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THERAPEUTICS FOR NICOTINE ADDICTION

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About 25% of adults in the United States smoke tobacco cigarettes. Most continue smoking because they are addicted to nicotine. That nicotine is central to maintaining tobacco use is well established (49). When asked, 70% of cigarette smokers report that they would like to quit. Each year, less than 1% will actually succeed without any therapeutic interventions. Few other conditions in medicine present nicotine addiction's mix of lethality, prevalence, cost, and relative therapeutic neglect, despite effective and readily available treatment interventions. Health care providers too often fail to assess or treat tobacco addiction despite substantial evidence that even brief therapeutic interventions are effective (2).

Worldwide potential benefits of prevention and adequate treatment are staggering (96). More than 1.2 billion people regularly smoke tobacco. During the twentieth century, only approximately 0.1 billion people died of tobacco use–related illnesses. If current smoking patterns continue, 1 billion additional people will die of smoking-related illness during this century. Half will die during middle age. About 4 million people died of tobacco-related disease in 1998. Projections indicate 10 million tobacco-related deaths yearly by the year 2030, with 70% of those deaths in developing countries. Reducing the number of current smokers by 50% would avoid 25 million premature deaths in the first quarter of this century and about 150 million more by midcentury (96).

Understanding the role of nicotine in sustaining tobacco addiction offers a basis for optimal and rational treatments for preventing or stopping smoking (49). Nicotine addiction has much in common with other addictions, so consideration of therapeutics should help in development of therapies for less common addictions to stimulants such as cocaine and amphetamines or to other drugs. Nicotine addiction resulting from tobacco cigarette smoking is emphasized. Other routes for nicotine delivery, chewing tobacco, buccal and nasal snuff, and smoked pipes and cigars, deliver substantial amounts of nicotine but with different pharmacokinetics, although the pharmacology is otherwise similar. Nicotine is addicting when it is delivered by any route, but special attributes and the ubiquity of cigarette delivery systems warrant special attention.

WHY DO PEOPLE SMOKE?

Although the pharmacologic effects of nicotine are essential to sustaining tobacco smoking, the beginnings of tobacco addiction result from nonpharmacologic learned or conditioned factors, social settings, personality, and genetics (4). Taking nicotine enhances an addicted smoker's mood and performance. Nicotine is rewarding. Smoking is an extremely effective way of rapidly and conveniently delivering concentrated doses of nicotine to the brain (4,5). Nicotine smokers appear able to discriminate small, rewarding effects from each individual puff and to titrate nicotine dose from each cigarette. From the typical 10 puffs per cigarette, a one pack-per-day smoker receives 73,000 distinct drug reinforcements per year. Although nicotine can enhance mood directly, what is even more important for understanding nicotine addiction therapeutics is that when nicotine is taken by an addicted smoker, the negative consequences of prior nicotine use are diminished. A nicotine withdrawal syndrome is relieved (4).

Most smokers say they want to stop smoking (2,13). Most adults have made several attempts to quit and require four or more attempts before quitting permanently. Relapse typically occurs because of disrupted emotional state, work performance, enjoyment of leisure activities, and interpersonal relationships. Life-threatening smoking-related illness should motivate one to quit, yet 50% of smokers after a

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myocardial infarction continue to smoke (13,49). Smokers with lung or throat cancer or those suffering from chronic obstructive lung disease behave similarly.

Tobacco-taking behavior is made more likely to recur, reinforced by the pharmacologic actions of nicotine (49). With each successive cigarette, a beginning smoker, usually an adolescent, learns to associate certain moods, situations, and environmental factors with the rewarding effects of nicotine. Associations between cues associated with smoking, anticipated nicotine effects and the resulting urge to use tobacco (craving) become all important in maintaining smoking.

Smoking is more likely in certain situations: after a meal, with coffee or alcohol, and with friends who smoke (49). Associations between events and smoking repeated thousands of times make for powerful cues facilitating an urge to smoke. Manipulation of smoking paraphernalia, taste, smell, and sensations from smoke in upper airways become associated with pleasurable effects. Unpleasant or dysphoric moods come to serve as conditioned cues for smoking. For example, an adolescent smoker, usually within the first year of smoking, learns that not having a cigarette available is associated with feelings of irritability and learns that just a few puffs from a cigarette diminish irritability and other dysphoric nicotine withdrawal symptoms. After hundreds of repeated experiences, irritability from any source serves as a cue for smoking.

Left to nature, it is unlikely that many people would make or find a cigarette, light it, and smoke it (49). Conditioning and learning linking nicotine pharmacology and environmental contingencies are facilitated by advertising encouraging, often in subtle ways, the use of tobacco. In the beginning, teenage smokers teach each other. Quickly, links between the pharmacologic actions of nicotine and associated behaviors become powerful (7). Conditioning loses its power only gradually without nicotine delivered in the right dose and context. Conditioning is a major factor in relapse to nicotine use after quitting. Dealing with it is important in any therapeutics for nicotine addiction.

Many smokers report that smoking improves concentration and elevates mood. Cigarette smoking or nicotine administration improves attention, reaction time, and problem-solving, particularly in recently abstinent smokers (55, 74). Smokers typically report enhanced pleasure and reduced anger, tension, depression, and stress after a cigarette. Whether enhanced performance and improved mood after smoking are mostly or entirely the result of the relief of abstinence symptoms or rather are intrinsic effects of nicotine on the brain remains unclear (49). Improvement in the performance of nonsmokers after nicotine suggests at least some direct enhancement (8).

NICOTINE PHARMACOKINETICS AND METABOLISM

Some special attributes of smoked nicotine delivery are important for understanding mechanisms and therapeutics of tobacco addiction (5,49). Nicotine, a tertiary amine structurally similar to acetylcholine, binds to nicotinic cholinergic receptors in the brain and elsewhere. During smoking nicotine, steam distilled from the burning tobacco is inhaled into the small airways and alveoli on small droplets of tar, buffered to a physiologic pH, absorbed rapidly into the pulmonary capillaries, and thence into systemic arterial blood. Initial arterial blood levels of nicotine are two to six times greater than venous levels (11). Within 10 to 20 seconds after each puff, relatively high levels of nicotine reach the brain. Nicotine levels in plasma and in brain tissue then decline rapidly because of rapid distribution into peripheral tissues.

During a typical smoker's day, peak and trough plasma and brain nicotine levels vary considerably before and after each cigarette, but nicotine gradually accumulates over 6 to 8 hours of repeated smoking because of nicotine's 2-hour half-life (5). By midafternoon, relatively constant, steady-state, venous plasma levels, 20 to 40 ng/mL, are reached, but with transient 50-ng/mL increments in arterial and brain levels after each cigarette. During sleep, plasma concentration of nicotine falls progressively but is still measurable on awakening when the first cigarette of the next day is smoked, typically within 30 minutes of awakening. Thus, smoking results in exposure of brain to nicotine 24 hours of each day but with regular brain level perturbations after each puff and each cigarette (5,12).

Smokers regulate smoked nicotine intake to maintain their preferred range of concentrations by varying puff and inhalation timing, volume, and number (49). Nicotine intake and resulting plasma levels vary. Smokers can compensate for differing machine-determined nicotine yields to obtain a preferred dose of nicotine whether smoking a high- or low-yield brand (39). Nicotine delivered by cigarettes offers smokers individualized control of nicotine dose unattainable by other nicotine delivery systems (49). The special attributes of smoked nicotine dosimetry are relevant when designing animal experiments to model human tobacco dependence properly (53) and when considering nicotine replacement therapies (NRTs). In contrast to smoking, chewing tobacco and snuff deliver nicotine through oral or nasal mucosa. Plasma and brain nicotine concentrations rise more gradually, reach plateau levels after about 30 minutes, and then decline slowly over the next few hours (5).

NICOTINE RECEPTOR–BASED NEURAL MECHANISMS RELEVANT TO THERAPEUTICS

Nicotine binds stereoselectively to a diverse family of nicotinic cholinergic receptors widely distributed in brain, autonomic ganglia, adrenal medulla, and neuromuscular junctions (15,16). Nicotine's effects on nicotinic cholinergic receptors in the brain enhance release of an array of neurotransmitters; dopamine, norepinephrine, acetylcholine, se-

rotonin, vasopressin, β-endorphin, glutamate, γ-aminobutyric acid, and others (12,49). Nicotinic cholinergic receptors have varied functional characteristics, different chemical conductances for sodium and calcium, and variable sensitivity to different nicotinic agonists (17,92). Receptor diversity probably accounts for the diverse effects of nicotine experienced by smokers (19). The undoubtedly complex relationships between specific nicotinic cholinergic receptor subtypes and release of specific neurotransmitters are still to be fully characterized (92). Neurotransmitter release is assumed to mediate nicotine effects such as arousal, relaxation, cognitive enhancement, relief of stress, and depression.

A brain nicotinic cholinergic receptor is a ligand-gated ion channel, with five subunits. Most brain nicotinic cholinergic receptors are composed of α and β subunits. The α subunits are responsible for ligand binding. The β subunits mediate other aspects of receptor function (29). The nicotinic cholinergic receptor, consisting of α-4 and β-2 subunits, accounts for 90% of high-affinity nicotine binding in rat brain and may play a critical role in stimulant and rewarding effects (21). The β-2 subunit is critical for dopamine release, judging from studies of knockout mice lacking that subunit who have less nicotine-induced dopamine release and do not self-administer nicotine as do wild-type mice (76).

When nicotine binds to nicotine receptors, allosteric changes lead to different functional states including a resting state, an activated state (channel open), and two desensitized states (channel closed) (10). Receptor change to the desensitized state probably accounts for tolerance and for the observation that tolerance to nicotine is associated with increased numbers of nicotinic cholinergic receptors in animals during chronic nicotine treatment and in brains of human smokers (24–27).

Nicotine's effects on brain dopaminergic and noradrenergic systems are important in reinforcing self-administration (49). The mesolimbic dopamine system is assumed to mediate pleasurable and other rewards from nicotine as with other drugs of abuse. Nicotinic receptors are on the nerve terminal membranes in the nucleus accumbens and on membranes of the dopamine-secreting neurons innervating nucleus accumbens located in the midbrain. Unlike cocaine and amphetamine, which exert effects by binding to presynaptic dopamine transporters on nerve terminal membranes, nicotine's effects depend more on modulating the flow of impulses to the terminal field (17). As happens after repeated exposure to other stimulants, repeated exposure to nicotine results in sensitization of its effects on dopamine release in the accumbens. There appears to be co-stimulation of *N*-methyl-D-aspartate (NMDA) receptors for glutamate because the development and the expression of the sensitized dopamine response is attenuated or blocked by the administration of NMDA-receptor antagonists. In this respect, some consequences of repeated nicotine exposure on these pathways are similar to those of other stimulant drugs. The consequences of nicotine's modulating effects on multiple neuronal systems remains to be determined (49).

Sustained exposure to nicotine desensitizes some but not all nicotinic cholinergic receptors and results in a state in which nicotine is needed to maintain normal neurotransmission. As nicotine levels decrease, diminished neurotransmitter release or altered modulation of neurotransmitter systems (17) contributes to a relative deficiency state and in humans, symptoms of lethargy, irritability, restlessness, inability to concentrate, depressed mood, and other symptoms making up the nicotine withdrawal syndrome. Plasma concentrations of nicotine in smokers are sufficient to desensitize mesolimbic dopamine neuron nicotinic receptors reinforcing nicotine self-administration. Thus, self-administration of eight to ten nicotine bolus doses (puffs) during the smoking of each cigarette would cause gradually decreasing dopamine release in the nucleus accumbens. With each successive cigarette and gradually rising levels of brain nicotine, desensitization would increase. If so, tobacco smokers continue to smoke during the latter half of each smoking day under conditions in which nicotine is less likely to stimulate neurotransmitter release than while smoking the first cigarettes of the day. Thus, other mechanisms likely contribute to the rewarding properties of nicotine in the latter portion of the daily cycle of smoking (49).

Nicotine increases or decreases brain serotonin levels, depending on concentration and pattern of exposure (16). A possible role for serotonin release in reward mechanisms is suggested by selective serotonin ($5\text{-}HT_3$) antagonists that reduce nicotine reinforcing effects. Chronic exposure to nicotine results in reduced capacity to synthesize 5-HT in serotonergic terminals. Postmortem human studies indicate that tobacco smoking is associated with reductions in hippocampal 5-HT and 5-hydroxyindole acetic acid (16). Functional consequences of the nicotine-induced changes in 5-HT remain to be established but could partially explain anxiety reduction commonly reported by smokers. Increased 5-HT release could result in anxiety and related symptoms common during the early stages of nicotine withdrawal (49).

Nicotine-mediated release of norepinephrine plays a role in the release of adrenocorticotropic hormone (ACTH) and cortisol. Nicotine, acting on α-7 cholinergic receptors, releases glutamate, enhances fast excitatory synaptic transmission possibly contributing to improved learning and memory (28,36), and regulates dopaminergic function. Activation of the locus ceruleus produces behavioral arousal with nicotine-increased burst firing an adaptive reaction to stressful situations (49). Activation of nicotinic cholinergic receptors in the adrenal medulla releases epinephrine and perhaps β-endorphin, a factor contributing to nicotine's systemic actions (12).

In addition to brain receptor-mediated effects, nicotine activates afferent nerves, an effect possibly accounting for the importance of sensory phenomena in cigarette smoking satisfaction and important in shaping conditioned aspects of smoking behaviors. For example, intravenous nicotine

produces burst firing of locus ceruleus neurons before injected nicotine reaches the brain (47). After an initial rapid onset, brief activation that can be blocked by a peripheral nicotine antagonist, a second longer-lasting activation, mediated by central nicotinic receptors, occurs (31).

NATURAL HISTORY OF NICOTINE DEPENDENCE

Most nicotine addicts begin smoking during adolescence. Adolescent smoking has been increasing since the 1990s. In the United States, about 3 million adolescents smoke. Each day, 6,000 more begin. Most perceive themselves to be dependent on nicotine within their first year of smoking. Adolescent daily smokers appear to inhale doses of nicotine similar to doses inhaled by adults. When asked, about 50% report wanting to quit, and 71% report having tried and failed (49). Adolescents report withdrawal symptoms similar to those reported by adults (32).

Without treatment interventions, smoking quitting rates in adolescent smokers in the United States are comparable to those of addicted adult smokers. Young, still experimenting smokers are likely to become regular smokers; however, the proportion of adolescents who go on to regular smoking and what influences the progression remain obscure. The first symptoms of nicotine dependence occur within weeks of the onset of occasional use, often before daily smoking begins (7). As many as one-third to one-half of adolescents experimenting with cigarettes become regular smokers.

Interventions to prevent progression to tobacco addiction in adolescents are less effective than in adult smokers (33). Adolescents have less interest in treatment, high treatment dropout rates, and low quitting rates (20). Reviews of adolescent tobacco smoking conclude that better characterization of nicotine dependence (35) and assessment of pharmacotherapies are needed, given the almost epidemic proportions of smoking in adolescents.

RISK FACTORS

Comorbidity

Some smokers report that smoking helps relieve their depression and other mood disorders. Others become severely depressed when they stop smoking (16,52). Smokers are more likely to have experienced major depression, and those who have are less likely to quit smoking (37). Several mechanisms may link smoking and depression (16). Depression sensitizes patients to the dysphoric effects of stressful stimuli. Smokers exposed to stressful stimuli become conditioned to nicotine's diminishing of the adverse effects. Nicotine-related decreases in 5-HT formation and release in the hippocampus could be a factor. Stopping addicting drugs, including tobacco, has been hypothesized to result in a negative affect state with dysphoria, malaise, and inability to experience pleasure that has been termed *hedonic dysregulation* (84). Smokers may be protected from such consequences by the antidepressant properties of nicotine.

Consistent with a notion that nicotine may be self-administered by some smokers to manage affective disorders is an uncontrolled study reporting that transdermal nicotine lessened depression in nonsmokers with major depression (56). Another intriguing connection is that cigarette smoking inhibits activity of brain monoamine oxidase (MAO) A and B as measured in the brains of smokers and nonsmokers by positron emission tomography using MAO ligands (40,41). Smokers have a 30% to 40% suppression of brain MAO A and B activity. Medications that inhibit MAO sometimes have antidepressant activity. Conceivably, cigarette smoking could have similar effects. Finally, some researchers suggest that links between depression and cigarette smoking result from a common genetic predisposition (42).

Schizophrenia is a risk factor for nicotine addiction; approximately 80% of patients with schizophrenia smoke (43). An abnormality in neuronal nicotinic acetylcholine receptor expression or function may be involved in the neuropathophysiology of schizophrenia. Nonschizophrenic smokers have increased nicotinic receptor binding in postmortem brain hippocampus, cortex, and caudate with increasing tobacco use. In contrast, schizophrenic smokers have reduced nicotinic receptor levels, a finding suggesting abnormal regulation of high-affinity neuronal nicotinic receptors after nicotine use (43). One theory linking schizophrenia and susceptibility to nicotine addiction comes from observations that schizophrenic patients often have abnormalities in auditory sensory gating. Sensory gating is mediated by functions of the α-7 nicotinic cholinergic receptor (44). Cigarette smoking and nicotine improve abnormal sensory gating in humans and animals. The abnormality of sensory gating in schizophrenia has been linked to the gene also encoding the α-7 subunit (45).

Dependence on alcohol, heroin, cocaine, and other drugs frequently coexists with nicotine addiction (4). Alcohol and nicotine addiction have common heritability (46,60). Stimulant drug exposure may cross-sensitize to neurochemical effects of other stimulants, so nicotine and other stimulants enhance the effects of one another (14,48). Because all addicting drugs release dopamine in the mesolimbic system, drugs may be interacting or substituting for one another to produce common changes in dopamine-related reinforcement.

Genetics

Nicotine addiction involves multiple genetic and environmental factors (50,51). Genetic factors account for a significant proportion in the variation in the use of tobacco in twin studies, with heritabilities estimated to be as high as

84% and 82% for liability to lifetime and current tobacco use, respectively (9), influencing both initiation and maintenance of tobacco smoking (60). Another twin pair study (51) reported a similar pattern, with genetic factors appearing more important than environment (78% versus 22%) in smoking initiation and in development of dependence (72% versus 28%). Genetic factors also appeared important for the appearance of alcohol dependence (55% versus 45%), consistent with a common genetic vulnerability and showing that nicotine and alcohol dependence occur together (60). Environmental factors more strongly determined age of first use of tobacco and alcohol, whereas latency between first use and patterns of regular use were more genetically determined (54). A major genetic influence accounting for about 70% of the variance in risk in a group of Vietnam era twin pairs is consistent with other studies suggesting that heritable traits such as sensitivity to nicotine are relevant to smoking prevention and treatment (18).

Genetically determined dopamine receptor functional differences and genetic variation in hepatic enzyme activity important in metabolizing nicotine suggest possible mechanisms. Individuals with TaqIA alleles (A1 and A2) and TaqIB (B1 and B2) of the D2 dopamine receptor gene had earlier onset of smoking, smoked more, and made fewer attempts to quit (58). Specific gene mutations, including those associated with dopamine D2 receptors (23) and dopamine transporter proteins (95), have been implicated as possible determinants for nicotine addiction. People lacking a fully functional genetically variable enzyme CYP2A6 important in the metabolism of nicotine to cotinine are slow nicotine metabolizers (30). This genotype may be important in protecting against tobacco dependence because of impaired nicotine metabolism and may be important as well in determining dose and response to NRTs.

Tobacco and Nicotine Exposure During Pregnancy

In the United States, about 25% of pregnant women smoke cigarettes, and so each year about 1 million babies are exposed *in utero* to tobacco smoke (89). That so many pregnant women smoke has important implications both for the determinants of tobacco addiction and its therapeutics. Tobacco smoking has long been known to present considerable fetal risks (59). Less well appreciated is that nicotine itself is a neuroteratogen (89). Nicotine given to rats during gestation or adolescence at levels assumed to be consistent with those in human smokers alters gene expression and produces long-lasting central nervous system cellular damage, by reducing cell number and impairing synaptic activity and cell signaling (62). Developing brain cells appear particularly vulnerable. In adult rats, similar exposure stimulates nicotinic cholinergic receptors without lasting cellular changes. Some of nicotine's effects on cell numbers continue post partum, well after termination of nicotine exposure. The alterations in synaptic function plausibly would account for associated behavioral disruptions evident in humans (98) and in animal models (1,62,89).

Nicotine doses that do not produce growth retardation still produce central nervous system cell damage, loss, and synaptic dysfunction. The fetal effects of nicotine may be greater during the later stages of pregnancy, a finding suggesting the first trimester is the most desirable period for NRT during pregnancy. Based on the rat data, it may be preferable to introduce NRTs early in pregnancy to try to reduce the fetal exposure to nicotine before the second or third trimester. In the rat models, episodic nicotine delivery, as happens with smoking, is associated with less nicotine exposure to the fetus than continuous exposure from a nicotine patch. Of course, fetal exposure to tobacco smoke presents a host of other toxins besides nicotine.

Maternal smoking during pregnancy has long-term behavioral consequences in humans (89,98). Cognitive deficits, behavioral problems in childhood, particularly attention-deficit/hyperactivity disorders, conduct disorders, and substance abuse in the exposed children are associated with maternal smoking. Children whose mothers smoked ten or more cigarettes daily during pregnancy had a fourfold increased risk of prepubertal-onset conduct disorder in boys and a fivefold risk in adolescent-onset drug dependence in girls (98). The outcomes are not explained by other risk factors. Maternal prenatal smoking appeared to be related to future criminal behavior in male children, with a dose–response relationship between intensity of third trimester smoking and arrest history of 34-year-old men whose mothers smoked during pregnancy (63). Although such studies are limited by retrospective maternal reports of smoking behaviors during pregnancy, there is a consistency with outcomes in studies directly assessing maternal smoking.

MANAGEMENT AND THERAPEUTICS OF NICOTINE ADDICTION

Ideally, therapeutics for nicotine addiction should be available for the 80% of the world's smokers who live in low- and middle-income countries. Within those countries, smokers have the lowest income, are the least educated, and have the poorest access to health care. Thus, from a world view, cost of therapeutics and access become important considerations. Prevention is obviously an important strategy, but strategies to prevent tobacco addiction must deal with a politically powerful and wealthy multinational industry promoting use of tobacco (64). The tobacco industry in the United States alone spent 6 billion dollars in 1998 to market cigarettes, about 18 million dollars each day. More is spent promoting tobacco use elsewhere in the world. Although successful prevention strategies exist (65), well-funded competition encouraging tobacco use will remain (64).

More intensive therapeutics typically include behavioral interventions combined with NRT delivered over a series of sessions. Individual or group behavioral treatments appear almost equally effective. Intensive treatment programs are effective in assisting even very dependent smokers to stop for a few months. However, as with other addictions, relapse is a major problem. Initial quitting rates of 50% to 60% at 1 month typically decrease to 20% to 30% at 1 year. Various relapse-prevention procedures have been tried. None has proven clearly effective. Most tobacco addicts repeat the quitting process on average every 3.5 years and try three or four times before finally stopping forever (66). In that respect, stopping smoking is similar to overcoming addictions to other psychoactive drugs. Tobacco addiction treatment programs are cost-effective. Average treatment costs per year of life saved are $1,000 to $2,000 per year for brief counseling alone and $2,000 to $4,000 per year of life saved with more intensive counseling and pharmacotherapy to aid in smoking cessation (34,67). Smoking cessation treatments are less costly per year of life saved than are generally accepted therapies for hypertension, hypercholesterolemia, and other chronic disorders.

Therapeutics: Clinical Guidelines

Guidelines for treating tobacco dependence were published in 2000 by the United States Public Health Service (2,13). The detailed report resulted from critical review of approximately 6,000 peer-reviewed articles on tobacco addiction therapeutics and 50 metaanalyses based on that literature (69).

The major general conclusions were as follows:

1. Tobacco dependence is a chronic condition warranting repeated treatment until abstinence is achieved.
2. Effective treatments for tobacco dependence exist. All tobacco users should be offered treatment.
3. Clinicians and health care systems must institutionalize consistent identification, documentation, and treatment of every tobacco user at every visit.
4. Brief tobacco dependence treatment is effective. Every tobacco user should be offered at least brief treatment.
5. There is a strong relationship between the intensity of tobacco dependence counseling and effectiveness.
6. Three types of counseling are especially effective: practical counseling, social support as a part of treatment, and social support outside of treatment.
7. Five pharmacotherapies for tobacco dependence are effective: nicotine gum, nicotine inhaler, nicotine nasal spray, nicotine patch, and bupropion. At least one of these medications should be prescribed in the absence of contraindications.
8. Tobacco dependence treatments are cost-effective when compared with other medical and disease prevention interventions. Health insurance plans should include as a benefit the counseling and pharmacotherapies identified as effective in the guideline (2).

Contemporaneous reviews of tobacco addiction therapeutics (59,70–73) and an extensive report on tobacco addiction pharmacology and therapeutics from the Royal College of Physicians (49) offered similar conclusions. A summary review from the Cochrane Tobacco Addiction Review Group identified and summarized evidence of efficacy for tobacco addiction therapeutics (91). Details of the 20 systematic reviews are available on the Internet in the Cochrane Library (75). The reviews used a similar strategy and reviewed much the same literature on tobacco addiction therapeutics as did the Public Health Service review.

The Cochrane reviews considered the results from randomized controlled trials having at least 6 months of follow-up (91). Sustained abstinence or point prevalence quit rates were used in the metaanalysis as necessary. Simple advice from physicians presented during routine care was studied in 31 trials that included 26,000 smokers in a variety of clinical settings. Brief advice increased quit rate more than no advice (odds ratio, 1.69; 95% confidence interval, 1.5 to 1.98). Individual counseling was better than brief advice or usual care. Group therapy was more effective than self-help materials alone but not consistently better than interventions with more personal contact. Self-help informational material and printed descriptions of behavioral strategies had a small treatment effect (75,91).

Nicotine Replacement Therapeutics

NRT decreases the discomfort of nicotine withdrawal. The relatively stable brain nicotine levels resulting from NRT should facilitate a desensitized state for some nicotinic cholinergic receptors. Because some nicotinic receptor subtypes are more desensitized than others, both nicotine agonistic and desensitization mechanisms could operate together in NRT. In a nicotine-induced desensitized state, norepinephrine release normally stimulated by endogenous acetylcholine would be diminished. Other neurotransmitter release normally stimulated by endogenous acetylcholine could be diminished as well. The resulting NRT modulation of mood states in itself could be rewarding. In addition, some blunting of the reinforcing effects of cigarettes smoked during cessation lapses is likely during NRT. However, the mechanisms of NRT still remain uncertain because the intensity of withdrawal alone is not a good predictor of success for ultimately stopping smoking (3). Even though withdrawal symptoms can be diminished by NRT, other mechanisms, learning coping skills, and replacing some of the positive effects of nicotine are important as well. Whatever the mechanisms, NRT is clearly effective and safe for helping smokers to quit (70).

The Cochrane review of clinical trials with nicotine gum, transdermal nicotine patches, nasal spray, and inhalers con-

cluded that NRT enhanced early cessation and reduced early relapse when compared with placebo (75,91). All products enhanced quitting smoking about twofold. Quitting rates, depending on intensity of concurrent behavioral interventions, ranged from 10% to 30% of patients with a 1-year follow-up. Higher nicotine doses were more effective, although the dose–response function is shallow. NRT did not appear to have significant dependence potential or to cause significant harm (70). Characteristics of long-term NRT users resembled those of treatment failures. It appeared many would be smoking or smoking more if NRT were not available.

However, 70% to 90% of addicted smokers fail to stop smoking despite NRT. Why (77)? Most studies included only nicotine-addicted smokers, so the usefulness of NRT for less addicted smokers remains uncertain. Although recommendations have been made for use of combinations of NRT products, for example, patch plus spray, patch plus gum, or higher-dose NRT, too few trials preclude clear evidence of effectiveness. Long-term reduction in smoking by concomitant use of NRT while smoking continues is being investigated (78). Nicotine inhalers and skin patches have been used safely and with sustained reduction in smoking for up to 30 months (79,80).

Particularly for highly dependent smokers, nicotine replacement from patches and gum probably delivers nicotine to the brain too gradually and without the transient but rewarding brief surges in brain nicotine levels from puffing on a cigarette (5,19). Nicotine nasal sprays or inhalers more closely approximate smoking in this respect, but only partially so, and clinically they do not offer advantages to patch failures (77). An inhaled nicotine aerosol would, in principle, be an ideal substitute nicotine delivery system, but despite many attempts, a practical inhaled aerosol system providing the control over dose offered by a tobacco cigarette has not been brought to market.

Non–Nicotine Replacement Pharmacotherapies

The consequences of neuroadaptive changes in brain function associated with chronic nicotine exposure should, in principle, be modified by appropriate neurochemical interventions (71,81,82). Pharmacotherapies mimicking nicotine's neurochemical effects by increasing or modulating brain levels of dopamine, epinephrine, serotonin, and other neurotransmitters should correct the neurochemical deficiency states associated with nicotine withdrawal. Pharmacotherapies may also mimic some of nicotine's actions on brain reward systems. Nicotinic receptor antagonism offers an additional strategy. Although treatment with anxiolytics did not improve outcome, antidepressants, bupropion, and nortriptyline increased quit rates (2,83,91). The mechanisms by which antidepressant drugs benefit smoking cessation are yet to be determined. The neurochemical consequences of chronic nicotine exposure have similarities to the effects of some antidepressants (16,52,84).

Bupropion

As with many pharmacotherapies, recognition that bupropion could be useful for treating tobacco addiction resulted from serendipitous observations. Smokers being treated with bupropion for depression reported less desire to smoke or greater success in stopping smoking. Bupropion is structurally related to phenethylamines resembling an anorectic drug diethylproprion and is believed to assist smoking cessation by blocking neuronal uptake of dopamine and norepinephrine and possibly by decreasing firing of the locus ceruleus (71). Bupropion and some other antidepressants functionally antagonize some nicotinic cholinergic receptors in muscle and autonomic ganglia and reduce receptor response to nicotine (85). Whether antidepressant drugs similarly antagonize brain nicotine receptors is undetermined.

Bupropion was effective judging from two large trials and two smaller unpublished ones (86). Bupropion alone or combined with a nicotine patch was more effective than the patch alone (87). Although the drug caused dry mouth and insomnia, serious side effects were uncommon. Bupropion was as effective in patients with a history of depression as with those without such a history (88). When given to a group of smokers not trying to quit permanently, bupropion decreased some withdrawal symptoms but had no effect on craving (86). Bupropion was a more cost-effective therapeutic agent for tobacco addiction than NRT (68).

Other Therapies With and Without Utility

Clonidine shares some pharmacologic effects of bupropion and tricyclic antidepressants. The Cochrane review of six clinical trials of clonidine found increased smoking quit rates, but side effects of sedation and postural hypotension posed problems for many patients (75,91).

Sensory stimulants mimic mouth and airway sensory responses to smoking that become associated with the pharmacologic effects of nicotine and thus become reinforcers. Ascorbic acid aerosols and citric acid inhalers evaluated in cessation trials reduce craving and some withdrawal symptoms over the short term (71).

The effects of opiate antagonists on cigarette smoking have been studied to examine how opioid systems modulate smoking behavior and to determine whether opioid antagonists could be useful to aid in smoking cessation (22). Naloxone precipitates opiate withdrawal-like symptoms and increases desire to smoke (38). The effects of naloxone or naltrexone on *ad libitum* smoking over brief periods in a laboratory were inconsistent, but some smokers smoked less. A clinical trial compared naltrexone, 50 mg daily for 12 weeks, or placebo, with or without transdermal nicotine (61). Only transdermal nicotine increased abstinence rates.

Naltrexone had no effect on cessation rates. Transdermal nicotine reduced craving and cigarette smoking in smokers who did not quit. Naltrexone had no such effects. Another 4-week trial of naltrexone or placebo found no difference in smoking 6 months later (93). Thus, the clinical trial data indicate no useful role for opioid antagonists in smoking cessation therapy despite the suggestive laboratory results.

Nicotinic receptor antagonism offers another possible strategy. A nicotine antagonist mecamylamine has been investigated as a cessation aid both alone and in combination with NRT (59,71). Mecamylamine started before quitting smoking and continued afterwards appeared useful in two studies (94). Combined use of mecamylamine and nicotine patch increased quit rate more than nicotine alone, a finding leading to consideration of mecamylamine blockade of nicotine's rewarding effects (97).

Circulating antibodies binding nicotine in blood and preventing its reaching the brain would be functionally equivalent to a receptor antagonist's preventing nicotine receptor access. Antibodies have been induced by immunization of rats with nicotine linked to an immunogen (68). Immunized animals had reduced brain nicotine concentrations and reduced behavioral and cardiovascular effects after intravenous nicotine (68). Whether immunization alters the reinforcing effects of nicotine remains to be determined.

Lobeline, a nonpyridine alkaloid and partial nicotine receptor agonist from the Indian tobacco plant *(Lobelia inflata),* has long been used in proprietary smoking treatments (59,71). Although no longer marketed in the United States, lobeline is available elsewhere. No clinical trials had more than a 6-month follow-up. The drug was judged unproven by the Cochrane review (75,91).

ACTH has been suggested to aid smoking cessation, based on the notion that nicotine increases ACTH and cortisol release and that during nicotine withdrawal, there may be a state of hypoadrenocorticism. Uncontrolled trials with small numbers of smokers given a few ACTH injections during the first week after quitting reported high quit rates or decreased smoking, but without controlled clinical trials, ACTH must still be considered unproven (71).

Silver acetate has long been available as an over-the-counter smoking deterrent in the form of chewing gum, lozenges, and spray. A reaction with cigarette smoke produces an unpleasant metallic taste, the basis for this aversive therapy. Several clinical trials reported short-term efficacy, particularly in less addicted smokers (71). Whenever the urge to smoke is great, it is easy to stop silver acetate use, so it does not appear an effective therapeutic for severe nicotine addiction.

The effectiveness of other aversion therapies, acupuncture, hypnotherapy, and exercise was at best considered uncertain (75,91).

FUTURE RESEARCH

As nicotinic cholinergic receptor subtype–specific agonists and antagonists are developed, more specific treatments for nicotine addiction in subtypes of smokers should result (49). Possibly, medications useful for treating affective disorders, schizophrenia, Alzheimer disease, and other brain disorders may result as well from such research. (15,16,43).

Adolescent smoking initiation rates remain high (49). Beginning smoking among young adults is common (90) and is perhaps increasing (57). Although we understand much about nicotine addiction (2), we still do not know enough to prevent people from becoming addicted or how best to treat highly dependent tobacco users (77).

Research on vulnerability to nicotine addiction should include linking of phenotypes of nicotine response and other aspects of tobacco dependence to genotypes related to specific receptors and other proteins involved in nicotine addiction (49). Study of the mechanisms of nicotine reinforcing effects in people with affective disorders (16), schizophrenia (43), and other drug dependence is important. Study of hormonal and psychosocial mechanisms will help us to understand gender differences in nicotine addiction (99). Longitudinal studies of children of mothers who smoke, with better measures of smoke exposure *in utero* and assessments of behavior through childhood, will better define the natural history of nicotine addiction and will lead to better strategies for prevention and cessation interventions (1,49,62,89,98).

CONCLUSION

Research since the early 1980s has expanded our understanding of nicotine addiction. Now the challenge is to translate knowledge of the biology of nicotine addiction into pharmacotherapies and other therapeutics addressing individual differences in addicted smokers. To do so will require the development of new drugs, better understanding of existing ones, and wisdom needed to match optimal therapies to individual smokers. Much the same could be said about therapeutics for all drug addictions.

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