-1220; email: NBenowitz@MedSFGH.ucsf.edu

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Abstract

Nicotine sustains tobacco addiction, a major cause of disability and premature death. Nicotine binds to nicotinic cholinergic receptors, facilitating neurotransmitter release and thereby mediating the complex actions of nicotine in tobacco users. Dopamine, glutamate, and gamma aminobutyric acid release are particularly important in the development of nicotine dependence, and corticotropin-releasing factor appears to contribute to nicotine withdrawal. Nicotine dependence is highly heritable. Genetic studies indicate roles for nicotinic receptor subtypes, as well as genes involved in neuroplasticity and learning, in development of dependence. Nicotine is primarily metabolized by CYP 2A6, and variability in rate of metabolism contributes to vulnerability to tobacco dependence, response to smoking cessation treatment, and lung cancer risk. Tobacco addiction is much more common in persons with mental illness and substance abuse disorders, representing a high proportion of current smokers. Pharmacotherapeutic approaches to tobacco addiction include nicotine replacement, bupropion, and varenicline, the latter a selective nicotine receptor partial agonist.

INTRODUCTION

Use of nicotine sustains tobacco addiction, which in turn causes devastating health problems, including heart disease, lung disease, and cancer, and increased susceptibility to a variety of infectious diseases. Smoking harms almost every organ of the body (1). Quitting smoking at any age leads to significant reductions in the risks associated with it, and the vast majority of smokers in the United States indicate an interest in quitting (2). Despite these facts, however, approximately 80% of smokers who attempt to quit on their own relapse within the first month of abstinence, and only approximately 3% remain abstinent at six months. This illustrates the powerful force of tobacco addiction and the chronic nature of the disorder.

Although most of the toxicity of smoking is related to other components of cigarette smoke, it is primarily the pharmacologic effects of nicotine that produce the addiction to tobacco. An understanding of how nicotine produces addiction and influences smoking behavior provides a necessary basis for optimal smoking cessation intervention. This article reviews the neurobiology of nicotine addiction and withdrawal, as well as the implications for nicotine addiction therapy.

MECHANISMS OF ACTION

Neuropharmacology

Nicotine is a tertiary amine consisting of a pyridine and a pyrrolidine ring. (S)-nicotine, found in tobacco, binds stereoselectively 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 (3). In the mammalian brain, there are as many as nine α subunits (α_2 to α_{10}) and three β subunits (β_2 to β_4). The most abundant receptor subtypes in the brains of humans are $\alpha_4\beta_2$, $\alpha_3\beta_4$, and α_7 (homomeric). The $\alpha_4\beta_2^*$ (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 β_2 subunit gene eliminates the behavioral effects of nicotine, such that nicotine no longer releases dopamine in the brain or maintains self-administration (4). Reinserting the β_2 subunit gene into the ventral tegmental area of a β_2 knockout mouse restores behavioral responses to nicotine (5). The α_4 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 (6). This mutation makes mice much more sensitive to nicotine-induced reward behaviors, as well as to effects on tolerance and sensitization. The $\alpha_3\beta_4$ nAChR is believed to mediate the cardiovascular effects of nicotine (7). The homomeric α_7 nAChR is thought to be involved in rapid synaptic transmission and may play a role in learning (8) and sensory gating (9). The $\alpha_4\beta_2^*$ receptor may include α_5 , α_6 , and/or β_3 subunits, which may modulate the sensitivity and function of the receptor. For example, α_5 knockout mice are less sensitive to nicotine-induced seizures and hypolocomotion (10).

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 (11). 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 (12, 13). 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 (14). Dopamine release is facilitated by nicotine-mediated augmentation of glutamate release and, with long-term treatment, by inhibition of GABA release (15). 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 (16). Inhibition of MAO facilitates acquisition of nicotine self-administration in rats, supporting the idea that MAO inhibition interacts with nicotine to reinforce tobacco dependence (17).

Dopamine release signals a pleasurable experience, and is critical to the reinforcing effects of nicotine and other drugs of abuse (13). Chemically or anatomically lesioning 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 (18). 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 (19). 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 (20). 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 $\alpha_4\beta_2^*$ nAChRs become unoccupied and recover to a responsive state during periods of abstinence such as during nighttime sleep (21). 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 (22). It is speculated that smokers maintain $\alpha_4\beta_2^*$ 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 (23, 24). 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 reinforcers associated with smoking such as the taste and feel of the smoke (23). Conditioning as a component of addiction is discussed in more detail below.

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 extrahypothalamic 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 (25). 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 extrahypothalamic 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.

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 (26). Nicotine withdrawal in untreated smokers produces mood disturbances comparable in intensity to those seen in psychiatric outpatients (27). 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 (28). 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.

Conditioned Behavior 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 (29, 30).

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 (31).

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 (32). 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 (33).

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 $\alpha_4\beta_2^*$ nAChRs, in which there is a loss or decrease in the biologic response to nicotine (23). 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 $\alpha_4\beta_2^*$ 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.

NICOTINE PHARMACOKINETICS AND METABOLISM

Nicotine is a weak base ($pK_a = 8.0$). 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 (34). 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 (35). 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 (34). 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.

Considerable genetic polymorphism in CYP2A6 and UGT activity is associated with wide individual variability and racial differences in the rate of nicotine metabolism (36, 37). Asians and African Americans metabolize nicotine on average more slowly than do Caucasians or Hispanics (38, 39). Sex hormones also substantially affect CYP2A6 activity. The rate of nicotine metabolism is faster in women than men (40). 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 (41). 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.

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 (37). 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 (39).

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 (42). 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 (43). 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 (37, 39). 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 (38, 44).

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 (45). Twin studies even demonstrate heritability in the nature of particular symptoms experienced when a smoker stopped smoking (46).

Numerous studies have attempted to identify genes underlying nicotine addiction, as summarized in a recent review (45). 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 (47). 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 (48, 49). 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 (50, 51).

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 (52). 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 (52). 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 (53). Smokers with a history of major depression are at increased risk for experiencing depression after cessation of smoking (54).

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 (55, 56). 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 $\alpha 7$ nAChRs may improve sensory gating, which is abnormal in schizophrenics (57). 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 (16). 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 (58). 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.

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 (59). 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 (60). 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.

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 (61). 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 (62). Nicotine also reduces sensitivity to insulin and may aggravate or precipitate

diabetes, and nicotine may contribute to endothelial dysfunction (63, 64). 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 (65). Clinical trials of nicotine patches in smokers with cardiovascular disease showed no increased risk of cardiovascular events compared with placebo (66). 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 (67).

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 (68). Nicotine also promotes angiogenesis in animals, an effect which could lead to greater tumor invasion and metastasis (69). 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 (70). 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 (71).

Suspected adverse reproductive effects of nicotine include most prominently fetal neuroteratogenic effects (72). 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 Scandinavia has been associated with an increased risk of pre-eclampsia (73). 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 (74).

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 (75). 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.

Nicotine Replacement Therapy

Nicotine medications act on nAChRs to mimic or replace the effects of nicotine from tobacco. Nicotine replacement medications are believed to facilitate smoking cessation in several ways. The principal action is the relief of withdrawal symptoms when a person stops tobacco use (76). Amelioration of these symptoms is observed with relatively low blood levels of nicotine. A second mechanism of benefit is positive reinforcement, particularly for the arousal and stress-relieving effects. The degree of positive reinforcement is related to the rapidity of absorption and the peak nicotine level achieved in arterial blood. Positive reinforcement is most relevant to rapid-delivery formulations such as nicotine nasal spray and, to a lesser extent, nicotine gum, inhaler, and lozenge. The use of these products allows smokers to dose themselves with nicotine when they have the urge to smoke cigarettes. Nicotine patches, on the other hand, deliver nicotine gradually and produce sustained nicotine levels throughout the day, thus not providing much positive reinforcement.

A third possible mechanism of benefit is related to the ability of nicotine medications to desensitize nicotinic receptors. This desensitization results in a reduced effect of nicotine from cigarettes; e.g., when a person lapses to smoking while on nicotine replacement therapy, the cigarette is less satisfying and the person is less likely to resume smoking.

Bupropion

Bupropion was marketed as an antidepressant medication before it was marketed for smoking cessation. The serendipitous observation of spontaneous smoking cessation among veterans treated with bupropion for depression led to the exploration of bupropion as a smoking cessation medication. Bupropion increases brain levels of dopamine and norepinephrine, simulating the effects of nicotine on these neurotransmitters (77). Bupropion also has some nicotine receptor-blocking activity, which could contribute to reduced reinforcement from a cigarette in the case of a lapse (78).

Varenicline

Varenicline was synthesized with the goal of developing a specific antagonist for the $\alpha_4 \beta_2$ nAChR (79). Varenicline is an analog of cytisine, a plant alkaloid that has been reported to have some benefit in smoking cessation but is thought to have generally poor oral bioavailability. Varenicline was shown in in vitro receptor binding studies to have high affinity for the $\alpha_4 \beta_2$ nAChR, and relatively little effect on other nAChR subtypes or neurotransmitter receptors. Varenicline is a partial agonist of the $\alpha_4 \beta_2$ receptor in vivo, as demonstrated by studies of dopamine release, measured with microdialysis in the nucleus accumbens of conscious rats (79). Nicotine, a full agonist, causes substantial dopamine release. Varenicline produces less of a response than nicotine (~50%) but at the same time blocks the effects of any nicotine added to the system. Clinical trials have found that varenicline is superior to bupropion in promoting smoking cessation, and prolonged administration of varenicline has been shown to reduce relapse in smokers who were abstinent 12 weeks after initial therapy (80, 81).

Medications in Development

Rimonabant is a cannabinoid (CB-1) receptor antagonist developed for treatment of obesity and the metabolic syndrome. Clinical studies have also shown rimonabant to be effective as an aid for smoking cessation (82). Cannabinoid receptors are believed to contribute to the reinforcing effects of nicotine action. Rimonabant has not been approved by the U.S. FDA owing to concern about adverse neuropsychiatric effects.

Nicotine vaccines are currently undergoing clinical trials (83). Acute immunization is performed so as to develop antibodies to nicotine. The antibody binds nicotine and slows its entry into the brain, thereby reducing the reinforcing effects of cigarette smoking. The nicotine vaccine is a logical approach to preventing relapse.

Other potential future medications for smoking cessation include monoamine oxidase inhibitors (MAOA and MAOB), which inhibit the metabolism of dopamine and therefore increase dopamine levels in brain, and dopamine D3 receptor antagonists and partial agonists, which modulate activity of receptors involved in drug-seeking behaviors (84). Inhibitors of CYP2A6 activity have also been proposed as smoking cessation aids that work by increasing nicotine levels from tobacco use and thereby reducing urges to smoke. Methoxsalen and tranylcypromine inhibit CYP2A6 activity and slow nicotine metabolism, but both have significant toxicity, making routine clinical use problematic. Finally, novel selective nicotinic cholinergic receptor agonists and antagonists, in addition to varenicline, are under development.

PERSONALIZING NICOTINE ADDICTION TREATMENT

Although a number of drugs are effective in enhancing smoking cessation, as discussed above, success rates are still relatively low, and most smokers require multiple quit attempts before they quit for good. Tobacco addiction differs in its manifestations from person to person. There are individual differences in the nature of reinforcement (that is, what benefit people say they get from smoking), in withdrawal symptoms, and in conditioned aspects of smoking. There has been much interest, therefore, in individualization of smoking cessation pharmacotherapy. The goal would be to select medications and doses based on individual characteristics of smokers. An area of much current research activity in this regard is pharmacogenetics of nicotine addiction treatment. A number of pharmacogenetic studies have been conducted, focusing primarily on candidate genes related to nicotine reward and nicotine metabolism pathways (47). For example, variants in the dopamine D2 receptor, dopamine transporter, dopamine β hydroxylase, and catechol-O-methyltransferase genes have been reported to affect response to transdermal nicotine and/or bupropion. Variation in the opiate mu 1 receptor gene has been reported to influence response to transdermal nicotine, and variants in the CYP2B6 gene have been found to predict response to placebo in bupropion clinical trials (85, 86). To date, few of these findings have been replicated, and the fraction of the total variance in smoking cessation response explained by single candidate genes appears to be small. Ongoing research is focusing on looking at multiple genes and looking at gene-gene interactions as predictors of treatment outcome.

Given the tendency of smokers to regulate their intake of nicotine, it is logical to consider nicotine metabolism genes, namely CYP2A6, as potential predictors of response to smoking cessation treatment. Unfortunately, the prevalence of CYP2A6 gene variants is too low, at least in Caucasians, to be able to detect significant genetic associations in most studies. An alternative to CYP2A6 genotyping is the use of the phenotype for the rate of nicotine metabolism. As mentioned previously, the 3HC to cotinine ratio is a phenotypic marker of the rate of nicotine metabolism (35), and this metabolite ratio has been studied as a predictor of response to pharmacotherapy. In one trial, comparing transdermal nicotine and nicotine nasal spray, the nicotine metabolite ratio was shown to be a strong predictor of smoking cessation both at the end of treatment and at six months in people treated with transdermal nicotine, but not with nicotine nasal spray (87). In smokers treated with transdermal nicotine, slow metabolizers had a better cessation response and a higher plasma nicotine concentration while using the patch compared with faster metabolizers, suggesting that higher nicotine levels might be responsible for better cessation outcome. In contrast, smokers treated with nicotine nasal spray showed no difference in plasma nicotine

concentration as a function of rate of nicotine metabolism, consistent with the idea that nicotine from the spray is titrated by the smoker to the desired effect.

Another recent trial examined the association between a nicotine metabolite ratio and a response to bupropion treatment (88). Faster metabolism of nicotine was associated with a lower success rate in quitting in the placebo-treated group, but among smokers receiving bupropion, the rate of nicotine metabolism had no differential effect. This finding is consistent with the idea that rapid metabolizers of nicotine are generally more dependent and have a harder time quitting compared with slow metabolizers. The mechanism of such a relationship has not been proven, but might be related to a faster elimination half-life in rapid metabolizers. Faster elimination would be expected to result in more severe withdrawal symptoms and therefore a greater compulsion for the next cigarette. In addition more rapid clearance of nicotine from the brain in rapid metabolizers would be expected to be associated with more rapid loss of tolerance between cigarettes and therefore a greater effect from the nicotine in the next cigarette, which would also enhance dependence. Future studies are needed to potentially test the idea of tailoring the type or dose of pharmacotherapy using phenotypes or genotypes of the rate of nicotine metabolism.

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POTENTIAL CONFLICTS OF INTEREST

Dr. Benowitz has served as a paid consultant to several pharmaceutical companies that market smoking cessation medications. He has also been a paid expert witness against tobacco companies in matters related to nicotine addiction.

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