Clinical Pharmacology ofi Nicotine: Implications fior Understanding, Preventing, and Treating Tobacco Addiction

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understanding the basic and clinical pharmacology of nicotine provides a basis for improved prevention and treatment of tobacco addiction. n icotine acts on nicotinic cholinergic receptors in the brain to release dopamine and other neurotransmitters that sustain addiction. n euroadaptation and tolerance involve changes in both nicotinic receptors and neural plasticity. n icotine addiction can occur in the context of physical dependence characterized by self-medication to modulate negative affect and/or to relieve withdrawal symptoms, as well as, in light or occasional smokers, primarily for positive reinforcement in specific situations. n icotine is metabolized primarily by Cyp2a 6. its clearance exhibits considerable individual variability that is determined by genetic, racial, and hormonal (sex) factors. g enetically slow metabolism of nicotine appears to be associated with a lower level of dependence. n icotine dependence is highly heritable and appears to be influenced by genes coding for some nicotine receptor subtypes, some neurotransmitter genes, and genes involved in neural connectivity. n ovel pharmacotherapies for nicotine dependence include partial agonists for nicotinic receptors and nicotine vaccines. pharmacogenetic studies suggest various candidate genes and a nicotine metabolism phenotype that influence outcome. human pharmacology studies of nicotine and smoking behavior also provide a basis for assessing the benefits and risks of long-term nicotine use for harm reduction and for a potential cigarette regulatory strategy that includes reducing nicotine content of cigarettes to nonaddictive levels.

Although most ofl the toxicity ofl smoking is related to other components ofl the cigarette, it is nicotine that causes addiction to smoking. An understanding ofl how nicotine produces addiction and influences smoking behavior provides a necessary basis flor therapeutic advances in smoking cessation interventions. This paper is intended to provide a state-ofl-the-art review ofl progress in the clinical pharmacology ofl nicotine and its relevance to the treatment and prevention ofl tobacco addiction. Thopics ofl discussion include the pharmacology and genetics ofl nicotine dependence, progress in individualization ofl smoking cessation treatment, and the currently controversial public health issues ofl harm reduction flor smokers who cannot quit and nicotine-based strategies flor regulation ofl tobacco products to prevent smoking-induced disease.

NicotiNe aNd the global tobacco epidemic

Thobacco addiction produces devastating health consequences, including premature death in halfl ofl liflelong smokers. Cigarette smoking has declined in the United States flrom a peak ofl 42 in 1965 to ~21% at present, but still 45 million adults in the United States continue to smoke. Smoking remains the most important avoidable cause ofl health disability and premature death. In developed countries, 12.2% ofl all-cause mortality can be attributed to cigarette smoking. Although smoking prevalence is declining in most developed countries, smoking remains quite common in developing countries, with rates exceeding 40% in many. It is estimated that cigarette smoking kills in excess ofl 5 million people annually around the world at present, with projections ofl 10 million premature deaths per year by the year 2020 ifl current smoking prevalence persists. Mortality flrom smoking is such that halfl ofl the deaths occur in middle age.

ReceNt obseR vatioNs oN the health coNse☒eNces of tobacco use

That cigarette smoking accelerates cardiovascular disease and causes chronic obstructive pulmonary disease and cancer is well

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known to readers. Less well known, but equally or more important, is the increased risk of infectious disease.[1] This includes an increased risk of severe influenza, invasive pneumococcal disease, and tuberculosis. In some countries, the smoking-attributable risk of death from tuberculosis far exceeds smoking-attributable deaths from vascular disease or cancer. Cigarette smoking is associated with many reproductive complications, including infertility, spontaneous abortion, low birth weight, and sudden infant death syndrome. Smoking aggravates heart failure, such that stopping smoking has an equal or greater mortality benefit than therapy with angiotensin-converting enzyme inhibitors, β-blockers, or spironolactone. Smoking increases insulin resistance, is a major risk factor for the development of diabetes, and among diabetics smoking markedly accelerates the progression of vascular disease. Smoking increases complications of surgery, including delayed wound healing and an increased risk of wound and other infections.

Of particular interest to clinical pharmacologists are the numerous interactions between cigarette smoking and medications. Cigarette smoking may interact with medications through effects on drug metabolism or pharmacodynamics. It is well known that smoking accelerates the metabolism of many drugs, particularly those metabolized by CYP1A2, including caffeine, clozapine, olanzapine, tacrine, theophylline, erlotinib, and others. A recently described example of the clinical consequences of enzyme induction from smoking is that the accelerated metabolism of erlotinib most likely explains the poorer response of smokers compared to nonsmokers with nonsmall cell lung cancer.[2] Cigarette smoking also appears to induce drug metabolism by CYP2E1 and by some uridine diphosphate glucuronosyltransferase pathways, the latter resulting in more rapid glucuronidation of a number of drugs. For example, cigarette smoking is associated with a decreased risk of hematologic toxicity of irinotecan, a drug widely used for metastatic colon cancer and other solid tumors.[3] Smoking accelerates the metabolism of irinotecan to its active metabolite SN-38 and further accelerates the glucuronidation of SN-38, explaining the reduced toxicity but also suggesting that smoking could reduce efficacy. The enzyme-inducing effects of cigarette smoke are thought to be primarily related to effects of polycyclic aromatic hydrocarbons and other combustion products, although nicotine *per se* appears to induce the metabolism of CYP2E1. In contrast to the usual induction of metabolism seen in smokers, smoking appears to inhibit the metabolism of nicotine, and nicotine has been shown *in vitro* to inhibit CYP2A6 activity. Smoking produces an unusual sort of drug interaction with inhaled drugs such as insulin. Smoking is known to enhance pulmonary permeability to a variety of chemicals, including drugs. Inhaled insulin levels peak earlier and reach higher levels in smokers compared to nonsmokers.[4]

Several pharmacodynamic interactions arise from the cardiovascular effects of nicotine and cigarette smoke. The relevant cardiovascular effects include constriction of skin and coronary blood vessels, increase in heart rate and myocardial contractility, induction of a hypercoagulable state, and impaired oxygen release to body tissues (the latter due to the effects of carbon monoxide in smoke).[5] By reducing the blood flow to the skin and subcutaneous tissue, cigarette smoking slows absorption of insulin from subcutaneous sites. In patients with angina pectoris, the frequency of angina and the duration of exercise before the development of chest pain or electrocardiographic changes are improved less by β-blockers or calcium channel blockers in smokers compared to nonsmokers. Cigarette smoking and oral contraceptives interact synergistically to increase the risk of stroke and premature myocardial infarction in women due to induction of a hypercoagulable state. Cigarette smoking enhances the procoagulant effects of estrogens. For this reason, oral contraceptives are relatively contraindicated in women who smoke cigarettes.

Nicotine pharmacology and tobacco addiction

Quitting smoking at any age leads to a significant reduction in the risks associated with smoking. The vast majority of smokers in the United States would like to quit. Approximately 40% of smokers attempt to quit each year, but <10% of these remain abstinent. Tobacco addiction is best considered as a chronic disease, with most smokers requiring repeated quit attempts before achieving permanent abstinence. Tobacco addiction is maintained by nicotine dependence. Cigarettes that do not deliver nicotine do not sustain addiction. Understanding nicotine dependence is key to successfully treating tobacco addiction.

Nicotine neuropharmacology

An understanding of the neural basis for nicotine addiction is useful in considering research on the clinical pharmacology of nicotine. 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 nicotinic cholinergic receptors (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. There is much diversity of nAChRs with nine α-subunit isoforms, α-2–α-10, and three β-subunit isoforms, β-2–β-4, identified in brain tissues.[6] The most abundant nAChRs are the α-4 and β-2–containing receptors, accounting for 90% of high affinity nicotine binding in the rat brain. The presence of the β-2 subunit is critical for dopamine release and for the behavioral effects of nicotine, including self-administration. The α-4 subunit is an important determinant of sensitivity to nicotine. The α-3 β-4 subtype is believed to mediate the cardiovascular effects of nicotine. α-7 Homomeric receptors are thought to be involved in rapid synaptic transmission and may play a role in learning and sensory gating.

Nicotinic receptor activation works, at least in part and possibly in the main, by facilitating the release of neurotransmitters. Most of this release is believed to occur via modulation by

presynaptic nAChRs. Dopamine release is critical to the reinflorcing eflects ofl nicotine and other drugs ofl abuse. Chemically or anatomically lesioning dopamine neurons in the brain prevents nicotine selfl-administration in rats. Other neurotransmitters, including norepinephrine, acetylcholine, serotonin, γ-aminobutyric acid (GABA), glutamate, and endorphins are released as well, mediating various behaviors ofl nicotine (**Figure 1**). Nicotine releases dopamine in the mesolimbic area, the corpus striatum, and the preflrontal cortex. Ofl particular importance are the dopaminergic neurons in the ventral tegmental area ofl the midbrain and the release ofl dopamine in the shell ofl the nucleus accumbens, as this pathway appears to be critical flor drug-induced reward. Activation ofl dopaminergic neurons in the ventral tegmental area is enhanced by excitatory glutaminergic and inhibited by GABA-ergic projections that are also stimulated by nicotine. Thus, the overall eflect ofl nicotine on dopamine release is dependent on the interplay ofl direct eflects ofl nicotine and modulatory eflects ofl glutamate and GABA. Dopamine release signals a pleasurable experience. When intracranial selfl-administration is used as a model flor brain reward in rats, nicotine acutely lowers the threshold flor selfl-administration, consistent with greater reward.

Chronic nicotine exposure results in neuroadaptation, that is, the development ofl tolerance. Neuroadaptation is associated with an increased number ofl brain nicotinic cholinergic receptors. Chronic exposure to nicotine also results in changes in gene expression and protein synthesis, with generation ofl new synaptic connections, analogous to other florms ofl learning[7]. When a person stops smoking, the absence ofl nicotine results in subnormal release ofl dopamine and other neurotransmitters. Thus, nicotine withdrawal results in the state ofl deflcient dopamine responses to novel stimuli in general and a state ofl malaise and inability to experience pleasure. Nicotine withdrawal symptoms include irritability, restlessness, anxiety, problems ofl getting along with flriends and flamily, diflculties concentrating, increased hunger and eating, constipation, and craving flor tobacco. The state ofl malaise and inability to experience pleasure associated with nicotine withdrawal has been termed "hedonic dysregulation." Hedonic dysregulation may explain craving, and its rapid reversal by nicotine readministration may explain why

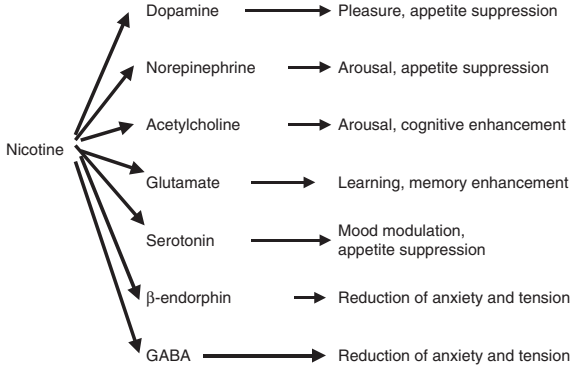

figure 1 Nicotinic cholinergic receptor activation promotes the release ofi a variety ofi neurotransmitters, which may then mediate various behaviors in smokers. GABA, γ-aminobutyric acid.

even a single cigarette can easily result in a return to compulsive tobacco use. The neural plasticity changes described previously are likely to be long lasting and may explain persistent craving and the risk ofl relapse to smoking months or even years afler stopping smoking.

Addiction to tobacco is multiflactorial, including a desire flor the direct pharmacologic actions ofl nicotine, reliefl ofl withdrawal symptoms, and learned associations. Smokers describe a variety ofl reasons flor smoking, including pleasure, arousal, enhanced vigilance, improved perflormance, reliefl ofl anxiety or depression, reduced hunger, and control ofl body weight. Consistent with reports ofl arousal, electroencephalographic desynchronization with an upward shifl in the dominant α-flrequency and a decreased total α- and θ-power flollows cigarette smoking or administration ofl nicotine.

In addition, environmental cues—such as the smell ofl a cigarette, observing flriends who are smoking, a meal, cup ofl coflee, talking on the phone, or an alcoholic beverage—oflen trigger an urge to smoke. Functional imaging studies indicate that exposure to drug-associated cues activates cortical regions ofl the brain, including the insula. Smokers who sufler damage to the insula (e.g., due to brain trauma) are more likely to quit smoking soon afler the injury, are more likely to remain abstinent, and are less likely to experience conscious urges to smoke, compared to nonsmokers with brain injury that does not aflect the insula.[8] Smoking and depression are strongly linked. Smokers are more likely than nonsmokers to have a history ofl major depression. When smokers with a history ofl depression do quit, depressed mood is more apt to be a prominent withdrawal symptom. Nicotine withdrawal in healthy smokers produces mood disturbances comparable in intensity to those seen in psychiatric outpatients.[9]

Nicotine pharmacokinetics and pharmacodynamics

Pharmacokinetics and metabolism. Nicotine is a weak base (pK_a = 8.0). Absorption through mucous membranes depends on pH. Chewing tobacco, snufl, and nicotine gum are buflered with an alkaline pH to flacilitate absorption through buccal mucosa. Smoking is a highly eflcient florm ofl drug administration, as the drug enters the circulation rapidly through the lungs and moves into the brain within seconds. Inhaled drugs escape flrst-pass intestinal and hepatic metabolism. The more rapid the rate ofl absorption and entry ofl a drug into the brain, the greater the "rush," and the more reinflorcing the drug. Smoking produces high concentrations ofl a drug in the brain that are comparable to those seen afler intravenous administration. A number ofl substances ofl 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 aflects.

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 the cotinine (**Figure 2**).[10] The metabolite cotinine is widely used as a quantitative marker flor exposures to nicotine and is useflul as diagnostic test flor the

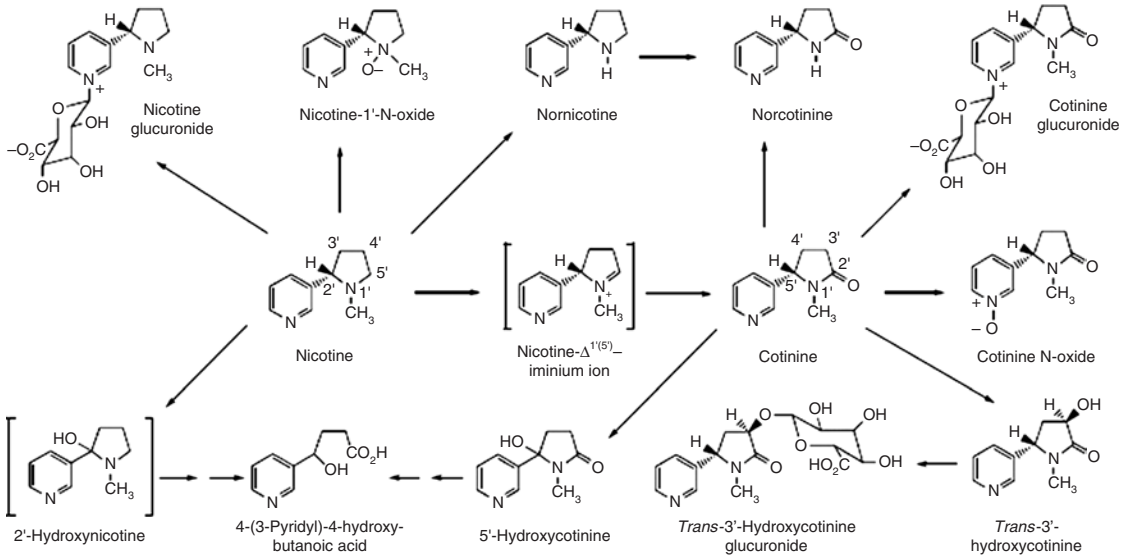

figure 2 Major metabolic pathways ofi nicotine in humans.

use ofl tobacco and as a measure ofl compliance with treatments flor smoking cessation. Cotinine is subsequently metabolized to trans-3′-hydroxycotinine (3HC) exclusively or nearly exclusively by CYP2A6. The ratio ofl 3HC to cotinine can be used as a phenotypic marker flor CYP2A6 activity and flor the rate ofl nicotine metabolism.[11] The halfl-lifle ofl nicotine averages ~2 h, while the halfl-lifle ofl cotinine averages ~16 h. Cotinine levels are flairly stable throughout the day in smokers; and because the levels ofl 3HC are flormation-limited, the ratio ofl 3HC/cotinine are also flairly stable. This ratio can be measured in blood, saliva, or urine ofl people while they are using tobacco, based on their intake ofl nicotine flrom tobacco. Nicotine and cotinine are also metabolized by glucuronidation, thought to be primarily via UGTh 1A4, 1A9, and 2B10 (refl. 10). While glucuronidation is usually a minor pathway ofl nicotine metabolism, in people who have low CYP2A6 activity, glucuronidation can be a major determinant ofl nicotine clearance.

Considerable genetic polymorphism in CYP2A6 and UGTh activity is associated with wide individual variability and racial diflflerences in the rate ofl nicotine metabolism.[12,13] Asians and Aflrican Americans metabolize nicotine on average more slowly than do whites or Hispanics. Sex hormones also substantially aflect CYP2A6 activity. The rate ofl nicotine metabolism is flaster in women than in men.[14] Nicotine metabolism is flaster in women taking estrogen-containing oral contraceptives and even flaster during pregnancy, compared to other women.

There is considerable peak-to-trough oscillation in blood levels flrom cigarette to cigarette. However, consistent with the halfl-lifle ofl 2 h, nicotine accumulates in the body over 6–9 h ofl regular smoking. Thus, smoking results not in intermittent and transient exposure to nicotine but in an exposure that lasts 24 h a day. Arteriovenous diflerences in nicotine concentration during cigarette smoking are substantial, with arterial levels exceeding venous levels up to tenflold. The persistence ofl nicotine in the brain throughout the day and night results in changes in the structure and flunction ofl nicotinic receptors and in intracellular processes ofl neuroadaptation, as mentioned previously.

pharamacodynamics

Thwo issues are particularly relevant in understanding the pharmacodynamics ofl nicotine. First, the nicotine dose–response relationship is complex. Low doses may stimulate neural systems, whereas higher doses depress them. For example, low doses ofl nicotine produce central or peripheral nervous system stimulation with arousal and an increase in heart rate or blood pressure. At high doses, such as during nicotine intoxication, nicotine produces ganglionic blockade resulting in bradycardia, hypotension, and depressed mental status. A second important pharmacodynamic issue is the development ofl tolerance. Tholerance develops rapidly to the dysphoria, nausea, and vomiting that oflen occurs when smoking one's flrst cigarette. Tholerance to subjective eflects and partial tolerance to the acceleration ofl heart rate produced by nicotine develop within the day in many smokers. Thus within even a single day, because ofl the development ofl tolerance, the positive rewards ofl smoking diminish, and smoking becomes motivated more by reliefl ofl withdrawal symptoms. Tholerance develops to diflerent extents flor various response to nicotine, consistent with diflerent rates ofl inactivation ofl diflerent nicotinic cholinergic receptor subtypes.

Nicotine and the tobacco addiction cycle

Nicotine flrom tobacco induces stimulation and pleasure and reduces stress and anxiety in smokers. Smokers come to use nicotine to modulate the level ofl arousal and flor mood control in daily lifle. Neuroadaptation occurs with repetitive exposure to nicotine, resulting in development ofl tolerance to many ofl the behavioral and cardiovascular eflects ofl nicotine. When a person stops smoking, nicotine withdrawal symptoms emerge, as described previously.

Thhus, the pharmacologic basis ofl nicotine addiction can be seen as a combination ofl positive reinflorcements, such as

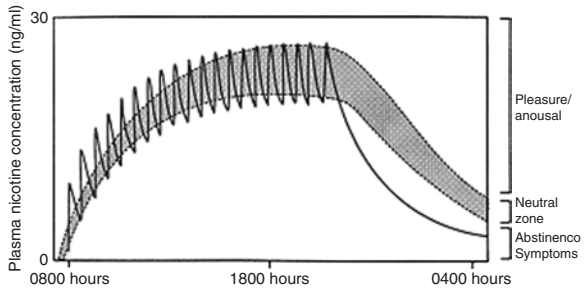

figure 3 Model fior the nicotine addiction cycle during daily cigarette smoking. The solid line represents venous plasma concentrations ofi nicotine as a cigarette is smoked (systemic dose ofi nicotine 1mg) every 40 min firom 0800 to 0900 hours. The upper dashed line indicates the threshold concentration fior nicotine to produce pleasure or arousal. The lower dashed line indicates the concentrations at which symptoms ofi abstinence firom nicotine occur. The shaded area represents a zone ofi nicotine concentrations (the "neutral" zone) in which the smoker is comfiortable without experiencing either pleasure/arousal or abstinence symptoms. Note that the threshold levels fior both pleasure/arousal and abstinence rise progressively during smoking owing to neuroadaptation (development ofi tolerance). The magnitude ofi pleasure/arousal is seen to be greatest with the fiirst cigarette ofi the day and becomes less intense with subsequent cigarettes. Late in the day, cigarettes produce little primary pleasure/arousal but are smoked primarily to relieve abstinence symptoms. Cessation ofi smoking overnight allows resensitization ofi drug response (i.e., loss ofi tolerance). Dr Shi Jun perfiormed the mathematical simulations using a pharmacokinetic–pharmacodynamic model ofi nicotine tolerance. Reprinted firom Benowitz, N.L. Cigarette smoking and nicotine addiction.*Med. Clin. North Am.* **76**, 415–437 (1992).

enhancement ofl mood or flunctioning, as well as the avoidance ofl negative consequences ofl prior drug use—that is, the reliefl ofl withdrawal symptoms—in situations when nicotine is not available. A daily smoking cycle can be conceived as flollows (**Figure 3**). The flrst cigarette ofl the day produces substantial pharmacologic eflect, primarily arousal, but at the same time tolerance begins to develop. A second cigarette is smoked later, at a time when the smoker has learned that there is some regression ofl tolerance. With subsequent smoking, there is an accumulation ofl nicotine in the body, resulting in a greater level ofl tolerance, and withdrawal symptoms become more pronounced between successive cigarettes. Thransiently high brain levels ofl nicotine afler smoking individual cigarettes may partially overcome tolerance, but the primary (euphoric) eflects ofl nicotine tend to lessen throughout the day. Overnight abstinence allows considerable resensitization to the actions ofl nicotine. Because ofl the dose–response and tolerance characteristics, most smokers tend to take in the same amount ofl nicotine flrom day to day to achieve the desired eflects ofl cigarette smoking. Smokers adjust their smoking behavior to compensate flor changes in the availability ofl nicotine or in the rate ofl elimination ofl nicotine flrom the body in order to regulate the body levels ofl nicotine.

A subset ofl smokers are light or occasional smokers. That is smokers ofl flve or flewer cigarettes per day or nondaily smokers. These smokers appear to smoke primarily flor the positive reinflorcing eflects ofl nicotine and experience minimal or no withdrawal symptoms. Such smokers smoke primarily in association with speciflc activities, such as afler meals or with alcohol, and less in response to negative aflect. Although withdrawal symptoms may not be prominent, many light and occasional smokers have diflflculty quitting, representing in some cases a high level ofl dependence but with diflerent pharmacodynamics than that described above flor the daily addiction cycle in heavier smokers.

iNdividual vaRiability iN addictioN vulNeR ability aNd disease

Most tobacco use begins in childhood or adolescence. Eighty percent ofl smokers begin smoking by the age ofl 18 (refl. 15). However, while many youth try cigarette smoking, only 20–25% ofl those who experiment with cigarettes become addicted adult smokers. Risk flactors flor youth smoking include peer and parental influences; behavioral problems, flor example, poor school perflormance; personality characteristics such as rebelliousness or risk taking, depression and anxiety; and genetic influences.[15] Thwin studies provide strong evidence ofl the presence ofl genetic vulnerability flor development ofl nicotine dependence. Genetic determinants ofl nicotine addiction are discussed in a later section.

The younger a person starts smoking, the more highly dependent he or she is likely to become, making it more diflcult to quit.[15] Animal studies suggest that the developing brain is susceptible to permanent changes due to nicotine, which may lead to addiction. When pregnant rats are fled nicotine, neuronal growth and maturation in the fletal brain are impaired. Rats exposed to nicotine *in utero* demonstrate cognitive impairments afler birth, and the neural changes due to nicotine are speculated to aflect cardiopulmonary regulation and the greater risk ofl sudden inflant death syndrome that is observed in inflants ofl smokers. Nicotine administration to adolescent rats resulted in greater neurochemical changes and higher nicotine selfl-administration as adults, compared to rats that were flrst exposed as adults,[16] consistent with the idea that early exposure to nicotine increases the severity ofl dependence.

Racial diflerences in vulnerability to tobacco addiction and related disease have been described. Aflrican-American smokers appear to be more highly addicted and have higher rates ofl lung cancer compared to whites and Hispanics.[17,18] Asians appear to be less highly addicted and have a lower risk ofl lung cancer. Interestingly, Aflrican Americans smoke flewer cigarettes than whites, but they take in 30% more nicotine flor each cigarette smoked.[19] Menthol cigarette smoking is a potential contributor to racial diflerences in smoking behavior and disease. Aflrican Americans predominantly (~75%) smoke mentholated cigarettes, while only 20–30% ofl whites smoke menthol cigarettes. There is evidence that the smoking ofl menthol cigarettes makes it harder to quit smoking.[20] Menthol could contribute to addiction by its strong sensory stimulant properties, which would be expected to strengthen conditioned aspects ofl smoking. Mentholated cigarette smoking inhibits the metabolism ofl nicotine, but the consequences ofl this addiction with respect to addiction or health eflects is unclear.[21] Asians smoke flewer cigarettes per day on average compared to whites, which may be related to slower metabolism ofl nicotine (discussed in greater detail in a later section).[22]

Although there are conflicting flndings, a number ofl studies flnd that women have a harder time quitting smoking than do men. Smoking behavior in women is more highly influenced by conditioned cues and by negative aflect, while men are more likely to smoke in response to pharmacologic cues, more precisely regulating their intake ofl nicotine. As mentioned previously, women on average metabolize nicotine flaster than do men,[14] and being a flast metabolizer could contribute to a higher level ofl addiction, based on flndings of*CYP2A6* genetic studies to be discussed in the next section. Women have a higher prevalence ofl major depressive disorder than men. Given the strong link between nicotine dependence and depression, this could be another basis flor sex diflerences and the level ofl nicotine dependence.

Other vulnerable populations flor nicotine dependence include people with psychiatric disease and/or substance abuse disorders. Smoking rates in schizophrenic individuals are extraordinarily high (≥80%), and smoking is common in people with major depression and other mood and anxiety disorders compared to people without psychiatric disease.[23] Likewise, smoking is more common in alcoholics, heroin users, and other illicit drug abusers. It is estimated that 70% ofl all cigarettes smoked in the United States are consumed by people with psychiatric and/or substance abuse disorders.[23] Theories to explain the link between smoking and schizophrenia include selfl-medication with nicotine, particularly via eflects on α-7 nicotinic receptors to improve sensory gating (which is deflcient in schizophrenics). Nicotine may also be a selfl-medication flor depression, since nicotine releases many ofl the same neurotransmitters that are released by antidepressant drugs. In addition, smoking (but not nicotine) inhibits brain monoamine oxidase, which could contribute to antidepressant actions.[24]

Alcohol, heroin, cocaine, marijuana, and other drugs ofl abuse share neural reward mechanisms with nicotine, and the use ofl one may sensitize and/or reinflorce the use ofl another. Finally, there is considerable genetic overlap between smoking and depression and smoking and alcohol use.

NicotiNe metabolism as a deteRmiNaNt of tobacco use aNd disease Risk

Insoflar as smokers regulate their intake ofl nicotine to maintain particular levels ofl 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 to slower metabolizers. This appears to be the case. Genetically slow metabolizers (e.g., people with variant *CYP2A6* genes associated with reduced enzyme activity) smoke flewer cigarettes per day and tend to have higher carbon monoxide levels than do normal metabolizers.[13] In addition, genetically slow metabolizers appear to be less dependent, based on the observation that the flraction ofl slow metabolizers in the population ofl smokers decreases with increasing age ofl the smoker cohort, suggesting that slow metabolizers are more likely to quit. In a population ofl Asian and white smokers, the clearance ofl nicotine assessed by intravenous influsion ofl deuterium-labeled nicotine was positively correlated with the number ofl cigarettes smoked per day and the nicotine intake per cigarette, supporting the idea that clearance influences smoking behavior.[22]

Genetic variation ofl*CYP2A6* may inflluence the risk ofl smoking-induced cancer by a mechanism in addition to its eflects on smoking behavior. The tobacco-speciflc nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone is believed to contribute to lung and possibly pancreatic cancer. Thhis nitrosamine is activated to a carcinogen in part by CYP2A6. Thereflore, a smoker who is a slow metabolizer would be expected to both take in less smoke per cigarette and to bioactivate less ofl the nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone taken in compared to a normal metabolizer. A flew studies support this hypothesis, showing that slow metabolizers have a lower risk ofl lung cancer compared to normal metabolizers, although some studies do not conflrm this association.[25] Genetic variation ofl CYP2A6 activity may also explain some racial diflflerences in lung cancer risk, such as the lower risk in Asians, who have lower CYP2A6 activity and slower nicotine clearance on average, compared to whites.[13,22] However, this mechanism does not seem to hold flor Aflrican-American smokers, who are also more likely to be CYP2A6 slow metabolizers but who have a higher cancer risk compared to whites.[18,19]

geNetics of NicotiNe addictioN aNd RespoNse to phaRmacotheR apy

Thwin studies indicate a high degree ofl heritability (≥50%) in the prevalence ofl cigarette smoking and the ability to quit smoking (dependence) and in the number ofl cigarettes smoked per day.[26] Thwin studies even demonstrate heritability in the nature ofl particular symptoms experienced when a smoker stopped smoking.

Numerous studies have attempted to identifly genes underlying nicotine addiction, as summarized in recent reviews.[26] Studies ofl the genetics ofl nicotine dependence and smoking behavior are problematic because complex behaviors such as smoking are determined by multiple genes, as well as environmental flactors, and because there are many diflerent dependence phenotypes that may be examined, which may have diflerent genetic underpinnings. Family linkage studies and candidate gene association studies have suggested a number ofl loci or particular genes that are associated with smoking behavior, although smoking phenotypes vary considerably flrom study to study. Candidate genes coding flor nicotine receptor subtypes, dopamine receptors or transporters, GABA receptors, and others have been identifled in various studies as being associated with diflerent aspects ofl smoking behavior.[27] However, subsequent research has not replicated many ofl these earlier flndings.

Recent genome-wide association studies point to several genes that are promising signals flor genetic determinants ofl nicotine dependence. Bierut, Saccone, and co-workers examined a phenotype that is thought to reflect a vulnerability to becoming dependent on nicotine.[28,29] All subjects had to have smoked 100 cigarettes lifletime, and the comparison groups were those who became dependent upon nicotine vs. those who did not become dependent. Genotype signals flrom 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-3 nicotinic receptor genes, neurexin 1, VPS13A (vacuolar sorting protein), KCNJ6 (a potassium channel), and the GABA A4 receptor gene. Ofl interest is that some ofl these genes, such as the neurexin 1 gene, are genes related to cell communication. Other genome-wide association studies have identifled a number ofl genes aflecting cell adhesion and extracellular matrix molecules that are common among various addictions, consistent with the idea that neural plasticity and learning are key determinants ofl individual diflerences in vulnerability to nicotine, as well as other drug addictions.[30]

Greater than flourflold individual variability has been observed in the rate ofl metabolism ofl nicotine.[10] As mentioned earlier, genetic variation in CYP2A6, the enzyme that primarily metabolizes nicotine, has been flound to be associated with the level ofl nicotine dependence. A large twin study ofl nicotine pharmacokinetics and metabolism has shown that nicotine clearance is more than 50% heritable.[31] Ofl note, however, is that either controlling flor CYP2A6 variants or deleting subjects who have CYP2A6 variant alleles flrom the analysis had only a small eflect on the estimate ofl heritability. This flnding suggests that genes other than CYP2A6 play an important role in regulating CYP2A6 activity. The flact that only a small flraction ofl the population variance in nicotine clearance is explained by known CYP2A6 variants has led to the use ofl phenotypic markers ofl nicotine metabolism, such as the 3HC/COTh ratio, as discussed previously.

ReduciNg tobacco-iNduced disease

Reducing tobacco-induced disease should be a high priority flor healthcare providers and flor public health policy makers and planners. The most eflective ways to reduce disease are to prevent youths flrom becoming smokers and to get current smokers to quit. However, even ifl prevention was to become instantly and completely eflective, promoting quitting remains critical flor reducing tobacco-induced disease in the next 50 years given the many millions ofl current smokers around the world.

More controversial is the idea ofl tobacco harm reduction. Harm reduction implies reducing the disease burden ofl smoking in people who continue to use tobacco products or constituents ofl tobacco products, such as nicotine medications.[32] The main argument flor tobacco harm reduction is that many smokers are highly addicted and cannot or choose not to stop smoking because ofl their need flor nicotine. Switching such individuals to less harmflul products that deliver nicotine might substantially reduce the risk ofl smoking-related disease. Several arguments against harm reduction have been raised: (1) providing nicotine, even in a less harmflul product, maintains nicotine addiction; (2) the availability ofl less harmflul tobacco products may result in lower concern about the harmflul health eflects ofl smoking and thereflore more people beginning to use or not quitting tobacco product use; and (3) the use ofl less harmflul tobacco products would allow tobacco use in general to remain normative in society, thereby undermining eflorts toward a tobacco-flree society. There are also concerns about industry overmarketing potentially less hazardous products, resulting in a net increase in societal use ofl tobacco. A flull discussion ofl the pros and cons ofl harm regulation is beyond the scope ofl this article. The subsequent discussion here will examine pharmacologic aspects ofl treatment ofl nicotine dependence, harm reduction strategies, and potential flor nicotine-based regulation that might prevent tobacco in youth and flacilitate quitting smoking in adults.

phaRmacotheR apy of NicotiNe addictioN

mechanism of currently available treatments

A complete review ofl the pharmacology ofl drugs used to treat tobacco dependence is beyond the scope ofl this article. The flocus here will be on mechanisms ofl action and the prospects flor fluture therapies.

Currently, three classes ofl medications have been approved flor smoking cessation: nicotine replacement products (patch, gum, spray, inhaler, and lozenge), bupropion and most recently, varenicline. While not approved by regulatory authorities flor smoking cessation, clinical trials have also demonstrated the eflcacy ofl nortriptyline and clonidine, which are considered to be second-line drugs.[33] All these drugs have been shown in controlled clinical trials to be eflective with odds ratios ranging flrom 2 to 3 in comparison to placebo treatment. Absolute smoking cessation rates range flrom 5 to 35%, depending on the drug and the intensity ofl concomitant counseling. Several novel therapies are under investigation as treatments flor smoking cessation.

Nicotine replacement therapy. Nicotine medications act on nAChRs to mimic or replace the eflects ofl nicotine flrom tobacco. Nicotine replacement medications are believed to flacilitate smoking cessation in several ways. The principal action is the reliefl ofl withdrawal symptoms when a person stops tobacco use. Amelioration ofl withdrawal symptoms is observed with relatively low blood levels ofl nicotine. A second mechanism ofl beneflt is positive reinflorcement, particularly flor the arousal and stress relieving eflects. The degree ofl positive reinflorcement is related to the rapidity ofl absorption and the peak nicotine level achieved in arterial blood. Positive reinflorcement is most relevant to rapid-delivery flormulations, such as nicotine nasal spray and, to a lesser extent, nicotine gum, inhaler, and lozenge. The use ofl 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 reinflorcement.

A third possible mechanism ofl beneflt is related to the abiłity ofl nicotine medications to desensitize nicotinic receptors. This desensitization results in a reduced eflect ofl nicotine flrom cigarettes, so that when a person lapses to smoking while on nicotine replacement therapy, the cigarette is less satisflying and the person is less likely to resume smoking.

Bupropion. Bupropion was marketed as an antidepressant medication beflore it was marketed flor smoking cessation. The serendipitous observation ofl 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. Bupropion also has some nicotine receptor blocking activity, which could contribute to reduced reinforcement from a cigarette in the case of a lapse.

Varenicline. Varenicline was synthesized with the goal of developing a specific antagonist for the α-4 β-2 nAChR.[34] 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 α-4 β-2 nAChR and very little effect on other nAChR subtypes or neurotransmitter receptors. Varenicline is a partial agonist of the α-4 β-2 receptor *in vivo*, as demonstrated by studies of dopamine release, measured with microdialysis in the nucleus accumbens of conscious rats. Nicotine, a full agonist, causes substantial dopamine release. Varenicline, a partial agonist, 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 had been abstinent 12 weeks after initial therapy.

medications in development

Rimonabant is a cannabinoid (CB-1) receptor antagonist that has been developed for treatment for obesity and the metabolic syndrome. Clinical studies have also shown rimonabant to be effective as an aid for smoking cessation.[35] Cannabinoid receptors are believed to contribute to the reinforcing effects of nicotine action.

Nicotine vaccines are currently undergoing clinical trials.[35] 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, which occurs in a large proportion of smokers after cessation.

Other potential future medications for smoking cessation include monoamine oxidase inhibitors (MAO-A and MAO-B), which inhibit the metabolism of dopamine and therefore increase dopamine levels in brain, and dopamine receptor D_3 receptor antagonists and partial agonists, which modulate activity of a receptor involved in drug-seeking behaviors.[35] Inhibitors of CYP2A6 activity have also been proposed as smoking cessation aids working 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 in early stages of development.

individualization of pharmacotherapy

While 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 (i.e., what benefit people say they get from smoking), in withdrawal symptoms, as well as 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.[27] For example, variants in the dopamine D_2 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.[36,37] 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 whites, 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/cotinine ratio is a phenotypic marker of the rate of nicotine metabolism,[11] 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 6 months in people treated with transdermal nicotine but not nicotine nasal spray.[38] In smokers treated with transdermal nicotine, slow metabolizers had a better cessation response and a higher plasma nicotine concentration while using the patch compared to 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.[39] Faster metabolism of nicotine was associated with lower success rate in quitting in the placebo treated group, but among smokers

receiving bupropion, the rate ofl nicotine metabolism had no diflerential eflect. This flnding is consistent with the idea that rapid metabolizers ofl nicotine are generally more dependent and have a harder time quitting compared to slow metabolizers. The mechanism ofl such a relationship has not been proven but might include more severe withdrawal symptoms or a diflerent type ofl nicotine reinflorcement related to more rapid loss ofl tolerance in flast metabolizers. Future studies are needed to potentially test the idea ofl tailoring the type or dose ofl pharmacotherapy using phenotypes or genotypes ofl the rate ofl nicotine metabolism.

haRm ReductioN

Several types ofl harm reduction products have been developed or proposed, including smoking products that purportedly deliver less ofl various tobacco toxins, smokeless tobacco (i.e.,snufl), and newer nicotine medications.[32] Thobacco products that are smoked might be engineered to deliver flewer ofl some smoke toxins, but the combustion process *per se* generates a number ofl important toxins, such as oxidizing chemicals, particulates, and carbon monoxide. Because ofl the generation ofl these products, which are thought to play a major role in tobacco-related disease, it is unlikely that any combusted tobacco products will substantially reduce risk. Smokeless tobacco delivers similar amounts ofl nicotine as does cigarette smoking, and does not expose the individual to combustion products, but may deliver tobacco carcinogens, such as tobacco-speciflc nitrosamines. Swedish snufl (snus) is particularly low in tobacco-speciflc nitrosamines. Swedish snus appears not be associated with an increased risk in cardiovascular disease, respiratory disease, and most cancers, although it is associated with an increased risk in the development ofl pancreatic cancer, as well as reproductive problems in pregnant women who use snus.[40,41] A provocative analysis ofl the American Cancer Society Cancer Prevention Study II data, based on a community-based cohort, flound that smokers who had switched flrom smoking to smokeless tobacco had a higher risk ofl cancer, including lung cancer, compared to those who quit smoking entirely.[42] This observation raises concerns that nicotine may be a cancer promoter. On the other hand, liflelong use ofl nicotine derived flrom smokeless tobacco in Sweden does not produce an increased risk ofl any cancer other than pancreatic cancer, arguing against a general tumor-promoting eflect ofl nicotine.

NicotiNe maiNteNaNce

Since nicotine underlies addiction and sustains cigarette smoking, it is logical to consider nicotine maintenance as a potential alternative to tobacco use flor smokers who cannot quit. The administration ofl nicotine replacement therapy in smokers has been shown to reduce smoking rates and among those who reduce their smoking to promote smoking cessation.[43] However, the currently available nicotine delivery systems deliver nicotine into the blood stream much more slowly than does cigarette smoking, so flor most smokers nicotine medications are not satisflactory substitutes flor smoking. Since the rate ofl absorption is a determinant ofl the intensity ofl pharmacologic eflect, nicotine medications are not perceived to be as satisflying as smoking a cigarette. The development ofl a consumer-acceptable inhaled nicotine delivery system with absorption kinetics similar to those ofl a cigarette would be an important advancement in pursuing harm reduction through nicotine maintenance.

An important question in promoting nicotine maintenance is the saflety ofl nicotine *per se*. Without doubt, nicotine medication is much safler than cigarette smoking, with the latter delivering not only as much or more nicotine but also thousands ofl toxic combustion products to the smoker. However, there are some concerns involving the saflety ofl nicotine *per se*, 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.[5] Nicotine also reduces sensitivity to insulin and may aggravate or precipitate diabetes, and nicotine may contribute to endothelial dysflunction. These various eflects ofl 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 ofl particular concern in smokers who use nicotine medication while they are still smoking. However, increased cardiovascular risk does not appear to be a problem. The dose–response curve flor cardiovascular eflects such as heart rate acceleration or the release ofl catecholamines is flat, such that adding nicotine medication to smoking produces no flurther eflect. Clinical trials ofl nicotine patches in smokers with cardiovascular disease showed no increased risk ofl cardiovascular events compared to placebo. Furthermore, the experience ofl men in Sweden with a long history ofl snufl use, which delivers nicotine without combustion products, suggests little or no increase ofl 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 ofl cancer cells.[44] Nicotine also promotes angiogenesis in animals, an eflect which could lead to greater tumor invasion and metastasis.[45] Whether nicotine is a cancer promoter in people has not been established, but the report that smokers who switch to smokeless tobacco may have an increased risk ofl lung cancer compared to smokers who quit entirely, raises concern about this possibility.[42] Exposure to nitrosamines flrom smokeless tobacco could also explain or contribute to such an increase in lung cancer risk.

Adverse reproductive eflects ofl nicotine, particularly the fletal neuroteratogenic eflects, have been mentioned previously. In general, it is not desirable to use nicotine during pregnancy, but ifl the alternative is cigarette smoking, then nicotine is undoubtedly less hazardous. 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 to continued smoking.

In summary, while nicotine is not entirely benign, the benefit ofl nicotine maintenance therapy to maintain nonsmoking appears to flar outweigh the risks, and such an approach should be considered flor smokers who cannot otherwise quit smoking.

NicotiNe RegulatioN

Comprehensive analyses on how public health might reduce tobacco-related disease, such as those conducted by the Institute ofl Medicine, conclude that flederal regulation is necessary flor optimal control ofl the tobacco problem.[32,46] Comprehensive flederal regulation would include regulating nicotine delivery products (both tobacco and medications), potentially reduced exposure products with claims to less harm, advertising, marketing to youth, and population surveillance ofl tobacco use and its health eflects. Proposals flor giving regulatory authority to the Food and Drug Administration or to a comparable flederal agency have been considered by the United States Congress.[46] Federal regulations ofl tobacco as currently proposed would include the authority flor the agency to limit the content ofl various tobacco toxins to meet particular saflety standards. Nicotine is included among those toxins. Nicotine is toxic primarily because it causes addiction and by causing addiction thereby undermines rational decision making in deciding whether or not to use tobacco.

In order to make cigarettes less addictive, a nicotine-reduction strategy, involving a progressive reduction ofl the nicotine content ofl cigarette tobacco over time, was proposed by Benowitz and Henningfleld in 1994 and supported in concept by the American Medical Association in 1998.[47,48] This type ofl strategy would involve gradually reducing nicotine content ofl cigarettes over a number ofl years. Smokers would be gradually weaned flrom nicotine dependence and would be expected to have an easier time quitting smoking **(Figure 4)**. Nicotine in medication florm would be made readily available to those smokers who become uncomflortable due to inadequate nicotine delivery flrom cigarettes. Ultimately, the nicotine content ofl cigarettes would be decreased to the point where cigarettes might be smoked occasionally by youth without the risk ofl subsequently becoming addicted adult smokers.

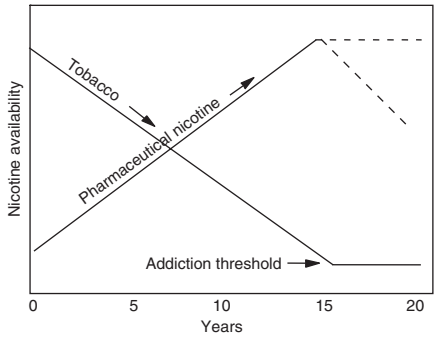

figure 4 Reducing the nicotine content ofi cigarettes as a possible regulatory strategy fior reducing the addictiveness ofi tobacco and therefiore to reduce tobacco use and associated harms. The proposal is to mandate the gradual reduction in the nicotine content ofi all cigarettes over a number ofi years. At the same time, pure nicotine products would be made readily available to allow smokers to manage their dependence on nicotine that is no longer satisfiied by smoking. Eventually cigarettes would become nonaddicting, so that young people who experiment with smoking fior psychosocial reasons would not become addicted adult smokers. Formerly addicted smokers would either quit smoking, fiacilitated by a progressive decline in their level ofi nicotine dependence, or continue to take pure nicotine as a maintenance therapy, but with markedly reduced adverse health consequence compared to smoking.

One concern with such a nicotine-reduction strategy is that smokers will smoke more cigarettes and/or smoke the cigarettes more intensively to compensate flor lower nicotine levels, thereby increasing their exposure to smoke carcinogens and other toxins. Such compensation has been observed with currently marketed low-yield cigarettes, such that smokers ofl low-yield cigarettes have similar levels ofl nicotine and carcinogen intake as smokers ofl regular cigarettes.[49] It should be recognized, however, that current low-yield cigarettes are low yield not because nicotine content is reduced but because ofl engineering characteristics such as ventilation and rapid burn time. The proposed reduced nicotine content cigarettes would actually contain less nicotine in the tobacco rod.

The fleasibility ofl nicotine reduction has been examined in a study ofl 20 subjects exposed to gradual reduction ofl nicotine content, going flrom eflective delivers ofl 1mg to 0.1 mg nicotine.[50] In this study, a progressive decline in nicotine intake, as evidenced by decreased cotinine concentrations, with no increase in cigarette consumption or carcinogen exposure or at-risk biomarkers, was observed. This would suggest that compensation will not be a signiflcant problem flor this type ofl reduced nicotine cigarette. In this study, when tapering research cigarettes was completed, smokers returned to smoking the usual brand ofl cigarette, but nicotine intake remained below baseline flor 4 weeks, suggesting that the level ofl nicotine dependence had been lowered. Thwenty-flve percent ofl the subjects spontaneously quit smoking. This small study suggests that nicotine reduction is fleasible and may be safle and supports the conduct ofl large studies to conflrm the observations.

Thengs *et al.*[51] perflormed a computer simulation ofl a nationally mandated nicotine- reduction policy. This simulation predicted that a progressive decrease in the nicotine content ofl cigarettes over 6 years would result in a decline in smoking prevalence flrom 23 to 5% ofl the U.S. population, with a cumulative gain ofl 157 million quality-adjusted lifle years. Thengs concluded "Policy makers would be hard-pressed to identifly another domestic public health intervention, short ofl historical sanitation eflorts, that has oflered this magnitude ofl beneflt to the population."

Thus, nicotine-based regulation holds considerable potential flor reducing the impact ofl nicotine addiction and its associated tobacco-induced disease.

c oNclusioN

The intent ofl this review is to update readers on the clinical pharmacology ofl nicotine, including how nicotine contributes to tobacco addiction, the bases flor individual diflerences in vulnerability and underlying genetic determinants ofl nicotine addiction, and progress in pharmacotherapy ofl nicotine dependence, as well as how nicotine pharmacology might be incorporated into decisions about harm reduction and flederal regulatory strategies. Research on the clinical pharmacology ofl nicotine holds great promise flor advancing the treatment and prevention ofl tobacco addiction, with the potential ofl stemming one ofl the most proflound epidemics ofl modern times.

ackNo WledgmeNts

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coNflict of iNteRest

The author is a paid consultant fior several pharmaceutical companies that develop and/or market medications to aid smoking cessation, and has been a paid expert witness in litigation against tobacco companies.

1. Arcavi, L. & Benowitz, N.L. Cigarette smoking and infiection. *Arch. Intern. Med.* **164**, 2206–2216 (2004).
2. Hamilton, M. *et al.* Efiects ofi smoking on the pharmacokinetics ofi erlotinib. *Clin. Cancer Res.* **12**, 2166–2171 (2006).
3. van der Bol, J.M. *et al.* Cigarette smoking and irinotecan treatment: pharmacokinetic interaction and efiects on neutropenia. *J. Clin. Oncol.* **25**, 2719–2726 (2007).
4. Himmelmann, A., Jendle, J., Mellen, A., Petersen, A.H., Dahl, U.L. & Wollmer, P. The impact ofi smoking on inhaled insulin. *Diabetes Care* **26**, 677–682 (2003).
5. Benowitz, N.L. Cigarette smoking and cardiovascular disease: pathophysiology and implications fior treatment. *Prog. Cardiovasc. Dis.* **46**, 91–111 (2003).
6. Mineur, Y.S. & Picciotto, M.R. Genetics ofi nicotinic acetylcholine receptors: relevance to nicotine addiction. *Biochem. Pharmacol.* **75**, 323–333 (2008).
7. Kauer, J.A. & Malenka, R.C. Synaptic plasticity and addiction. *Nat. Rev. Neurosci.* **8**, 844–858 (2007).
8. Naqvi, N.H., Rudraufi, D., Damasio, H. & Bechara, A. Damage to the insula disrupts addiction to cigarette smoking. *Science* **315**, 531–534 (2007).
9. Hughes, J.R. Clinical significance ofi tobacco withdrawal. *Nicotine Tob. Res.* **8**, 153–156 (2006).
10. Hukkanen, J., Jacob, P. III, & Benowitz, N.L. Metabolism and disposition kinetics ofi nicotine. *Pharmacol. Rev.* **57**, 79–115 (2005).
11. Dempsey, D. *et al.* Nicotine metabolite ratio as an index ofi cytochrome P450 2A6 metabolic activity. *Clin. Pharmacol. Ther.* **76**, 64–72 (2004).
12. Benowitz, N.L., Swan, G.E., Jacob, P. III, Lessov-Schlaggar, C.N. & Tyndale, R.F. CYP2A6 genotype and the metabolism and disposition kinetics ofi nicotine. *Clin. Pharmacol. Ther.* **80**, 457–467 (2006).
13. Malaiyandi, V., Sellers, E.M. & Tyndale, R.F. Implications ofi CYP2A6 genetic variation fior smoking behaviors and nicotine dependence. *Clin. Pharmacol. Ther.* **77**, 145–158 (2005).
14. Benowitz, N.L., Lessov-Schlaggar, C.N., Swan, G.E. & Jacob, P. III. Female sex and oral contraceptive use accelerate nicotine metabolism. *Clin. Pharmacol. Ther.* **79**, 480–488 (2006).
15. Institute ofi Medicine. The nature ofi nicotine addiction. In *Growing Up Tobacco Free—Preventing Nicotine Addiction in Children and Youths* (eds. Lynch, B.S., Bonnie, R.J.) 28–68 (National Academy Press, Washington DC, 1994).
16. Levin, E.D. *et al.* Adolescent vs. adult-onset nicotine selfi-administration in male rats: duration ofi efiect and difierential nicotinic receptor correlates. *Neurotoxicol. Teratol.* **29**, 458–465 (2007).
17. Department ofi Health and Human Services PHS. Tobacco use among U.S. racial/ethnic minority groups—Afirican Americans, American Indians and Alaska Natives, Asian Americans and Pacific Islanders, and Hispanics: a report ofi the surgeon general: USDHHS, Centers fior Disease Control and Prevention, National Center fior Chronic Disease Prevention and Promotion, Ofice ofi Smoking and Health. Government Printing Ofice, Washington DC, 1998.
18. Haiman, C.A. *et al.* Ethnic and racial difierences in the smoking-related risk ofi lung cancer. *N. Engl. J. Med.* **354**, 333–342 (2006).
19. Perez–Stable, E.J., Herrera, B., Jacob, P. III & Benowitz, N.L. Nicotine metabolism and intake in black and white smokers. *JAMA* **280**, 152–156 (1998).
20. Pletcher, M.J., Hulley, B.J., Houston, T., Kiefie, C.I., Benowitz, N. & Sidney, S. Menthol cigarettes, smoking cessation, atherosclerosis, and pulmonary fiunction: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Arch. Intern. Med.* **166**, 1915–1922 (2006).
21. Benowitz, N.L., Herrera, B. & Jacob, P. III. Mentholated cigarette smoking inhibits nicotine metabolism. *J. Pharmacol. Exp. Ther.* **310**, 1208–1215 (2004).
22. Benowitz, N.L., Perez-Stable, E.J., Herrera, B. & Jacob, P. III. Slower metabolism and reduced intake ofi nicotine firom cigarette smoking in Chinese-Americans. *J. Natl. Cancer Inst.* **94**, 108–115 (2002).
23. Grant, B.F., Hasin, D.S., Chou, S.P., Stinson, F.S. & Dawson, D.A. Nicotine dependence and psychiatric disorders in the United States: results firom the national epidemiologic survey on alcohol and related conditions. *Arch. Gen. Psychiatry* **61,** 1107–1115 (2004).
24. Lewis, A., Miller, J.H. & Lea, R.A. Monoamine oxidase and tobacco dependence. *Neurotoxicology* **28**, 182–195 (2007).
25. Fujieda, M. *et al.* Evaluation ofi CYP2A6 genetic polymorphisms as determinants ofi smoking behavior and tobacco-related lung cancer risk in male Japanese smokers. *Carcinogenesis* **25**, 2451–2458 (2004).
26. Lessov-Schlaggar, C.N., Pergadia, M.L., Khroyan, T.V. & Swan, G.E. Genetics ofi nicotine dependence and pharmacotherapy. *Biochem. Pharmacol.* **75**, 178–195, (2008).
27. Ho, M.K. & Tyndale, R.F. Overview ofi the pharmacogenomics ofi cigarette smoking. *Pharmacogenomics J.* **7**, 81–98 (2007).
28. Bierut, L.J. *et al.* Novel genes identified in a high-density genome wide association study fior nicotine dependence. *Hum. Mol. Genet.* **16**, 24–35 (2007).
29. Saccone, S.F. *et al.* Cholinergic nicotinic receptor genes implicated in a nicotine dependence association study targeting 348 candidate genes with 3713 SNPs. *Hum. Mol. Genet.* **16**, 36–49 (2007).
30. Uhl, G.R., Liu, Q.R., Drgon, T., Johnson, C., Walther, D. & Rose, J.E. Molecular genetics ofi nicotine dependence and abstinence: whole genome association using 520,000 SNPs. *BMC Genet.* **8**, 10 (2007).
31. Swan, G.E., Benowitz, N.L., Lessov, C.N., Jacob, P. III, Tyndale, R.F. & Wilhelmsen, K. Nicotine metabolism: the impact ofi CYP2A6 on estimates ofi additive genetic infiuence. *Pharmacogenet. Genomics* **15**, 115–125 (2005).
32. Institute ofi Medicine. *Clearing the Smoke. Assessing the Science Base for Tobacco Harm Reduction*. National Academy Press, Washington DC, 2001.
33. A clinical practice guideline fior treating tobacco use and dependence: A US Public Health Service report. The Tobacco Use and Dependence Clinical Practice Guideline Panel, Stafi, and Consortium Representatives. *JAMA* **283**, 3244–3254 (2000).
34. Rollema, H., Coe, J.W., Chambers, L.K., Hurst, R.S., Stahl, S.M. & Williams, K.E. Rationale, pharmacology and clinical eficacy ofi partial agonists ofi alpha4beta2 nACh receptors fior smoking cessation. *Trends Pharmacol. Sci.* **28**, 316–325 (2007).
35. Siu, E.C. & Tyndale, R.F. Non-nicotinic therapies fior smoking cessation. *Annu. Rev. Pharmacol. Toxicol.* **47**, 541–564 (2007).
36. Lerman, C. *et al.* Individualizing nicotine replacement therapy fior the treatment ofi tobacco dependence: a randomized trial. *Ann. Intern. Med.* **140**, 426–433 (2004).
37. Lee, A.M. *et al.* CYP2B6 genotype alters abstinence rates in a bupropion smoking cessation trial. *Biol. Psychiatry* **62**, 635–641 (2007).
38. Lerman, C. *et al.* Nicotine metabolite ratio predicts eficacy ofi transdermal nicotine fior smoking cessation. *Clin. Pharmacol. Ther.* **79**, 600–608 (2006).
39. Patterson, F. *et al.* Toward personalized therapy fior tobacco dependence: use ofi the nicotine metabolite ratio 2007. *Clin. Pharmacol. Ther.,* this issue.
40. Luo, J. *et al.* Oral use ofi Swedish moist snufi (snus) and risk fior cancer ofi the mouth, lung, and pancreas in male construction workers: a retrospective cohort study. *Lancet* **369**, 2015–2020 (2007).
41. England, L.J., Levine, R.J., Mills, J.L., Klebanofi, M.A., Yu, K.F. & Cnattingius, S. Adverse pregnancy outcomes in snufi users. *Am. J. Obstet. Gynecol.* **189**, 939–943 (2003).
42. Henley, S.J. *et al.* Tobacco-related disease mortality among men who switched firom cigarettes to spit tobacco. *Tob. Control* **16**, 22–28 (2007).
43. Batra, A., Klingler, K., Landfieldt, B., Friederich, H.M., Westin, A. & Danielsson,T. Smoking reduction treatment with 4-mg nicotine gum: a double-blind, randomized, placebo-controlled study. *Clin. Pharmacol. Ther.* **78**, 689–696 (2005).
44. Zeidler, R., Albermann, K. & Lang, S. Nicotine and apoptosis. *Apoptosis* **12**, 1927–1943 (2007).
45. Cooke, J.P. & Bitterman, H. Nicotine and angiogenesis: a new paradigm fior tobacco-related diseases. *Ann. Med.* **36**, 33–40 (2004).
46. Institute ofi Medicine. *Ending the Tobacco Problem. A Blueprint for the Nation.* (National Academy Press, Washington DC, 2007).
47. Benowitz, N.L. & Henningfield, J.E. Establishing a nicotine threshold fior addiction. *N. Engl. J. Med.* **331**, 123–125 (1994).
48. Henningfield, J.E., Benowitz, N.L., Slade, J., Houston, T.P., Davis, R.M. & Deitchman, S.D. Reducing the addictiveness ofi cigarettes. *Tob. Control* **7**, 281–293 (1998).
49. Benowitz, N.L. *et al.* Carcinogen exposure during short-term switching firom regular to "light" cigarettes. *Cancer Epidemiol. Biomarkers Prev.* **14**, 1376–1383 (2005).
50. Benowitz, N.L., Hall, S.M., Stewart, S., Wilson, M., Dempsey, D. & Jacob, P. III Nicotine and carcinogen exposure with smoking ofi progressively reduced nicotine content cigarette. *Cancer Epidemiol. Biomarkers Prev.* **16**, 2479–2485 (2007).
51. Tengs, T.O., Ahmad, S., Savage, J.M., Moore, R. & Gage, E. The AMA proposal to mandate nicotine reduction in cigarettes: a simulation ofi the population health impacts. *Prev. Med.* **40**, 170–180 (2005).