NICOTINE IN PSYCHIATRY
Psychopathology and Emerging Therapeutics

Edited by Melissa Piasecki, M.D. Paul A. Newhouse, M.D.
NICOTINE IN PSYCHIATRY

Psychopathology and Emerging Therapeutics
CLINICAL PRACTICE

Judith H. Gold, M.D., F.R.C.P.C.
Elissa P. Benedek, M.D.
Series Editors
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Melissa Piasecki, M.D.
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Note: The authors have worked to ensure that all information in this book concerning drug dosages, schedules, and routes of administration is accurate as of the time of publication and consistent with standards set by the U.S. Food and Drug Administration and the general medical community. As medical research and practice advance, however, therapeutic standards may change. For this reason and because human and mechanical errors sometimes occur, we recommend that readers follow the advice of a physician who is directly involved in their care or the care of a member of their family.

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Introduction to the Clinical Practice Series

The Clinical Practice Series is dedicated to the support of continuing education and enrichment for the practicing clinician. Books in this series address topics of concern and importance to psychiatrists and other mental health clinicians. Each volume provides up-to-date literature reviews and emphasizes the most recent treatment approaches to psychiatric illnesses. Theoretical and scientific data are applied to clinical situations, and case illustrations are used extensively to increase the relevance of the material for the practitioner.

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Series Editor
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Smoking as a behavioral disorder is the most deadly (50% of users die from a tobacco-related illness; Peto et al. 1992), most prevalent (25% of Americans still smoke; “Cigarette smoking” 1996), and most costly (more than $50 billion a year; U.S. Department of Health and Human Services 1994) disorder in medicine. It is also one of the most treatable disorders, with more than 12 scientifically proven therapies (Hughes et al. 1996). Despite this, it is one of the least diagnosed disorders (less than half of physicians mention it in their patient care documentation) and one of the least reimbursed (less than 60% of health plans cover cessation treatment; Pinney Associates 1995). Smoking has the smallest number of specialists of all major disorders; for example, the Society for Research on Nicotine and Tobacco includes fewer than 300 persons. Finally, even though smoking accounts for 20% of all mortality, it receives less than 2% of the total health research budget (Hughes 1994). What historical accident caused this striking situation?

The earliest research studies on nicotine or smoking were the classical studies identifying nicotinic receptors in ganglia and muscle endplates in the early 1900s (Jaffe 1980). These were followed, between the 1930s and 1960s, by a small set of studies on the behavioral and psychophysiological effects of smoking (U.S. Department of Health and Human Services 1988a). Treatment research began in the 1960s, when behavioral psychologists had developed learning-based therapies and were looking for behavioral endpoints on
which to demonstrate the power of their behavioral therapies. Smoking was an objective behavior that one could count and appeared to be influenced by environmental variables. These phenomena led in the 1970s to the scientific validation of several behavioral therapies for smoking (Glasgow and Lichtenstein 1987). However, behavior therapists soon realized that even though their treatments were effective, most insurance companies would not pay for, most physicians would not refer to, and most smokers would not participate in these therapies (Hughes 1993a; Shiffman 1993). Thus, an era of developing exportable, generalizable treatments began (e.g., brief advice, telephone counseling and mass media) in the 1970s–1980s (Lichtenstein and Glasgow 1992). Many of these treatments were proved scientifically effective, but the magnitude of their treatment effect was small (Hughes et al. 1996; Smoking Cessation Guideline Panel 1996).

Meanwhile, during the 1960s–1980s, scientists were documenting that, for many smokers, smoking was due to nicotine dependence (U.S. Department of Health and Human Services 1988b). In the 1970s–1990s, pharmaceutical companies noticed that the market for smoking cessation (50 million smokers in the United States) was the largest market for any product, and these companies developed effective medications based on the data in nicotine dependence studies. In a slightly different time frame (1980s–1990s), neuroscientists were making truly groundbreaking discoveries about nicotine as an important neuromodulator and possible therapeutic agent in the central nervous system (Clarke 1992). Finally, with the discovery that secondhand smoke can harm nonsmokers and with evidence that the tobacco industry was involved in cover-ups, social pressure to stop smoking became enormous in the 1980s–1990s. This social pressure has led to a situation in which remaining smokers appear to be those with severe pharmacological dependence on nicotine or those with significant psychiatric or life problems (Hughes 1993a).

Despite all this activity, two major factors have led to the neglect of studies on smoking and nicotine. First, smoking still has no academic home. Most disorders or treatments have a central home—for example, psychoses are the purview of psychiatrists and behavioral therapy is generally the purview of psychologists. But smoking is treated by primary care physicians, psychologists, health educators,
and others. One could argue that significant advances in the understanding and treatment of a disorder cannot occur unless some professional group claims the disorder as part of its turf. One other major factor is the timing of scientific discoveries concerning nicotine and smoking. The major recognition that there are effective treatments for smoking occurred in the 1980s. Unfortunately, this was the period of major efforts to cut back the cost of health care. Despite all the evidence that it is effective and also more cost effective than any treatment in medicine (Warner and Luce 1983), smoking cessation treatment arrived too late.

There are at least three other reasons why the conceptualization of nicotine dependence and smoking treatments lacks acceptance. First and foremost, many smokers (40%–50%) have quit on their own (“Cigarette smoking” 1996). Many of these (especially, it seems, those in authority positions) believe that since they did it alone, with enough “willpower,” anyone can do it. Second, drug dependence is usually thought of in terms of dire actions to obtain the drug, chronic intoxication, abusive and neglectful relationships, violence, and related severe problems (Hughes 1993b). None of these occur with smoking, because tobacco is so readily available and because nicotine does not cause behavioral intoxication (Hughes 1993b). Third, there is no patient advocacy group for smoking treatment. The advocacy groups for alcoholism have arisen in large part because of the camaraderie of Alcoholics Anonymous, a phenomenon that is rare with smokers.

Through all these developments, we have arrived at a situation in which the most important and the most preventable disorder in medicine is neglected. For example, think of the time that clinicians have invested in trying to talk patients out of bad relationships or self-denigration, or the time spent trying to talk them into taking medications or trying new jobs. If we are willing to spend time with these matters, why do we clinicians shirk spending time on a behavior that has a 50% chance of killing our client? Even compared to behavioral disorders with high rates of mortality such as alcoholism, smoking causes more deaths (Hurt et al. 1996). How many funerals of patients we treated for mental disorders but who died of smoking-related illnesses will we need to attend before we see smoking as an important problem? If we as clinicians pride ourselves on treating
the whole patient, on not being limited by the external contingencies of social approval or finances, and on treating important problems, then how can we not treat (and research) smoking?

In addition to this moral imperative as a reason to learn about nicotine and smoking, there is the simple fact that nicotine and its psychological and neurochemical effects are truly fascinating. For example, in this book there are chapters that review and discuss the following topics:

- There are true nicotine receptors in everyone’s brain.
- We probably know more about nicotine receptors than about any other receptor in the brain.
- Smoking does the exact opposite of most drugs of abuse: first, it increases rather than decreases the number of its receptors; second, it blocks as well as stimulates its receptor.
- Smoking appears to protect one from getting Alzheimer’s and Parkinson’s diseases as well as ulcerative colitis.
- Nicotine is a renaissance drug—it can do many things: improve mood, increase concentration, suppress weight, and decrease anger.
- Smoking is at least as genetically based as alcoholism.

In summary, I think you will find that this book not only will motivate you either to research or to treat smoking, the primary problem in health behavior, but also will convince you that doing so is intellectually stimulating.

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This book grew out of a symposium on nicotine held at an annual meeting of the American Psychiatric Association. In recent years, the interest in and research on nicotine has been phenomenal. This growth is the result not only of interest on the part of the public and the medical industry, but also of enormous talent in the field.

This talent is reflected in the work of the authors of this book’s chapters; the editors would like to thank all the authors.

Dr. Piasecki also thanks her “editor’s editor” and husband, Joe Phelan, for his patience and assistance in preparing the text.
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SECTION I

Background
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Neurobiology and Clinical Pathophysiology of Neuronal Nicotinic Acetylcholine Receptors

Stephen P. Arneric, Ph.D.

Introduction

The focus of this chapter is the neurobiological basis for the neurotropic and neurotoxic aspects of nicotine via modulation of the nicotine receptor. The nicotine receptor, also known as the nicotinic acetylcholine receptor (nAChR), is a ligand-gated ion channel. Although first isolated from the neuromuscular junction, it exists in the brain as well, and in that location it is described as the neuronal nAChR. In this chapter I present a brief overview of the emerging molecular biology, expression, and biophysical and pharmacological properties of nAChRs as well as potential targets for drug discovery. In particular, I outline evidence that certain disorders are attributable to abnormal cellular functions linked to a pathology of this channel-type receptor, a so-called channelopathy. Also highlighted are examples whereby newly discovered modulators of nicotinic ligand-gated ion channels present in the nervous system may become viable therapeutic agents. Collectively, these agents are termed cholinergic-channel modulators (ChCMs), a term that helps to avoid the negative connotations associated with the use of nicotine in its tobacco form. ChCMs may have the potential to treat a variety of
disorders associated with attentional deficits (attention-deficit/hyperactivity disorder, age-associated mental impairment), neurodegeneration (Alzheimer’s and Parkinson’s diseases), epilepsy, chronic pain, prostate dysfunction, inflammatory bowel disease, and obstructive sleep apnea.

**Acetylcholine and Cholinergic Receptors**

Although acetylcholine was identified as a peripheral neurotransmitter in the early part of the century, it was only in the late 1950s that evidence of neurotransmission within the central nervous system was produced by means of demonstration of cholinergic transmission at motor neuron–Renshaw cell synapses in the spinal cord (Curtis and Eccles 1958). Cholinergic pathways have been traced in the brain by using the presence of the synthesizing enzyme choline acetyltransferase, which forms a series of cell groups reaching from the telencephalon to the spinal cord (Feldman et al. 1997). Acetylcholine receptors are divided into two quite different subtypes, now identified as muscarinic and nicotinic. This differentiation originally reflected the mimicry of the actions of acetylcholine by the plant alkaloids muscarine and nicotine, but it is now understood to indicate significant structural, electrophysiological, and functional differences. Muscarinic receptors are G-protein–linked, so-called metabotropic receptors, with a slower onset and offset of action compared with nicotinic receptors. Muscarinic receptors can be either excitatory or inhibitory, and their actions can be blocked by atropine or scopolamine. By contrast, nicotinic receptors are part of a structurally related superfamily of ligand-gated (to distinguish them from voltage-gated) ion channels (including excitatory amino acid receptors and the like). Nicotinic cholinergic receptor action is predominantly excitatory, occurs very quickly (a few milliseconds), and can rapidly terminate or desensitize. Blocking agents include d-tubocurarine and mecamylamine. The roles of the two basic receptor subtypes within the central nervous system appear to be quite different, and the functional roles of central nicotinic receptors and their importance for brain functioning remain an area of active and intense investigation.
Cloning of Neuronal Nicotinic Acetylcholine Receptors

The neuromuscular nAChR is the most extensively studied member of a superfamily of receptors made up of five subunits (i.e., α, β, γ, δ, ε) (Changeux et al. 1992; Lena and Changeux 1993; McGehee and Role 1995; Sargent 1993). The nAChR subunit genes encode for peptide sequences that have a relatively hydrophilic amino terminal portion, making up a major extracellular domain of the receptor protein where ACh is thought to bind. This is followed by three hydrophobic transmembrane domains (M1–M3), a large intracellular loop, and a fourth hydrophobic transmembrane domain (M4). All subunit genes encode for a protein with 2 cysteines separated by 13 residues that align with cysteines 128 and 142 of the muscle α subunit. Of the neuronal genes cloned across different species, eight (α2–α9) code for α subunits (Arneric et al. 1995a; Elgoyhen et al. 1994; Sargent 1993). Three non-α subunits have been identified (β2–β4). As a group, β subunits are as different from each other as they are from α subunits (Sargent 1993). Rat, human, and chick nAChR genes of the same name are highly homologous (>70% amino acid identity) (Anand and Lindstrom 1990; Chini et al. 1992; DoucetteStamm et al. 1994; Sargent 1993; Tarroni et al. 1992). Of all the subunits cloned across species, only α6 and α8 have not been identified in human tissue. Continued cloning efforts will probably result in the identification of new nAChR subtypes.

Distribution of Nicotinic Acetylcholine Receptors

On the basis of the molecular diversity and the different distribution of subunits throughout the body (Table 1–1), the potential clearly exists for many nAChR subtypes. Indeed, eight subunit combinations have been found to form functional receptors in heterologous expression systems with properties similar to the receptors found in native tissues (McGehee and Role 1995; Sargent 1993). However, high-affinity radioligand probes selective for only three classes of these subtypes exist. These sites are
1. A high-affinity (-)-nicotine site labeled with $[^3\text{H}]$ acetylcholine (Schwartz et al. 1982), $[^3\text{H}]$(-)-nicotine (Marks et al. 1986), or $[^3\text{H}]$(-)-cytisine (Pabreza et al. 1991).

2. A site that binds $[^{125}\text{I}]\alpha$-bungarotoxin (Clarke and Pert 1985).

3. Sites selective for $[^{125}\text{I}]$neuronal bungarotoxin (n-BgT) (Schulz et al. 1991).

Although currently available nAChR ligands have limited selectivity for the different neuronal nAChR subtypes, various nAChR ligands have different binding characteristics at these different sites (Decker et al. 1995). On the basis of immunoprecipitation experiments, the predominant nAChR in brain is the $\alpha_4\beta_2$ subtype (Flores et al. 1991).

### Biochemical and Biophysical Properties of Nicotinic Acetylcholine Receptors

Like the neuromuscular nAChR, neuronal nAChRs are thought to combine as a pentamer to form a homooligomeric or a heteromeric ion-channel complex (Bertrand and Changeux 1995; Sargent 1993). The ion conductance of a channel is determined by the conformation and amino acid sequence composition of the ion channel itself (Changeux et al. 1992; Papke 1993; Sargent 1993) in such a fashion that subunits having different sequences in their transmembrane do-

#### Table 1–1. Relative abundance and distribution of neuronal nicotinic acetylcholine receptor (nAChR) subunits in mammals

<table>
<thead>
<tr>
<th>Abundance</th>
<th>Distribution</th>
<th>Subunit</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Widespread</td>
<td>$\alpha_4, \beta_2$</td>
</tr>
<tr>
<td>Medium</td>
<td>Widespread: brainstem motor nuclei, locus ceruleus, thalamus, autonomic ganglia, hippocampus, interpeduncular nucleus, immune cells</td>
<td>$\alpha_3, \alpha_7, \beta_4$</td>
</tr>
<tr>
<td>Low</td>
<td>Restricted: hippocampus, thalamus, autonomic ganglia, ventral tegmental area, interpeduncular nucleus, cortex</td>
<td>$\alpha_2, \alpha_5, \alpha_6, \beta_3$</td>
</tr>
<tr>
<td>Very low</td>
<td>Focal: hair cells, tongue, skin</td>
<td>$\alpha_9$</td>
</tr>
</tbody>
</table>

Source. Data from Elgoyhen et al. 1994; McGehee and Role 1995; Sargent 1993.
mains will have different single-channel conductances. Indeed, the Ca\(^{2+}/Na^+\) permeability ratios of several neuronal nAChRs are significantly higher than those of the muscle nAChR in various preparations (Seguela et al. 1993; Vemino et al. 1992). The potential for long-term modulation through second-messenger cascades from the influx of Ca\(^{2+}\) clearly exists, as in the well-documented cascade of the N-methyl-D-aspartate (NMDA) receptor. More recently, disease states have been linked to alterations in Ca\(^{2+}\) permeability mediated by nAChR function. An insertion mutation of the \(\alpha_4\) nAChR gene in a family with autosomal-dominant nocturnal frontal-lobe epilepsy (ADNFLE) resulted in a significantly lower calcium permeability that may correspond to a loss of synaptic regulation (Steinlein et al. 1997). Thus, it is possible that modulators of nAChRs, selective for certain subtypes, will be able to cause cell- and regionally selective modulation of synaptic function with clinical implications. Studies of the single-channel properties of neuronal nAChRs transiently expressed in oocytes and stably expressed in cell lines have indicated considerable diversity among heterologously expressed subunit combinations. Both the \(\alpha\) and \(\beta\) subunits dictate functional properties of a defined subunit combination (e.g., channel open times, rates of desensitization, ion selectivity) (Papke 1993; Papke and Heinemann 1993; Papke et al. 1993). Results of recent electrophysiological studies in cultured hippocampal cells have been consistent with these suppositions (review by Albuquerque et al. 1997).

**Pharmacological Properties of Nicotinic Acetylcholine Receptors**

**Selective Responsivity of nAChR Subtypes**

Much is known of the pharmacological properties of different subunit combinations from studies using in vitro heterologous expression systems (for reviews, see Arneric et al. 1995a; McGehee and Role 1995; Sargent 1993). Whereas initial pharmacological characterization of defined nAChR subtypes relied almost exclusively on studies in *Xenopus* oocytes injected with various subunit combinations, more recently a number of cell lines stably expressing chick \(\alpha_4\beta_2\), rat \(\alpha_7\), rat
α_3β_4, and human α_4β_2 and α_7 have been described (Gopalakrishnan et al. 1995, 1996; Puchacz et al. 1994; Whiting et al. 1991; Wong et al. 1995).

As seen with the biophysical properties, the α and β subunits give the pharmacological properties of a defined subunit combination (i.e., agonist/antagonist sensitivity) (Papke 1993; Papke and Heinemann 1993; Papke et al. 1993) not only via interactions at the agonist (i.e., ACh) binding site located on the α subunit but also though noncompetitive activator sites (Albuquerque et al. 1997; Maelicke et al. 1995; Pereira et al. 1993). When expressed with the same β subunit (e.g., β_2), α_2, α_3, and α_4 form channels that vary in their pharmacological sensitivity to antagonists (Luetje et al. 1990). The β subunits appear to regulate the rate at which agonists and antagonists dissociate from the channel and the rate at which channels with bound ligand will open (Papke 1993). The α_9 homooligomer nAChR has unusual pharmacology in that it is gated by ACh and unresponsive to nicotine (Elgoyhen et al. 1994). In fact, nicotine, α-BgT, n-BgT, and strychnine are reversible antagonists at this subtype of channel. The finding that strychnine is a potent antagonist suggests that this receptor shares some pharmacological properties with glycine receptors (Elgoyhen et al. 1994). The nAChRs are allosteric proteins whose functional properties can be modulated by interactions at sites distinct from the ACh or the nicotine-binding site (Bertrand and Changeux 1995; Changeux et al. 1967; Lena and Changeux 1993; Monod et al. 1965; Rubin and Changeux 1966). Alternative antagonist-binding sites have also been identified where noncompetitive blockers such as histrionicotoxin, phencyclidine, and MK-801 antagonize neuronal nAChR function (Lena and Changeux 1993). Additional sites distinct from both the ACh binding site and the ion channel include a site where steroids antagonize neuronal nAChR function (Valera et al. 1992) and a possible dihydropyridine-binding site with both facilitatory and inhibitory effects (Damaj et al. 1993; Donnelly-Roberts et al. 1995). There is a site where calcitonin gene-related peptide may enhance receptor desensitization (Mulle et al. 1988) and also a site where arachidonic acid may inhibit function (Vijayaraghavan et al. 1995). Further characterization of these alternative binding sites on neuronal nAChRs may provide opportunities for targeting the nAChRs with therapeutic drugs.
**Nomenclature: Transitions From Old to New**

History and pharmacology have led to calling functional combinations of these novel neuronal gene products related to the neuromuscular receptor **nicotinic receptors**. This nomenclature has led to calling all compounds that interact with nAChRs either nicotinic agonists or nicotinic antagonists. A stigma still pervades the scientific and lay communities regarding the terms **nicotinic receptors** and **nicotinic ligands**. An alternative nomenclature that refers to compounds interacting with nAChRs as **cholinergic-channel modulators** (ChCMs) serves three vital goals: 1) to highlight the difference in receptor mechanisms compared to muscarinic receptors, which are not ligand-gated ion channels but do bind acetylcholine, 2) to acknowledge the different interactions of nicotine at the various subtypes, and 3) to open our minds to the potential therapeutic uses of these compounds. The term **ChCM** then defines the broad class of agents that includes competitive activators, allosteric activators, and allosteric facilitators (collectively: cholinergic-channel activators, ChCAs). **ChCM** also includes cholinergic-channel inhibitors (ChCIs), which may act through any of at least four likely mechanisms: competitive antagonism, noncompetitive (allosteric) inhibition, ion-channel blockade, or receptor inactivation (i.e., desensitization). The term **cholinergic-channel modulator** further emphasizes that it is possible for a compound to possess one set of properties (e.g., activating) at one subtype of nAChR and a different set of properties (e.g., inhibitory) at a different subtype. A modulator may also have different properties at the same subtype, depending on the conditions (e.g., either activating or desensitizing, depending on concentration of the ChCM). ChCMs with combinations of select modulatory properties at nAChR subtypes may produce neurotropic effects of therapeutic benefit without having the neurotoxic side-effect liabilities associated with nicotine.

**Pharmacological Tools**

In summary, the stoichiometry of the five neuronal nAChR subunits present dictates the pharmacological and functional properties of that nAChR (i.e., ion selectivity for Na⁺, K⁺, or Ca²⁺, channel open times, and rates of desensitization) not only via interactions at the
ACh and nicotine-binding site, but also through separate sites, as shown in Figure 1–1.

**Physiological Consequences of Nicotinic Acetylcholine Receptor Activation**

**Synaptic Transmission, Presynaptic Modulation, and Synaptic Plasticity**

The nAChRs have a pivotal role in mediating neuromuscular and ganglionic transmission (Taylor 1990), yet there is scant evidence for an analogous role in fast excitatory transmission in the brain (McGehee and Role 1995). The difficulty of identifying such a function, together with recognition of the high Ca\(^{2+}\) permeability of neuronal nAChRs, has reinforced the concept that nAChRs may have a more modulatory role in the central nervous system (CNS) (Role and Berg 1996). Presynaptic receptors at or near the nerve ter-

**Cholinergic channel activators**  **Cholinergic channel inhibitors**

![Diagram](image)

**Figure 1–1.** Cross-sectional schematic of a prototypic neuronal nicotinic acetylcholine receptor (nAChR) as an allosteric ligand-gated ion channel protein, with distinct sites modulating function through structurally diverse ligands.
minal can positively or negatively modulate transmitter release directly or can influence the probability of an action potential that in turn can result in release of a neurotransmitter. Functional presynaptic nAChRs have been identified by using electrophysiological recordings and neurochemical techniques to follow the release of neurotransmitters from synaptosomes and tissue slices (Wonnacott 1997). The predominant finding is that these prejunctional nAChRs positively modulate transmitter release. Unlike metabotropic presynaptic receptors that only influence stimulated release, nAChRs can elicit Ca^{2+}-dependent transmitter release under resting conditions. Both nAChRs on ACh-containing terminals (i.e., autoreceptors) and nAChRs modulating the release of transmitters other than ACh (i.e., heteroreceptors) have been identified (Wonnacott 1997). Just as there is diversity in the regional expression of nAChR subunits, there is increasing pharmacological evidence for heterogeneity in the nAChR subtypes that modulate transmitter release from different brain pathways (Wonnacott 1997). Alternatively, nAChRs may serve as a signaling mechanism for informing or modulating other aspects of nerve-terminal function, such as nerve-terminal function outgrowth and pathfinding (Role and Berg 1996). The α-BgT–sensitive receptors have been demonstrated to have a role in modulating calcium homeostasis, which may be equivalent to or higher than some of the NMDA receptors (Seguela et al. 1993) in mediating cell-cell signaling (Rathouz and Berg 1994) and in modulating neurotrophin messenger RNAs (mRNAs) such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) (Freedman et al. 1993). Control of these fundamental cell survival mechanisms may have a profound effect on the synaptic plasticity of cells bearing nAChRs.

**Local Cerebral Glucose Utilization**

Nicotine, via central mechanisms, can produce profound changes in mood, behavior, and autonomic functions. Systemically administered nicotine given acutely to rats produces marked stimulation of regional cerebral glucose utilization (RCGU) in brain regions involved with reward/reinforcement (ventral tegmental area, habenula), emotion and motivation (Papez circuit), motor and coor-
dination (cerebellum, substantia nigra), neuroendocrine function, visual processing (superior colliculus, accessory optic system), and autonomic functions (London 1995). In contrast to the effects in rats, nicotine given acutely to humans reduces RCGU (London 1995). In this regard, nicotine is one of a wide variety of drugs of abuse—including alcohol, barbiturates, benzodiazepines, amphetamine, cocaine, and morphine—that produce a generalized reduction in RCGU in human subjects.

**Cerebral Circulation**

Neuronal nAChRs participate in the neurogenic control of cortical cerebral blood flow (CBF). Modulation of this receptor function may have clinical significance. Electrical or chemical microstimulation of the basal forebrain elicits remarkable increases in cortical CBF (up to 250% of control subjects’) that are not linked to changes in metabolism (Linville et al. 1993). This response is selectively decreased by the nAChR channel blocker, mecamylamine, and demonstrates age-related impairments (Linville and Arneric 1991). This closely parallels the characteristic cortical perfusion abnormality in Alzheimer’s disease, which is thought to reflect nAChR deficits. Mecamylamine, but not the muscarinic receptor antagonist scopolamine, can reduce resting cortical perfusion in the parietotemporal cortex of humans (Gitelman and Prohovnik 1992), the area most consistently implicated in functional brain imaging of Alzheimer’s disease patients (Heiss et al. 1990). Reduced CBF responses mediated by nicotine are consistent with the loss of nAChRs reported in several cortical regions in Alzheimer’s disease (Smith and Giacobini 1992), as well as with losses within the basal forebrain nAChR population (Shimohama et al. 1986). The basal-forebrain–elicited cortical CBF response is site specific (Linville et al. 1993) and may be mediated by a subtype of nAChR.

**Advances in Nicotinic Acetylcholine Receptor Imaging**

Recent advances have been made with several new radiolabels that have varying degrees of selectivity and potential utility as positron-
emission tomography (PET) ligands to study receptor distribution and dynamics in humans. Two major technical considerations limit absolute utility of $[^{11}\text{C}]$nicotine to study nAChRs: the uptake of tracer is flow dependent, and the tracer is extensively metabolized (Maziere and Delforge 1995). Despite major technical limitations with the existing tracers, PET studies have been able to monitor demonstrable changes in brain nAChRs following drug treatments as well as in disease states. The well-known upregulation of nAChRs by nicotine (Wonnacott 1990) can be demonstrated with an increased uptake of $[^{11}\text{C}](-)$-nicotine into the brain of smokers compared to nonsmokers (Nybak et al. 1994). A decreased $[^{11}\text{C}](-)$-nicotine binding has been observed in Alzheimer’s disease and corresponds to loss of cognitive functioning (Nordberg 1995). Moreover, long-term treatment of Alzheimer’s disease patients with the cholinesterase inhibitor tacrine results in enhanced uptake of $[^{11}\text{C}](-)$-nicotine. Thus, we have the potential to monitor changes in nAChR function resulting from a disease as well as from the pharmacological treatment of the disease. New agonists that are not metabolized or flow dependent are likely to be developed as tools to understand the dynamics of nAChR function in normal and diseased brain (Villemagne et al. 1999).

**Nicotinic Acetylcholine Receptors as Targets of Neurotoxic Events and Neurotropic Intervention**

**Disorders Related to Point Mutations of nAChRs**

There is a growing understanding that some disorders may be related to changes in an nAChR. Single point mutations of nAChRs can lead to a myriad of consequences, including subtle changes in receptor desensitization, alterations in ion selectivity (cation to anion preferences), or the initiation of series of events leading to programmed cell death. In this section I focus on the recently recognized channelopathies related to abnormal nAChR functioning.
**Myasthenia Gravis**

Congenital myasthenia is a rare autosomal-recessive disorder of neuromuscular transmission. This disease usually begins in childhood with ophthalmoplegia. In contrast to the common form of myasthenia gravis, the congenital form is not caused by an autoimmune attack of the nAChR, since nAChR antibodies are absent. Rather, missense mutations of the $\alpha_1$ subunit occur (e.g., T264P, L269F, and G153S) and result in inefficient nAChR-mediated neuromuscular transmission (Engel et al. 1993).

**Neurodegeneration**

A mutated nAChR belonging to the $\alpha_7$ family has been shown to cause neuronal degeneration in *Caenorhabditis elegans* (Treinin and Chalfie 1995). The phenotypic outcome of neurons expressing these dysfunctional nAChRs is an active process of apoptosis resulting in a systematic loss of the neurons involved in a simple reflex motor response. Incubations of *C. elegans* in the presence of the competitive antagonist tubocurarine prevents the loss of these neurons and preserves the reflex motor response. The demonstration that pharmacological “rescue” from this neurodegenerative process is possible raises the intriguing possibility of pharmacological treatment of similar nAChR channelopathies in humans.

**Schizophrenia**

Altered cholinergic systems are implicated in schizophrenia. Approximately 90% of the schizophrenic population smoke (and therefore self-administer a cholinergic agonist), as compared with 45%–70% of patients with other psychiatric disorders and 33% of the general population (Hughes et al. 1996). The reasons for such a high prevalence of smoking is unclear, although one hypothesis is that it is a genetic trait. One genetically linked characteristic of schizophrenia (Waldo et al. 1991) is a diminished gating of the P50 auditory evoked response to repeated stimuli (Adler et al. 1992; Freedman et al. 1991). In individuals without psychiatric illness, the evoked response to a second stimulus in a pair of stimuli is less than the response to the first stimulus. Persons with schizophrenia typically have higher ratios for
the second response, indicative of decreased gating of neuronal responses to auditory stimuli. Disruption of the hippocampal cholinergic input, $\alpha$-BgT administration, and treatment with $\alpha_7$ antisense oligonucleotide all impair auditory gating. In postmortem tissue from schizophrenic patients, there is an accompanying decrease (40%) in $\alpha$-bungarotoxin–binding sites in the dentate gyrus and the hippocampus and in $\alpha_7$ mRNA (Adler et al. 1992, Leonard et al. 1999). There are also less consistent decreases in $[^3H]$cytisine binding, as well as loss of small inhibitory interneurons that are thought to contain $\gamma$-aminobutyric acid (GABA). In nonsmoking relatives of persons with schizophrenia, nicotine enhances deficient P50 sensory gating, but this effect is short in duration and probably reflects nAChR desensitization (Adler et al. 1992). Regardless of whether a disposition toward smoking is distributed with genes for schizophrenia, or whether smoking reflects an attempt to self-medicate with nicotine, smoking may lead to reduction in negative symptoms, such as social withdrawal, that are associated with schizophrenia and may also enhance attentional processes.

**Epilepsy**

Different forms of epilepsy appear to be inherited, which has led to the hypothesis that there is a genetic link (Berkovic and Scheffer 1997). Nicotine in toxic doses can, via interactions with neuronal nAChRs, lead to convulsions and death (Taylor 1990). Point mutations in neuronal nAChRs are implicated in some genetic forms of epilepsy. Indeed, single point mutations in some subtypes of neuronal nAChRs can lead to profound changes in ion conductance properties of the channel, the rates of receptor desensitization, and the receptor pharmacology. Mutations in the $\alpha$ subunit, which is found in postsynaptic membranes, are present in patients with autosomal-dominant nocturnal frontal-lobe epilepsy (ADNFLE; Steinlein et al. 1995). This type of epilepsy is associated with a gene on chromosome 20 at location q12.2q13.3 (Phillips et al. 1995) and correlates with a missense mutation in the gene coding for the $\alpha_4$ nAChR subunit (Steinlein et al. 1995, 1997). This initial mutation documented in an Australian pedigree corresponds to a substitution of a serine residue by a phenylalanine (S248F) in the TM-2 segment forming the channel.
The resulting abnormality is an ACh-evoked current that never exceeds 10% of the normal nAChRs (Weiland et al. 1996). Recently, a Norwegian family was identified who had a novel mutation consisting of a three-nucleotide (GCT; i.e., leucine) insert at position 776 of the C-terminal end of the TM-2 segment (Steinlein et al. 1997). This mutation produced no detectable abnormalities in current amplitude level or desensitization. However, it did cause a tenfold increase in apparent affinity for ACh, and it remarkably reduced the channel permeability for Ca\(^{2+}\). In light of the evidence that presynaptic nAChRs modulate neurotransmitter release (Wonnacott 1997), the leucine insertion could result in an indirect loss of function. The gene for another clinically distinct dominant epilepsy, benign familial neonatal convulsions (BFNC), maps very close to the ADNFLE gene and may be allelic, but whether mutations in the \(\alpha_4\) subunit exist in BFNC is uncertain (Beck et al. 1994).

**Therapeutic Opportunities for Modulators of Dysfunctional Nicotinic Acetylcholine Receptors**

**Myasthenia Gravis**

It is possible that compounds that selectively interact with abnormal nAChRs could overcome the hypoexcitability created by the aberrant receptor and reverse the clinical findings in this disorder. Novel therapeutic agents would have a potentially reduced side-effect liability if they did not interact with the normal nAChRs.

**Neurodegeneration**

At this time no nAChR channelopathies have been identified with the neurodegenerative disease states of Alzheimer’s disease or Parkinson’s disease. Nonetheless, activating nAChRs has beneficial effects that may counteract other ongoing neurodegenerative events and result in a net neurorestorative effect for these two disease states. Neurodegeneration due to excitotoxic damage is thought to be involved in the etiology of both Alzheimer’s disease and Parkinson’s disease (Maragos et al. 1989). Nicotine and a number of experimen-
tally derived ChCMs (GTS-21, ABT-418, and ABT-089) have all been shown to decrease glutamate-induced neurotoxicity in vitro (Arneric et al. 1996a, 1996b). The mechanisms mediating the neuroprotective actions of ChCMs may depend on interactions with subtypes of nAChRs such as $\alpha_7$. Activation of rat cortical nAChRs by nicotine afforded in vitro neuroprotection against glutamate toxicity (e.g., excitotoxicity) mediated by NMDA receptors (Akaike et al. 1994). The neuroprotective effects of nicotine were observed when it was given several hours before, but not following, exposure to NMDA. This finding suggests that some early-immediate gene process may be involved in mediating the beneficial effects. Nicotine can also prevent transneuronal degeneration following neurotoxic destruction of the basal forebrain (Martin et al. 1994). These neuroprotective actions of nicotine may account for the inverse relationship found between smoking and later development of Alzheimer’s disease or Parkinson’s disease (Van Duijn and Hofman 1991).

**Schizophrenia**

One way to overcome the possibly limiting nAChR desensitization effect of nicotine is to use compounds that allosterically modulate the nAChR. ABT-418 can restore normal gating in animals displaying gating deficits at doses tenfold lower than the doses of nicotine required for the same effect. Unfortunately, both ABT-418 and nicotine lose their ability to restore gating with rapid, repeated administration. This reduced effectiveness of nicotine is also seen clinically with nicotine patches, but not with intermittent smoking (Leonard et al. 1999). This may reflect the very rapid desensitization and subsequent recovery of $\alpha_7$ nAChR function. Compounds with $\alpha_7$ partial agonist activities, like GTS-21, may not desensitize with repeated administration (R. Freedman, personal communication, December 1997). Subtype-selective compounds like GTS-21 have the potential to show efficacy without the same desensitization seen with nicotine.

**Epilepsy**

Many of the widely used anticonvulsants affect neurotransmitter receptors or channels in the postsynaptic membrane. They rely on the hypothesis that overexcitability of the postsynaptic neuron creates
the uncontrolled neuronal firing that characterizes the disease. Compounds that selectively interact with mutant, but not normal, nAChRs may restore the thalamocortical imbalance created by the aberrant receptor, with potentially reduced side effects. It is unclear whether early treatment could result in normalization of CNS ontogenesis.

**Other Therapeutic Opportunities for Modulators of Nicotinic Acetylcholine Receptors**

In the past several years, a number of pharmaceutical and biotechnology companies, including SIBIA Neurosciences, Taiho, Abbott, Bayer, Astra Arcus, Lundbeck, CytoMed, Pfizer, and Merck, have devoted medicinal chemistry resources to identifying novel agonist ligands for neuronal nAChRs targeting CNS disorders like Alzheimer’s disease, Parkinson’s disease, chronic pain, and attention-deficit/hyperactivity disorder (ADHD). The most advanced of these compounds are ABT-418, ABT-089, GTS-21, and SIB-1508Y (see Figure 1–2 for structures). All are congeners of nicotine that have more favorable side-effect profiles than do existing agents because of their ability to interact selectively with subtypes of neuronal nAChRs. For instance, ABT-418, which is a full agonist at the $\alpha_4\beta_2$ nAChR, is about tenfold less active than nicotine in activating the ganglionic nAChRs (Arneric et al. 1995b). The compound ABT-089, a ChCM with partial agonist activity, is $>100$ times less active at the cardiac nAChRs responsible for inducing tachycardia, arrhythmias, and hypertension (Arneric et al. 1996a).

**Attention/Cognition**

In a variety of animal model paradigms, nicotine has been shown to be an attention-enhancing agent (Evendon et al. 1993; Levin 1993; Levin et al. 1996). Thus, in both lesioned and aged animals, primates as well as rodents, nicotine can facilitate attentional activities. This finding has been extended to humans in studies using both intravenous nicotine and nicotine patches. Nicotine may enhance cognition by direct effects on attention and by interacting with presynaptic
Figure 1–2. Structures of compounds that can modulate neuronal nicotinic acetylcholine receptor (nAChR) function.
nAChRs to facilitate the release of ACh, glutamate, dopamine, norepinephrine, serotonin, and GABA (all neurotransmitters that have been implicated in cognitive function) (Wonnacott 1997). In human studies, Newhouse et al. (1988) and Sahakian et al. (1989) showed that nicotine, acutely administered, can facilitate attentional processes in Alzheimer’s disease patients (see Kirch, Chapter 5, this volume). These studies have been extended to the evaluation of ABT-418 in Alzheimer’s disease patients, where the compound was shown to be effective in similar experimental protocol, including the Buschke recall paradigm (Newhouse et al. 1996). In contrast, activation of nAChRs with nicotine or ABT-418 had no effect in normal rats performing attentional tasks (Turchi et al. 1995), which is probably related to the high baseline performance observed in normal animals. In contrast, the cholinergic-channel blocker mecamylamine and the mixed ChCA/ChCl (-)-lobeline impaired performance in normal rats in a sustained-attention task (Turchi et al. 1995). These results are consistent with a report that nicotine normalizes attentional deficits produced by experimental disruption of the cholinergic input to the cortex (Muir et al. 1995). Nicotine may also be effective in the treatment of ADHD, a cognitive deficit in both children and adults characterized by difficulty in maintaining attention (Ernst and Zametkin 1995). (For further discussion of this topic, see Levin et al., Chapter 9, this volume.) ChCMs may provide an alternative approach to the treatment of ADHD, because they may be effective in safely treating both the attentional and the other cognitive aspects of ADHD. By targeting nAChRs, it may be possible to directly improve deficiencies in cortical cholinergic transmission and dopaminergic transmission without the side-effect liabilities of nicotine or non-selective stimulants.

**Parkinson’s Disease**

Parkinson’s disease is a neurodegenerative disease characterized by tremors at rest, rigidity, bradykinesia, and a loss of postural reflexes. These extrapyramidal effects are a consequence of dysfunction of the nigrostriatal dopaminergic system, associated with degeneration of dopaminergic neurons in the substantia nigra of the brain (German et al. 1989). The primary treatment strategies for Parkinson’s disease"
involve the use of the dopamine precursor L-dopa, which is converted to dopamine in the CNS, or other directly acting dopamine agonists. Epidemiological studies indicate an inverse relationship between smoking and Parkinson’s disease (Smith and Giacobini 1992), and a reduction in nAChRs in brains from Parkinson’s disease patients has been found, suggesting a potential beneficial role for nicotine and ChCMs in treating Parkinson’s disease. Nicotine can increase dopamine levels and reduce dopamine use in the substantia nigra of animals after partial dimesencephalic hemitranssection (Janson et al. 1989). Chronic nicotine infusion in rats can protect against a lesion-induced loss in the number of nigral tyrosine hydroxylase–like immunoreactive neurons (Janson and Moller 1993). Furthermore, in six patients with early-onset Parkinson’s disease, cigarette smoking, but not nicotine gum, was found to reduce tremor, rigidity, bradykinesia, and gait disturbances (Ishikawa and Miyatake 1993). In addition to motor disturbances, Parkinson’s disease patients also have dementia that may be associated with loss of cholinergic function similar to that observed in Alzheimer’s disease. SIB-1508Y is an nAChR ligand with high affinity (Kᵢ = 9 nM) for [³H](–)-nicotine binding in rat brain (Menzaghi et al. 1999). In vitro, SIB-1508Y induces the release of dopamine from striatal slices and can also elicit ipsilateral rotations in unilaterally 6-hydroxydopamine–lesioned rats, suggesting that SIB-1508Y also causes release of dopamine in vivo. This effect can be blocked by mecamylamine. SIB-1508Y can also reverse haloperidol-induced catalepsy, a classical animal model of extrapyramidal motor dysfunction. These properties, as well as the ability to improve retention in a passive-avoidance paradigm, suggest that SIB-1508Y may be useful for treating both the motor and the cognitive aspects of Parkinson’s disease. Several hypotheses have been suggested to explain the inverse relationship between smoking and Parkinson’s disease (Smith and Giacobini 1992). One is that nicotine facilitates dopamine release and dopaminergic transmission in the striatum, which would help to alleviate the nigrostriatal extrapyramidal effects found in Parkinson’s disease. Another is that because of its neuroprotectant properties, nicotine may protect dopaminergic neurons in the substantia nigra from destruction by neurotoxins derived from the environment or diet. In summary, an inverse relationship between smoking and Parkinson’s
disease suggests a possible beneficial effect of nicotine in Parkinson's disease, and experimental data support this contention.

**Anxiety**

Part of the popular folklore associated with tobacco consumption is that nicotine is an aid to "stressed nerves." This is somewhat controversial, since part of the antianxiety effect of nicotine is thought to result from treating the symptoms of nicotine withdrawal (Corrigal 1993; Pomerleau 1986). Nonetheless, controlled studies have demonstrated that nicotine is anxiolytic in humans (Gilbert et al. 1989) and in animal models of anxiety (Brioni et al. 1993). The anxiolytic effects of nicotine are mediated through neuronal nAChRs, since these effects are blocked by mecamylamine. Unlike the benzodiazepines, nicotine has anxiolytic-like actions that are not accompanied by amnestic or sedative effects, and it does not potentiate the narcotic effects of alcohol. The anxiolytic-like action of nicotine is not a common property of all ChCMs, since it may be mediated by a distinct subtype of the neuronal nAChR. When tested in rodents by using the elevated plus-maze, other ChCMs like (-)-cytisine, ±-anabasine, GTS-21, and (±)-epibatidine have no anxiolytic-like properties in a dose range in which other recognized nAChR-mediated effects are observed (Decker et al. 1995).

**Tourette's Syndrome**

Tourette's syndrome is characterized by motor tics and involuntary verbalizations and is typically treated with neuroleptics such as haloperidol. These agents are effective in only 70% of the cases and produce a variety of side effects, including sedation and attentional problems (Erenberg et al. 1987; Shapiro and Shapiro 1988). Long-term haloperidol use is also associated with the risk of tardive dyskinesia. Nicotine potentiates the behavioral effects of neuroleptics in a number of animal models (Emerich et al. 1991; Sanberg et al. 1989) and has provided the basis for studying the effects of co-administration of nicotine in Tourette’s syndrome patients receiving neuroleptics. Conceptually, nicotine may potentiate the beneficial effects of the neuroleptic treatment with a concurrent reduction of side effects. Preliminary open trials with nicotine gum and patches
in Tourette’s syndrome patients receiving neuroleptics have been positive, resulting in reductions in tic frequency (McConville et al. 1991). These beneficial effects of nicotine can last days to weeks following discontinuation of treatment (Silver and Sanberg 1993). These encouraging results suggest the need for double-blind, placebo-controlled studies to test the validity of these results and to establish the effect of nicotine alone in the treatment of Tourette’s syndrome.

**Smoking Cessation**

Although tobacco contains a large variety of substances, its addictive properties are most probably due to the reinforcing actions of nicotine (Benowitz 1996; Corrigal 1993; Rose 1996). Animals (Cox et al. 1984) and human volunteers (Henningfield and Goldberg 1993) self-administer nicotine, a response that appears to involve the mesolimbic dopaminergic system. Nicotine addiction is complex and multidimensional, involving both physiological and psychological components; as a result, no current smoking cessation treatment has broad efficacy (Oates et al. 1988; Stolerman and Jarvis 1995). The best-known use of nicotine other than reinforcement of tobacco consumption is in the form of gum or transdermal patch for use in the treatment of smoking cessation. (For further discussion of nicotine replacement therapies and alternative strategies, such as blockade of the nAChRs with mecamylamine or the use of a partial agonist, see Westman and Rose, chapter 10, this volume.) Lobeline, an nAChR ligand that has full-agonist, partial-agonist, and full-antagonist properties, depending on the nAChR subtype studied, is also in phase 3 clinical trials for smoking cessation (Schnieder 1996).

**Analgesia**

Nicotine is known to produce weak antinociception (analgesia) in a variety of species (Pomerleau 1986; Tripathi et al. 1982). This effect is attenuated by pretreatment with the nAChR antagonist mecamylamine. The precise location of action for nicotine-induced analgesia is unclear; however, a central site of action is suggested because the antinociceptive effect is not blocked by the peripherally acting nAChR antagonist, hexamethonium. Nicotine may activate nAChRs
located on cell bodies in subcortical areas of the brain, resulting in ACh release and ultimately pain modulation via activation of descending pain inhibitory pathways (Pert 1987). Alternatively, nAChR stimulation of the spinal cord may increase intracellular calcium, leading to an activation of antinociceptive mechanisms (Bannon et al. 1995; Damaj et al. 1993). A potent antinociceptive alkaloid called epibatidine (Figure 1–2; Badio and Daly 1994) is 100 times more potent than morphine as an analgesic agent and produces its effects via nAChR activation. Both the (+) and (-) enantiomers of epibatidine produce analgesia (Qian et al. 1993). However, this compound can be toxic and cause severe hypertension, convulsions, and ultimately respiratory depression (Sullivan et al. 1994). The poor separation between antinociceptive and toxic doses represents a major challenge in developing such compounds as analgesics.

**Prostate Function**

An epidemiological study reported an association between smoking and prostate function (Roberts et al. 1997). The study consisted of a cohort of Japanese smokers and showed a protective effect of smoking on lower urinary tract symptoms in aging males who smoked 1 to 1.4 packs per day. This was reflected as an inverse relationship between tobacco consumption and peak urinary flow. The association between prostate volume and smoking was less clear with consumption of more than 1.5 packs of cigarettes per day. Either there was no change or there were modest benefits associated with less cigarette consumption.

**Inflammatory Bowel Disorders**

As in the cases of Parkinson’s disease and Alzheimer’s disease, epidemiological data suggest that smoking may reduce the risk of ulcerative colitis (Calkins 1989). Clinical trials with nicotine patches have demonstrated clinical benefits, although these appear to be more effective in the active stage of the disease than in remission (Pullan et al. 1994; Thomas et al. 1995). Interestingly, Crohn’s disease, a transmural inflammatory disease associated with the distal ileum and colon, is exacerbated by smoking, which is consistent with the known differences in the etiology of these inflammatory bowel disorders.
Several mechanisms may contribute to the favorable effects of nicotine in active ulcerative colitis. Nicotine has been shown to downregulate the expression of E-selectin in intestinal tissue biopsies. This substance is thought to be responsible for modifying the properties of inflammatory cell infiltrates (Bhatti et al. 1997). In addition, nicotine significantly reduces basal and mitogen-stimulated IL-8 production (Bhatti and Hodgson 1997). Although transdermal nicotine seems to be of value in active ulcerative colitis, it is often associated with side effects. Pilot clinical studies using nicotine enemas as topical therapy show promising results that may improve the tolerability of nicotine (Green et al. 1997). Randomized controlled studies using such topical formulations with nicotine are ongoing. It is unknown whether any of the newer nAChR ligands have activity against ulcerative colitis or other inflammatory bowel disorders.

**Obstructive Sleep Apnea**

Preclinical observations that nicotine can stimulate ventilation have suggested that nicotine gum could reduce apneic episodes in obstructive sleep apnea (Gothe et al. 1985; Wali and Kryger 1995).

**Summary**

The therapeutic potential for nicotine is not a new concept (Jarvik 1991). However, the side effects and the negative perception of nicotine by the public may limit its widespread acceptance as a therapeutic agent. The emerging molecular neurobiology of neuronal nAChRs has provided the impetus for exploring the functional role of neuronal nAChRs and may provide targets for the development of selective ChCMs with specific therapeutic effects. The concept of multiple receptor subtypes for nAChRs is not unique, as can be seen from the distinct clinical pharmacology of other ligand-gated ion channels such as GABA receptors. With a thorough understanding of the pharmacological and functional characteristics of more of the putative nAChR subtypes, one can envision the possibility of predicting in vivo effects on the basis of in vitro profiles (Brioni et al 1996). Once this knowledge is acquired, the design and development
of less toxic, more effective ChCMs will be possible, which will be of benefit in a variety of CNS diseases.

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Introduction

Nicotine is the addictive principle of tobacco and is responsible for the compulsive use of tobacco in cigarettes and other forms. Nicotine is also available—in the form of chewing gum, transdermal patches, nasal spray, and inhaler—as a pharmaceutical agent to facilitate smoking cessation, and nicotine is being investigated as a therapeutic agent for various conditions, including ulcerative colitis, Parkinson’s disease, and Alzheimer’s disease. An understanding of the pharmacokinetics and pharmacodynamics of nicotine is essential for devising effective interventions for smoking cessation and for developing nicotine as a therapeutic agent.

In this chapter we examine the pharmacokinetics of nicotine, its mechanisms of action, its cardiovascular, metabolic, and endocrine effects, and the implications of pharmacological properties of nicotine for its biobehavioral effects.

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Chemistry of Nicotine and Tobacco Smoke

Cigarette smoke is composed of volatile and particulate phases. Some 500 gaseous compounds have been identified in the volatile phase; they include nitrogen, carbon monoxide, carbon dioxide, ammonia, hydrogen cyanide, and benzene. The gaseous phase accounts for about 95% of the weight of cigarette smoke; particulates account for the other 5%. There are about 3,500 different compounds in the particulate phase, of which the major compound is the alkaloid nicotine. Other alkaloids include nornicotine, anatabine, and anabasine (Hoffmann et al. 1997). The particulate matter less its alkaloid and water content is called tar. Many carcinogens have been identified in cigarette tar, among them polynuclear aromatic hydrocarbons, N-nitrosamines, and aromatic amines. Nicotine is the addictive substance in tobacco, and it is the reason that people smoke.

Nicotine is a tertiary amine consisting of a pyridine and a pyrrolidine ring. There are two stereoisomers of nicotine. (S)-nicotine is the active isomer that binds to nicotinic cholinergic receptors, and it is found in tobacco. During smoking, some racemization takes place, and small quantities of (R)-nicotine are found in cigarette smoke. (R)-nicotine is a weak agonist of cholinergic receptors.

Pharmacokinetics of Nicotine

Absorption of Nicotine From Cigarettes and Other Delivery Systems

Nicotine is distilled from burning tobacco, and small droplets of tar containing nicotine are inhaled and deposited in the small airways and alveoli. Nicotine is a weak base, and thus its absorption across cell membranes depends on pH. The pH of smoke from most American cigarettes (blonde tobacco) is acidic (pH 5.5); at this pH, nicotine is mostly ionized and does not freely cross the membranes. Consequently, nicotine from blonde-tobacco cigarette smoke is not absorbed through the buccal mucosa. On the other hand, the pH of smoke from tobacco in pipes and cigars is alkaline (pH 8.5). At this pH, nicotine is mostly un-ionized and well absorbed from the mouth.
Once nicotine from cigarette smoke reaches the small airways and the alveoli of the lung, it is buffered to physiological pH and rapidly absorbed. Once absorbed, nicotine enters the circulation and distributes rapidly to different tissues, including the brain. It takes about 10–19 sec for nicotine to reach the brain; at that time, the brain is exposed to high levels of nicotine, because the arterial levels of nicotine following cigarette smoking exceed venous levels two- to six-fold (Gourlay and Benowitz 1997; Henningfield et al. 1993). Levels of nicotine in the plasma as well as the brain decline rapidly owing to both distribution to peripheral tissues and elimination (Figure 2–1). When smokers smoke multiple cigarettes during the day, there are oscillations between peak and trough plasma nicotine levels. However, because of its half-life of 2 h, nicotine accumulates over 6–8 h, and nicotine levels persist in the body overnight (Figure 2–2). Plasma nicotine levels during the day typically range from 20 to 40 ng/mL (Benowitz et al. 1982b). However, there is considerable variability between people in their plasma nicotine levels and in their intake of nicotine from a cigarette (Benowitz et al. 1982a, 1997). The smoker can manipulate the intake of nicotine from each cigarette smoked, in order to achieve and maintain the desired level of nicotine, by changing puff volume, the number of puffs per cigarette, the intensity of puffing, and the depth of inhalation and by blocking ventilation holes in the filter (Herning et al. 1983).

Nicotine from nicotine gum, as well as from chewing tobacco and snuff, is absorbed through the oral mucosa. Plasma nicotine concentrations rise slowly, reach plateau after about 30 min, and slowly decline over the next 2 h (Figure 2–1). Nicotine is continually released throughout the time of chewing. The extraction of nicotine from the gum by the chewer is incomplete (53% for 2 mg gum and 72% for 4 mg gum), with substantial individual variability (Benowitz et al. 1987). Also, a considerable amount of nicotine from the gum is swallowed. Consequently, the systemic dose of nicotine is much lower than the amount of nicotine originally contained in the gum, and plasma nicotine levels after chewing the gum are lower than the levels after smoking (Benowitz et al. 1987, 1988; McNabb 1984).

Transdermal nicotine patches deliver on average between 15 and 22 mg of nicotine over 16–24 h, depending on the patch (Benowitz
Nicotine is slowly absorbed, with plasma levels rising slowly over 6–10 h, remaining at steady level for about 7–8 h, and declining during the final 6 h (Figure 2–3). There is about a two- to threefold individual variability in the dose of nicotine and nicotine plasma levels during the patch use (Benowitz et al. 1997). The average levels of plasma nicotine achieved with patch use are considerably lower than the plasma nicotine levels of heavy smokers (Benowitz 1995; Benowitz et al. 1997). Transdermal absorption of nicotine is affected by cutaneous blood flow (Benowitz 1995). Consequently, it is possi-

**Figure 2–1.** Mean (±SEM) blood concentrations of nicotine in 10 subjects who smoked cigarettes for 9 min (1.3 cigarettes), used oral snuff (2.5 g), used chewing tobacco (mean, 7.9 g), and chewed nicotine gum (two 2-mg pieces). Shaded bars above the time axis indicate the period of exposure to tobacco or nicotine gum.

Figure 2–2. Mean (±SEM) blood nicotine and carboxyhemoglobin concentrations in cigarette smokers. Subjects smoked cigarettes every half-hour from 0830 h to 2300 h for a total of 30 cigarettes/day. The cigarettes smoked were research cigarettes that were high or low in nicotine content (as distinguished from commercial cigarettes, which differ in yield but not in nicotine content). COHb = carboxyhemoglobin (concentration).

Source. Adapted from Benowitz et al. 1982b.
ble that vasoconstrictors may decrease and vasodilators increase the transdermal absorption of nicotine.

Nicotine nasal spray delivers 1 mg of nicotine, of which 50% is absorbed. However, the individual variability in the actual dose of nicotine absorbed from the nasal spray is five- to sixfold—a variability that is higher than for cigarette smoking or for transdermal nicotine patches (Benowitz et al. 1997). Nicotine from the nasal spray is rapidly absorbed, but the plasma levels of nicotine are low compared with those in cigarette smoking. Similar to cigarette smoking, arterial plasma levels of nicotine from nasal spray are 2–3 times higher than venous levels, and the peak levels of nicotine in arterial

![Figure 2–3. Plasma nicotine concentration–time curves during and after application of transdermal nicotine delivery systems. Patches were worn by cigarette smokers following at least 24 h abstinence from tobacco. The Habitrol (Novartis), Nicoderm (SmithKline Beecham), and Prostep (Elan) patches were worn for 24 h; the Nicotrol (Pharmacia-Upjohn) patch was worn for 16 h. Source. Adapted from Benowitz 1993.](image-url)
blood are reached about 20 min earlier than are peak venous levels (Gourlay and Benowitz 1997).

The nicotine inhaler is a plastic device with a refillable nicotine cartridge that delivers nicotine as an aerosol to the mouth and upper airway, but not to the lungs. The dose of nicotine and its absorption and time course profile resemble that of nicotine gum (Molander et al. 1996).

The elimination half-life of nicotine is about 2–3 h, although there is a great degree of interindividual variability (Benowitz et al. 1982a). Nicotine is extensively metabolized, primarily in the liver, but also to a small extent in the lung and the brain. About 70%–80% of nicotine is metabolized to cotinine via C-oxidation, and another 4% to nicotine N’-oxide (Benowitz and Jacob 1994; Benowitz et al. 1994) (Figure 2–4). There is a considerable individual variability in the rate of metabolism of nicotine to cotinine (Benowitz et al. 1982a), and smokers have, on average, slower nicotine clearance than do nonsmokers (Benowitz and Jacob 1993; Lee et al. 1987). Several cytochrome P450 (CYP) enzymes, as well as flavin monooxygenases, are purported to play a role in nicotine metabolism, but CYP 2A6 appears to be the principal enzyme involved in converting nicotine to cotinine, via an intermediary metabolite nicotine Δ^{1(5′)}⁻iminium ion (Cashman et al. 1992; McCracken et al. 1992). Cotinine is further metabolized to trans 3’-hydroxycotinine, which is the major nicotine metabolite found in urine (Neurath et al. 1987). CYP 2A6 is also the enzyme presumably responsible for the oxidation of cotinine (Nakajima et al. 1996). Cotinine has a much longer half-life than nicotine (14–20 h) and consequently is used as a marker of nicotine intake (Benowitz et al. 1983; DeSchepper et al. 1987; Zevin et al. 1997). Nicotine, cotinine, and trans-3’-hydroxycotinine are further metabolized by glucuronidation (Benowitz et al. 1994). While an individual is using tobacco or nicotine medications, the strongest predictor of the individual’s plasma nicotine levels is nicotine clearance, whereas plasma cotinine levels are most strongly correlated with nicotine dose and, to a lesser extent, fractional conversion of nicotine to cotinine and cotinine clearance (Benowitz et al. 1997).

Renal clearance of nicotine depends on urine pH (increases in acidic urine and decreases in alkaline urine) and accounts for 2%–35% of total nicotine clearance (Benowitz and Jacob 1985).
Pharmacodynamics of Nicotine

Nicotine acts through nicotinic cholinergic receptors that are found in the brain, autonomic ganglia, and the neuromuscular junction. There are two subclasses of nicotinic receptors: muscle and neuronal. The neuromuscular nicotinic receptors have been well characterized. They are composed of five subunits ($\alpha_2\beta\gamma\delta$ or $\alpha_2\beta\varepsilon\delta$) and operate as ligand-gated ion channels (Karlin 1993). Neuronal nicotinic receptors are composed of $\alpha$ and $\beta$ subunits. A variety of different subunit combinations, $\alpha_2$ to $\alpha_9$ and $\beta_2$ to $\beta_4$, have been identified in neuronal tissues, which means that there is a multitude of different subtypes of neuronal nicotinic receptors (Karlin 1993; McGehee and Role 1995). Different nicotinic receptors are found in different brain regions and have different agonist-binding affinities and different electrophysiological responses to stimulation (Karlin 1993; McGehee and Role 1995); this may explain the diversity of the effects of nicotine in the body.

When nicotine binds to the receptor, there are allosteric changes in the receptor subunits, resulting in an activated state with an open ionic channel and subsequently a desensitized state.

Figure 2–4. Chemical structure of nicotine and major pathways of nicotine metabolism.
with the channel closed (Lena and Changeux 1993). The persistence of the desensitized state can explain the occurrence of tachyphylaxis. An interesting observation is that prolonged exposure to nicotine is associated with increased number of nicotinic receptors (Benwell et al. 1988; Collins et al. 1994). In other systems, such a receptor upregulation response is associated with exposure to receptor antagonists.

Nicotinic receptor activation causes the release of neurotransmitters, including acetylcholine, norepinephrine, dopamine, serotonin, β-endorphin, glutamate, and others. Nicotine also facilitates the release of growth hormone and adrenocorticotropic hormone (ACTH). Addiction to nicotine and its psychologically rewarding properties has been most strongly linked to the release of dopamine (Corrigall et al. 1994), but release of other neurotransmitters probably also contributes to addiction.

Two issues are particularly important in understanding the pharmacodynamics of nicotine: a complex dose-response relationship and the development of tolerance after exposure to nicotine. At low doses, such as smokers are exposed to, nicotine causes sympathetic activation primarily through activation of chemoreceptors or direct effect on the brain, with a resultant increase in heart rate and blood pressure. At higher doses, nicotine acts directly on the peripheral neural system, producing ganglionic stimulation and catecholamine release from the adrenals. At very high doses, nicotine causes hypotension and bradycardia as a result of ganglionic blockade, as well as possible vagal stimulation and direct depressor effects through actions in the brain.

After exposure to nicotine, tolerance develops, which means 1) that repeated doses of the drug produce less effect than the first dose did, or 2) that after repeated exposure, the same plasma drug concentration produces less effect than that observed initially with the same concentration. Tolerance develops to many effects of nicotine, including cardiovascular and toxic effects (nausea, vomiting, dizziness). Tolerance to heart rate acceleration, a nicotine effect, is not complete. The half-life of development of tolerance is about 35 min (Porchet et al. 1988). The rapid but partial development of tolerance probably explains the flat dose-response curve seen with administration of intravenous or transdermal nicotine.
Cardiovascular, Endocrine, and Metabolic Effects of Nicotine

Nicotine effects on the cardiovascular system are mediated by sympathetic neural stimulation associated with an increase in the levels of circulating catecholamines. Nicotine causes sympathetic stimulation through central and peripheral mechanisms. Mechanisms mediated by the central nervous system include activation of peripheral chemoreceptors, particularly the carotid chemoreceptor, and direct effects on the brain stem and spinal cord (Su 1982). Peripheral mechanisms include release of catecholamines from the adrenal glands and from vascular nerve endings. These effects of nicotine result in an acute increase in heart rate and blood pressure when nicotine is delivered via cigarettes, chewing gum, nasal spray, or intravenous infusion (Benowitz et al. 1982a, 1988; Sutherland et al. 1992). Transdermal nicotine causes less intense changes (Benowitz et al. 1993). Substantial but incomplete tolerance develops to the cardiovascular effects of nicotine, with a short half-life of approximately 35 min; there is a persistent effect of nicotine, which is about 20% of the predicted effect if tolerance did not exist (Porchet et al. 1988). After brief dosing, when the arterial plasma nicotine levels are determined, no acute development of tolerance is seen. The reason for the difference in the observations between venous and arterial plasma levels may be that the level of nicotine in arterial blood reflects the concentration of nicotine at the receptors, unlike the concentration of nicotine in the venous blood, which reflects the level of nicotine after distribution to the tissues. There is a lag time between the decline in venous level compared to arterial level, which could account for “pseudotolerance,” as assessed by venous blood-level–response curves (Gourlay and Benowitz 1997; Porchet et al. 1987).

Nicotine differentially affects blood flow to different organs, causing vasoconstriction in some vascular beds (e.g., skin) and vasodilatation in others (e.g., skeletal muscle). Cutaneous vasoconstriction results in a decrease in the fingertip temperature (Benowitz et al. 1982a). Nicotine induces vasoconstriction in coronary arteries, as evidenced by a lack of increased blood flow in response to an increase in oxygen demand (Moreyra et al. 1992) and by direct observation, particularly in arteries with atherosclerosis (Kaijser and
Coronary vasoconstriction appears to be mediated by catecholamines and can be abolished by the \( \alpha \)-adrenergic blocker phentolamine (Winniford et al. 1986).

One of the important mechanisms by which smoking increases the risk of acute cardiac events is by inducing endothelial injury and enhancing thrombosis (Celermajer et al. 1993; Kiowski et al. 1994; Nowak et al. 1987). Nicotine does not appear to significantly affect platelet function or to have an effect on endothelial injury, as evidenced by the results of studies with transdermal nicotine, oral snuff, and chewing gum (Benowitz et al. 1993; Mundal et al. 1995; Nowak et al. 1996; Thomas et al. 1995).

Prostacyclin is an endothelial-derived vasodilator and an inhibitor of platelet aggregation. Nicotine has been shown to inhibit prostacyclin synthesis in vitro (Wennmalm and Alster 1983). However, studies of smokers, smokeless tobacco users, and nicotine patch users found no evidence of decreased prostacyclin production (Benowitz et al. 1993; Nowak et al. 1987).

Alterations in the lipid profile, with an increase in very-low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) and a decrease in high-density lipoprotein (HDL) cholesterol, are believed to be important mechanisms in smoking-induced atherosclerosis (Freeman et al. 1993). Nicotine, via release of catecholamines, increases lipolysis and releases free fatty acids, which are then taken up by the liver (Hellerstein et al. 1994). This process may be expected to promote the synthesis of VLDL and decrease the synthesis of HDL, consistent with the changes seen in smokers. However, these abnormalities were not found in people undergoing nicotine replacement therapy (Quensel et al. 1989; Thomas et al. 1995).

Nicotine affects the metabolic rate, and smokers weigh on average 4 kg less than nonsmokers (Perkins 1992). The lower weight is maintained by an increase in metabolic rate, with concomitant appetite suppression (Perkins 1992). Both cigarette smoking and intravenous nicotine increase the metabolic rate (Arcavi et al. 1994). Quitting cigarette smoking is associated with an increase in appetite and caloric intake and a subsequent weight gain over 6–12 months. After that period, the caloric intake and the weight return to baseline (Perkins 1993).
Nicotine has a variety of endocrine effects, including ACTH and cortisol release (Baron et al. 1995) and β-endorphin release (Seyler et al. 1986), and it has been shown to have antinociceptive effects (Pomerleau et al. 1984).

Cigarette smoking is a risk factor for osteoporosis (Hopper and Seeman 1994), although the mechanism and the role of nicotine are not clear. Possible mechanisms include lower body weight, which is induced by nicotine, and possibly lower estrogen levels found in postmenopausal women smokers taking estrogen replacement therapy (Cassidenti et al. 1992). This may be a result of enzyme induction of estrogen metabolism by cigarette smoke.

Special Populations

Gender Differences

Studies in rats (Kyerematen et al. 1988) and macaques (Seaton et al. 1991) have reported that males metabolize nicotine more rapidly than females. Studies of nicotine clearance in humans have shown differing results. One study showed that the clearance of nicotine, when normalized for body weight, was significantly greater in men than in women (Benowitz and Jacob 1984), but a more recent study reported no gender difference in clearance normalized for body weight (Benowitz and Jacob 1994). Although it is unclear whether drug metabolic activity expressed per body weight differs, it should be noted that, because men weigh on average more than women, total body clearance of nicotine is expected to be on average greater in men than in women.

The absorbed dose of nicotine per cigarette has been estimated by using plasma cotinine concentration during ad libitum cigarette smoking, along with individual pharmacokinetic data (Benowitz and Jacob 1994). In a comparison of 10 men and 10 women, men had a tendency toward a higher intake of nicotine per cigarette (0.91 mg) than did women (0.84 mg per cigarette). Large population studies indicate that, with regular smoking of similar numbers of cigarettes, plasma nicotine and cotinine concentrations are similar in men and women (Bjornson et al. 1995; Wagenknecht et al. 1990; Woodward and Tunstall-Pedoe 1993). It is likely that the lower absorbed dose of
nicotine per cigarette taken by women is compensated for by the lower clearance of nicotine in women, so that on balance, in a steady-state condition (i.e., with regular smoking), the level of nicotine in the blood normalized for cigarette consumption is similar.

Relatively little is known of nicotine pharmacodynamic differences between men and women. An in vitro study showed that progesterone can alter the function of some nicotinic cholinergic receptors (Valera et al. 1992). In rats, the ACTH response to nicotine was found to be greater in males than in females (Andersson et al. 1988).

In humans, a few studies of responses to nicotine nasal spray suggested that women are less sensitive to the effects of nicotine than are men. Response differences included a lesser rate of self-administration (Perkins et al. 1996), a lesser degree of regulation of nicotine intake (Perkins et al. 1996), and a less accurate drug discrimination (Perkins et al. 1995).

Women gain more weight after stopping smoking than do men (Williamson et al. 1991). How much this difference is due to different sensitivity to the metabolic or appetite-suppressant effects of nicotine in men and in women, and how much it is related to behavioral factors, such as the use of cigarettes in lieu of eating, remains to be determined.

Because levels of sex hormones change throughout the menstrual cycle, it follows that the menstrual cycle might influence the pharmacology of nicotine. No data are available on the effect of the menstrual cycle on nicotine metabolism. One study indicated that women smoke more cigarettes in the premenstrual phase (Steinberg and Cherek 1989), but others did not find such an effect (Allen et al. 1996; Pomerleau et al. 1994). An increase in nicotine withdrawal symptoms and a greater craving for cigarettes at the time of menses has been reported by several investigators (Allen et al. 1996; DeBon et al. 1995; O’Hara et al. 1989; Pomerleau et al. 1992). However, it is difficult to interpret these data, because the symptoms of nicotine withdrawal overlap with menstrual symptomatology. The craving for cigarettes could reflect a response to negative affect associated with the premenstruum rather than a response to more intense nicotine withdrawal. In any case, potential implications of these findings for smoking cessation are that the quit date and the type of coping...
skills that the potential quitter is taught should take into account the influence of the menstrual cycle on cigarette cravings and on negative affect.

**Pregnant Women**

Pregnancy can affect the metabolism of some drugs, and there is evidence that pregnancy produces large changes in the metabolism of nicotine and cotinine. In a study in which pregnant smokers received infusions of nicotine and cotinine during pregnancy and again postpartum, the clearance of nicotine was 50% higher and the clearance of cotinine 100% higher on average during pregnancy (Dempsey et al. 1998). The increased clearance explains the observation that cotinine levels, normalized for cigarettes smoked per day, are much lower in pregnant women than in nonpregnant women (Rebagliato et al. 1998). The implications of rapid metabolism for smoking behavior and smoking cessation treatment during pregnancy remain to be determined.

**Implications of Pharmacokinetics and Pharmacodynamics in Understanding Biobehavioral Effects of Nicotine**

Most smokers are addicted to nicotine; addiction is a complex phenomenon encompassing many physiological, psychological, and social factors. Understanding the pharmacological factors that contribute to nicotine addiction is an important step toward devising optimal ways to treat it.

Both animals and humans self-administer nicotine. Nicotine self-administration appears to be motivated by both positive and negative reinforcement. Positive reinforcement effects include relaxation, improved cognitive function, and mood. Negative reinforcement effects are the relief of nicotine withdrawal symptoms, including nervousness, irritability, anxiety, and impaired concentration and cognitive function (Hughes and Hatsukami 1986).

When nicotine is inhaled during cigarette smoking, its rapid absorption and the high arterial levels that reach the brain allow for rapid behavioral reinforcement from smoking. The falling nicotine
levels between the smoking of individual cigarettes allow time for the brain nicotinic receptors to become somewhat resensitized between the cigarettes. Rapid delivery of nicotine to the brain also allows smokers to manipulate and titrate the dose of nicotine from a cigarette to achieve a desired effect. Tolerance to the toxic effects of nicotine (such as nausea) rapidly develops and persists, and the reinforcing effects of nicotine are renewed with each cigarette. Thus, what is typically a noxious pharmacological experience for the novice smoker becomes an addictive pharmacological experience for the experienced smoker.

When nicotine is delivered through a transdermal system, the rise in plasma levels is slow and gradual and peak arterial levels are low; therefore, most of the reinforcing effects may be lost and almost complete tolerance may develop. Putative mechanisms of action for this mode of nicotine replacement in smoking cessation are the relief of withdrawal symptoms and the blunting of the positive reinforcement from the cigarette if the quitter slips up and smokes (Benowitz 1993).

Nicotine gum delivers nicotine intermittently, thus allowing time for resensitization of nicotinic receptors and also allowing for use whenever there is an urge to smoke. However, plasma nicotine levels are lower than those in heavy smokers, and there are local side effects such as unpleasant taste and jaw fatigue. Also, because the delivery system is intermittent, there is a risk of becoming dependent (Benowitz 1991).

Nicotine nasal spray has a closer resemblance to smoking. It was shown that with nasal spray the arterial plasma nicotine levels rise rapidly and are 2–3 times higher than venous plasma levels, in a way that is similar to results of cigarette smoking, although the plasma levels are lower (Gourlay and Benowitz 1997). The potential for addiction has been of concern with the use of nicotine nasal spray, although there is little evidence to date that addiction is a significant problem with clinical use.

Most of the nicotine replacement therapies currently approved for treatment produce nicotine plasma levels lower than those in heavy smokers (Benowitz 1995; Benowitz et al. 1988, 1997). It is likely that such low levels would produce less reinforcement and/or less desensitization of brain nicotinic receptors than does nicotine in smokers, who are exposed to higher levels of nicotine. Conse-
quently, the doses of nicotine replacement therapy for smoking cessation may be suboptimal. Doses might be optimized by individualizing the dose of nicotine to approximate plasma nicotine levels during smoking.

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CHAPTER 3

Behavioral Factors Influencing the Effects of Nicotine

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Introduction

As is plainly evident from other chapters in this volume, nicotine can have a wide variety of effects in humans. Some of these effects are presumably important for maintaining nicotine self-administration behavior (e.g., via tobacco use), other effects may have therapeutic utility (e.g., in the treatment of dementia), and still others may have toxic effects (e.g., increasing risk of heart disease). Nevertheless, it is misleading to merely list effects of nicotine. This is due to the fact that behavioral factors play a crucial role in determining many acute effects of nicotine, just as in the case of other drugs (e.g., Falk and Feingold 1987). Nonpharmacological factors such as the environmental setting, schedule of drug administration, behavioral history, and baseline state can determine the magnitude of nicotine effects. These factors can even influence whether a specific dose of nicotine will act as a positive reinforcer versus an aversive event, increase or decrease subjective arousal and stress, or produce tolerance over the course of repeated administrations. Thus, any examination of the effects of nicotine must take into account how such effects are mediated by behavioral factors.

In this chapter we focus on examining how nicotine’s effects can be influenced by selected behavioral factors, in complement to the
influences of pharmacological (e.g., dose, route of administration) and individual difference (e.g., sex, personality) variables. These other factors are covered in detail elsewhere (e.g., Perkins and Stitzer 1998; Zevin and Benowitz, Chapter 2, this volume) but nevertheless are important to reiterate here. For example, the observed effects of nicotine may differ depending on the route and speed of administration, because methods resulting in more rapid delivery to the brain can produce greater effects (e.g., increased subjective effects with smoking than with the transdermal patch). Nicotine can also have nonlinear or biphasic effects with respect to dose such that low doses may increase subjective or behavioral activation, whereas high doses may produce the opposite effect, sedation. In addition, examination of the effects of nicotine delivered by tobacco smoking ignores the serious difficulties involved in controlling dose exposure (because of the ease of altering intake by changing puffing characteristics, such as intensity and duration of puffs) and fails to isolate the effects of nicotine per se as opposed to the effects of the thousands of compounds in tobacco, only one of which is nicotine. Similarly, effects of nicotine or smoking can vary significantly, depending on a number of stable individual differences, including subject gender (Jamner et al. 1998; Perkins 1996), history of nicotine or other drug exposure (i.e., chronic tolerance and cross-tolerance: Collins and Marks 1995; Perkins 1995), personality or psycho-pathology (Gilbert 1995), genetic differences (Lerman et al. 1998), and exposure to long-term environmental stress (Peck et al. 1991). Thus, the impact of such pharmacological and individual difference factors should be controlled for, or otherwise ruled out, in order to clearly identify behavioral influences on nicotine effects.

Instead of summarizing the effects of nicotine in a variety of response domains (e.g., subjective effects, acute performance effects), we have organize this chapter by the type of factors that are important in determining the effects of the drug (e.g., environmental context, predrug baseline state). Such an approach emphasizes how nonpharmacological factors mediate nicotine’s effects across a wide range of measurement domains, including drug seeking, drug taking, and drug effects. In addition, it is hoped that such a presentation will broaden the reader’s perspective, from which other research is viewed. Given space limitations, it is not possible to review thor-
oughly the broad range of behavioral factors that have been shown to influence response to nicotine. Therefore, we selectively present some key areas of research.

**Baseline State**

Pharmacology as a discipline traditionally organizes drugs into classifications, often based on their purported function. Thus, a number of psychoactive drugs influencing mood or behavior are sometimes labeled *stimulants or depressants* on the basis of observed or presumed effects. However, it has long been recognized that the behavioral state of an organism before drug exposure (i.e., the baseline state) can be an important factor in determining the response to a drug (Dews and Wenger 1977). For example, research by Peter Dews in the 1950s showed that amphetamine administration increased the rate of behavioral responding in animals engaging in low baseline rates of that behavior but decreased the rate of responding in the same animals engaging in high baseline rates of the behavior (Dews and Wenger 1977). Furthermore, when the response requirements for reward were manipulated, the same animals could be trained to respond at low and high baseline rates, either concurrently for different rewards or at different times for the same reward. Amphetamine administration then altered the direction of response rate (increase or decrease) within the same animals, depending on the predrug baseline rate of responding. Similar findings have been reported for the effects of amphetamine and methylphenidate on the behavior of adults and children (Robbins and Sahakian 1979). These results clearly called into question the standard classification of some drugs as stimulants or depressants and led to the emergence of the field of behavioral pharmacology.

The action of nicotine is similarly baseline dependent in altering self-reported arousal, stress, and other subjective effects, as well as altering locomotor behavior in animals. Beyond the biphasic effect of dose, noted previously, the same dose of nicotine can increase locomotor activity in animals with low baseline activity rates but decrease activity in animals with high baseline rates (Rosecrans 1971). Nicotine can also increase activity when animals are in an open field, where baseline activity is low (i.e., defensive “freezing”) but fail to
have an effect when these same animals are in an enclosed space, where baseline activity is often high (Vale and Balfour 1989).

Evidence for baseline-dependent effects of nicotine in humans is perhaps more anecdotal than empirical; smokers very commonly report that smoking stimulates them when they are tired or bored and calms them when they are tense. However, we have conducted studies of the effects of nicotine or smoking as a function of baseline state in smokers, conceptually comparable to these animal studies. In the first study (Perkins et al. 1992a), male smokers rested quietly before being administered either 15 μg/kg nicotine (comparable to yield of one cigarette) or placebo by nasal spray, with the different sprays administered on separate days. Nicotine was presented by nasal spray to provide fairly rapid delivery while standardizing dose and isolating the effects of nicotine per se (pharmacological factors requiring control as previously noted). Subjective arousal was measured before and after each spray. The men were then divided into low- and high-baseline arousal subgroups on the basis of a median split of their prenicotine baseline scores. Men in the low-arousal subgroup reported a large and significant increase in arousal following nicotine but not placebo, whereas those in the high-arousal subgroup reported no significant change following either. It is important to note that these changes did not appear to be due to ceiling or floor effects, since levels were well below maximum and above minimum scores. Another study involving men and women smokers who were administered nicotine by tobacco smoking revealed virtually identical results, showing that the baseline dependency of nicotine’s effects was not specific to our nasal spray delivery method but generalized across routes of administration.

Since this study did not determine whether the difference in subjective state at baseline was due to a stable individual difference (e.g., trait anxiety) or to transient situational variability, we conducted a follow-up study to manipulate subjective stress before tobacco smoking (Perkins et al. 1992b). Male and female smokers engaged in two tasks on two different days, a difficult computer memory task on one day and an easy recognition task on the other. On both days, half of the subjects smoked by means of a controlled-exposure procedure and the other half puffed at the same rate on an unlit cigarette (i.e., sham smoked). As expected, the difficult task increased
self-reported stress and the easy task did not. Relative to sham smoking, it was shown that tobacco smoking decreased subjective stress during the difficult task but had no effect during the easy task, demonstrating that the stress-reducing influence of smoking within individuals was dependent on baseline stress level. Thus, as with the earlier animal research, whether nicotine had any effect on subjective arousal and stress in these two studies depended on the baseline subjective state.

Notably, in both studies the effects of smoking or nicotine by nasal spray on heart rate and blood pressure were essentially the same, regardless of baseline cardiovascular level (Perkins et al. 1992a; 1992b). This observation demonstrates response-specificity of the baseline-dependent effects of nicotine, in that subjective (human) and behavioral (animals, perhaps humans) responses, but not cardiovascular effects, were influenced in this way. On the other hand, smoking has been shown to increase skin conductance, one measure of physiological arousal, during quiet rest but to decrease skin conductance during a noise stressor (Mangan and Golding 1984), suggesting substantial generalizability in the baseline dependency of nicotine’s effects. Consistent with these findings, nicotine has been shown to have stimulant-like effects on electroencephalograms (EEGs) during quiet conditions but minimal effects during high-noise conditions (Gilbert et al. 1997).

Such divergent effects may provide a mechanism for nicotine to be reinforcing under a wide range of conditions and may provide a clear explanation for the seemingly paradoxical reports of smokers that tobacco use has both stimulating and tranquilizing effects (Gilbert 1995). Nicotine may act in a stimulating fashion when smokers experience a low level of arousal (e.g., when fatigued) but act in a tranquilizing fashion when they experience a high level of arousal (e.g., when anxious). Supporting this view is research showing that smokers increase tobacco use under both low- and high-arousal conditions (Parrott 1998; Rose et al. 1983).

**Physical Activity**

As noted above, nicotine can produce increased subjective arousal when prenicotine baseline arousal level is low. However, other
predrug conditions can alter the magnitude of subjective responses to nicotine without significantly influencing baseline state. For example, low-intensity, casual physical activity similar to that involved in the performance of typical daily tasks (office work, driving, walking, etc.) has been shown to attenuate subjective arousal response to nicotine despite no influence on pre-nicotine baseline arousal (Perkins et al. 1994b). In this study, 15 µg/kg nicotine or placebo by nasal spray was administered intermittently to male and female smokers under conditions of light physical activity (very casual pedaling of bicycle ergometer) or quiet rest. All subjects received all four conditions—rest/placebo, rest/nicotine, activity/placebo, and activity/nicotine—in a within-subjects design. Additional sessions involved administration of 5 mg/kg caffeine (orally) versus no caffeine during activity or rest, for comparison with nicotine. Subjective arousal was significantly increased by nicotine under rest conditions, as typically observed, but completely attenuated during activity (Figure 3–1, top). Similar results were found for subjective vigor scores. Notably, activity had no significant influence on the arousing effects of caffeine, demonstrating pharmacological specificity (i.e., specificity to nicotine). There was also no influence of activity on the cardiovascular effects of nicotine, showing response specificity. These results indicate that some subjective effects often attributable to nicotine intake may be less prominent when smokers smoke while engaged in casual activity. An increase in intensity of smoking (and amount of nicotine intake) may therefore be necessary in order to overcome this attenuating effect of activity.

In contrast, the effect of nicotine on energy expenditure (i.e., acute metabolic increase) is substantially enhanced in conjunction with light physical activity, compared with rest (Perkins et al. 1989), as shown in Figure 3–1 (bottom). As in the other studies described, this influence of activity was specific to energy expenditure, and the cardiovascular effects of nicotine were comparable during activity and rest. Since smoking lowers body weight, partially by increasing energy expenditure, this finding can help explain some of the variability in weight-reducing effects of smoking and weight gain after quitting; those who tend to smoke while engaging in these light activities would weigh less (and gain more af-
Figure 3–1. Change (mean ± SE) from baseline rest or activity in self-reported subjective arousal (top) and in energy expenditure (bottom) following 15 µg/kg nicotine or placebo by nasal spray during quiet rest or activity. Arousal study involved 19 male and female smokers participating in all four conditions; subjective arousal was assessed with a 14-item scale (arbitrary units ranging from 0 to 42). Energy expenditure study involved 10 male smokers receiving nicotine during rest and activity and 10 other male smokers receiving placebo during rest and activity. Abbreviations: kJ = kilojoules.

*P < .05. ***P < .001.

ter quitting) than those who tend to smoke at quiet rest, all other things being equal.

In sum, light physical activity can attenuate subjective arousal and vigor effects of nicotine and enhance acute metabolic effects of nicotine, but such activity has no particular influence on the cardiovascular effects of nicotine. Thus, the results of nicotine studies conducted with subjects at quiet rest (as is the case in most laboratory studies) may not generalize to the effects of nicotine in the natural environment, where smokers often engage in casual activity during or just after smoking.

Environmental Context: Role of Distractors

The discussion above demonstrates how the conditions surrounding nicotine administration can moderate the effects of the drug. Another environmental factor shown to moderate the effects of nicotine and smoking is the presence of an environmental distractor. For example, the presence of distracting stimuli has been shown to moderate the effects of nicotine on short-term memory performance (Grobe et al. 1998). In this study, 20 µg/kg nicotine and placebo were administered via nasal spray on separate days to smokers and non-smokers. Short-term memory performance was assessed with a memory search task: participants were presented with a short list of stimuli, known as the memory set. Participants were then presented with test items and had to indicate as quickly as possible whether each test item was in the memory set. During half the memory sets, an auditory distraction was presented. Compared with placebo, nicotine improved short-term memory performance, but primarily in smokers and in the presence of the environmental distractor. Improvements with nicotine were not reliably seen in the control condition—no distraction—which has been the typical condition used in previous research. These findings clarify some of the inconsistent findings in previous research and clearly demonstrate a moderating effect of environmental context in determining the effects of nicotine on cognitive performance.

In a similar fashion, environmental context has been shown to influence the effects of tobacco smoking on anxiety (Kassel and Shiffman 1997). In this study, a state of anticipatory anxiety was in-
duced in smokers and nonsmokers by instructing participants that they would deliver a speech to a video camera on the topic of what they disliked about their physical appearance. Half the participants were then exposed to a benign distractor, which consisted of rating art slides (distraction condition). The other half did not view art slides (no-distraction condition). In addition, half the smokers in each condition smoked a cigarette prior to the stress manipulation. Smokers who smoked and were in the distraction condition reported the greatest reductions in anxiety, whereas smokers who smoked in the no-distraction condition reported no changes in anxiety. These findings suggest that environmental distractors mediate the effects of smoking on anxiety. Smoking may not inherently reduce anxiety, but rather may increase the smoker’s focus of attention on benign distractors. If such stimuli are present, they divert attention away from thoughts that would otherwise elicit anxiety. In any case, this study and the one mentioned above emphasize the role that environmental context may have on the effects of nicotine.

**Control Over Drug Administration**

The degree to which an organism can control environmental events can significantly affect the responses to those events (Mineka and Hendersen 1985). Control can be defined as the opportunity to make an instrumental response that influences consequent outcomes, and this variable has been shown to mediate responses to drug administration (Dworkin et al. 1992). The defining characteristic of drug reinforcement is the response-dependent administration of the drug: the animal performs an instrumental response to obtain the drug and thus exerts some control over its delivery. Clearly, tobacco use in humans involves performing behaviors that control exposure to nicotine. However, the vast majority of animal research on nicotine’s effects has used an experimenter-administered paradigm: the animal receives the drug regardless of its behavior and thus has no control over its delivery. Even human studies typically involve subjects smoking according to experimenter instructions, and subjects generally are not given control over their exposure. Although these studies have produced many important findings, the relevance of this work to our understanding of nicotine reinforcement is limited by the as-
sumption that noncontingent drug administration will produce the same effects as drug self-administration. As shown below, this assumption may not always be true. Furthermore, drug effects specific to contingent self-administration may represent effects that are a function of drug reinforcement (Dworkin et al. 1992); such effects may play an important role in mediating drug-seeking behavior (Kiyatkin et al. 1993).

The influence of controllability of drug exposure (i.e., self-administration versus noncontingent administration) on drug effects has been shown in a number of studies using a standard triadic design, in which one group has control over the pattern and amount of drug administration (i.e., drug delivery is contingent on the animal’s response); a second group is yoked to the self-administering group, in that the same pattern and amount of drug is administered noncontingently; and a third group receives the same pattern of placebo noncontingently. As an example of the power of this design, a recent study found that self-administered infusions of cocaine are reinforcing in rat, whereas the same doses given noncontingently can be lethal (Dworkin et al. 1995). Unfortunately, there are virtually no published reports regarding how control over nicotine administration may mediate the effects of the drug. However, Donny et al. (1996) found that rats self-administering nicotine showed little increase in epinephrine and norepinephrine blood plasma levels, whereas rats receiving the identical pattern of nicotine injections noncontingently showed significantly greater increases.

Interestingly, controllability over nicotine exposure has apparently received more attention in clinical research than in basic studies. Perhaps the most impressive clinical demonstration of the possible influence of controllability was reported by Cinciripini et al. (1995). Smokers received cognitive-behavioral cessation counseling and were randomly assigned to one of several conditions determining the degree of control (scheduled smoking versus smoking at will) and amount of reduction (gradual reduction in smoking versus no reduction) in their smoking behavior over the 4 weeks prior to quitting. Thus, the four treatment groups were as follows: 1) participants smoking a decreasing number of cigarettes per day according to times set in advance by the experimenter (scheduled reduction), 2) participants smoking a decreasing number of cigarettes but hav-
ing control over when they wanted to smoke (nonscheduled reduc-

ing), 3) participants smoking their normal number of cigarettes per
day but according to times set by the experimenter, and 4) partici-
pants smoking at their normal rate and having complete control 
over the timing of cigarettes (smoking at will). One-year abstinence
rates for these groups were 44%, 18%, 32%, and 22%, respectively.
Both groups in which the smoking pattern was determined by ex-
perimenter instructions (groups 1 and 3) did better than those who 
retained control over their smoking. Furthermore, withdrawal se-
verity and urge to smoke during the quit week were attenuated in 
the scheduled reduction group relative to the other three groups.
These results show that reducing subject control and reducing expo-
sure to smoking minimized the symptoms of tobacco withdrawal 
and facilitated subsequent abstinence. Having a high degree of con-
trol over drug use may increase the degree of dependence, and dis-
rupting this control during treatment may facilitate smoking 
cession.

Control over drug use may also affect the efficacy of nicotine re-
placement therapies. Patients on a fixed regimen of nicotine gum 
(instructed to chew at least 12 pieces of gum per day) were more suc-
cessful in maintaining smoking abstinence than those instructed to 
use nicotine gum at will (Killen et al. 1990). In contrast, allowing pa-
tients to have a choice of the type of treatment may facilitate adher-
ence and success. In a smoking reduction program (Fagerström et al. 
1996), patients given a choice of method of nicotine replacement af-
ter sampling the various medications (gum, patch, nasal spray, 
vapor inhaler, and sublingual tablet) had improved outcomes com-
pared with those randomly assigned to a treatment. However, in 
neither of these nicotine replacement studies was the dose of nico-
tine controlled for between subjects; thus, it is impossible to deter-
mine whether controllability or differential nicotine dosing was 
responsible for the observed effects. It may be that reducing control 
over smoking, allowing patients to have control over nicotine re-
placement, and also encouraging adequate use of nicotine replace-
ment may result in improved cessation outcomes. Such a pattern 
would be consistent with the studies of other drug effects men-
tioned above (e.g., improved outcome with patient-controlled an-
algesia).
Nicotine Consumption and Schedule of Administration

The schedule or pattern by which a drug is presented plays a role in determining the resulting effects. For example, nicotine administration contingent on lever-press responding has been shown to increase this responding (Spealman and Goldberg 1982); thus, nicotine is acting here as a positive reinforcer. However, under situations where responding will postpone a non-contingently scheduled administration of nicotine, animals will work to avoid identical doses of nicotine (Spealman 1983). This pattern of responding resembles that obtained by postponement of electric shock and, thus, nicotine here is acting as an aversive event. Such a pattern is consistent with the clinical studies presented above. These opposite effects are clearly not due to differences in pharmacological actions of nicotine but to the specific contingencies in each study between behavior and delivery of nicotine (i.e., schedule of administration). Similar patterns have been demonstrated with other drugs of abuse such as cocaine (Spealman 1979).

The importance of the schedule of drug availability is highlighted by the fact that many past attempts to demonstrate nicotine self-administration in animals have failed (see Corrigall 1992). Aside from problems with finding the optimum doses and dosing speed, among others, many of these studies used a continuous reinforcement schedule, in which each response resulted in an injection of nicotine. However, more recent studies found that nicotine could maintain high rates of responding (characteristic of other drugs of abuse) when the frequency of drug administrations was limited by incorporating time-out periods between nicotine injections, by using an intermittent (time-based) schedule of reinforcement (Goldberg and Henningfield 1988), or by using more complex, second-order schedules (Spealman and Goldberg 1982; see discussion below). It is likely that limiting the frequency of nicotine administrations prevents overdosing of nicotine and thus avoids exposing the animal to aversive effects that may serve to punish responding. In any case, this research demonstrates that nicotine can serve as an effective reinforcer in both animals and humans and that behavioral factors such as the schedule of drug delivery play a crucial role in mediating these effects.
Stimuli Associated With Nicotine Delivery

The presence of other sensory stimuli associated with nicotine delivery can affect responding. One important finding is that the reinforcing value of nicotine may increase with the presence of other stimuli under second-order schedules (Schindler et al. 1988). Under such a schedule, the completion of some number of responses results in the brief presentation of a sensory stimulus (e.g., a light). However, after a fixed interval of time, a response by the animal will result in both the presentation of the sensory stimulus and the delivery of the drug (e.g., nicotine). In such a context, animals will maintain high rates of responding for nicotine, similar to those seen with cocaine administration (Goldberg et al. 1981; Spealman and Goldberg 1982). Subsequent omission of the sensory stimulus without any change in the actual availability of nicotine will decrease responding. In addition, once responding has been established under a second-order schedule (i.e., with nicotine), presentation of the sensory stimulus in the absence of any nicotine availability can maintain responding—that is, the animal is working for presentations of the sensory stimulus, which now acts as a secondary reinforcer. Thus, not only can stimuli associated with nicotine delivery contribute to the reinforcing value of the drug, but the stimuli themselves can become powerful reinforcers.

The role of secondary reinforcing stimuli may be particularly important in reinforcing tobacco smoking, in which nicotine delivery always is paired with a variety of other sensations (e.g., odor, sight, flavor, and feel of smoke). Given that a typical pack-a-day smoker experiences more than 7,000 such pairings a year, it is easy to see how these stimuli can come to play a major role in responses to tobacco use. Presentation of sensory cues of smoking (e.g., inhalation of smoke) in the absence of nicotine delivery has been shown to cause an acute reduction in craving and withdrawal and increase in smoking satisfaction (Butschky et al. 1995). Similarly, inhalation of regenerated smoke containing very little nicotine has been shown to alleviate stress during a difficult task (Levin et al. 1991). Thus, in experienced smokers, responses to smoking are not necessarily due to the simple pharmacological actions of nicotine.
Although some of these effects could result from direct actions of the sensory stimuli, it is likely that most result from conditioned responses arising from previous paired associations of these cues with nicotine intake (Rose and Levin 1991). Such effects could be used in smoking cessation treatments: providing sensory stimuli that safely mimic the effects of smoking may help reduce tobacco withdrawal and increase tobacco abstinence (Butschky et al. 1995).

The studies discussed above suggest that stimuli associated with nicotine delivery may elicit conditioned responses similar to the effects of nicotine, such as reduced withdrawal and increased smoking satisfaction. Such stimuli may thus become reinforcing in their own right, and their presentation may lead to reductions in drug-seeking behavior (e.g., reduced craving). However, presentation of cues associated with smoking may also elicit responses that lead to increases in drug-seeking behavior. For example, the presence of smoking cues has been shown to increase the reinforcing value of smoking (Perkins et al. 1994c). In this study, behavioral responses in a computer game were reinforced by puffs on a cigarette. The presence of a lit cigarette increased the amount of responding reinforced by smoking, compared with conditions where no smoking cues were present. These results suggest that such conditioned responses may have motivational relevance in that reactivity to the cues associated with smoking may be associated with increases in drug-seeking behavior. Many smokers exhibit psychophysiological reactivity (e.g., increased heart rate) to stimuli associated with smoking (for review see Niaura et al. 1988). Furthermore, cue reactivity before smoking cessation has sometimes been shown to predict relapse after a quit attempt (Niaura et al. 1988), suggesting potential usefulness of cue-exposure/response-extinction procedures in smoking cessation treatments. Nevertheless, it not completely clear what the conditions are under which secondary cues will lead to increases versus decreases in the reinforcing value of smoking. It may be that cues predictive of nicotine availability (e.g., the sight of cigarettes) will lead to increased drug seeking, whereas cues associated with the actual delivery of nicotine (e.g., smoke inhalation) will lead to decreased drug seeking.

The examples given above of the effects of secondary stimuli have focused on how cues associated with nicotine delivery may go
on to elicit responses when presented alone (conditioned reinforce-
ment). However, the presence of stimuli previously paired with nic- 
otine delivery can play a significant role in determining responses to 
nicotine. A major way this can happen is through the development 
of conditioned tolerance. A history of chronic exposure to nicotine 
administration can result in the development of tolerance, or a re-
duced level of responding to a given dose (Perkins et al. 1994a). 
Historically, the development of tolerance was thought to de-
pend solely on repeated drug exposure (i.e., resulting purely from 
pharmacological factors). However, Caggiula et al. (1989, 1991) 
have shown that the development of tolerance to nicotine is influ-
enced by conditioning—learned associations of environmental 
stimuli predicting drug delivery. For example, rats given daily 
injections of nicotine develop tolerance to the antinociceptive ef-
fects of nicotine—that is, their pain sensitivity does not differ 
from that of animals given saline. However, when the stimuli 
paired with nicotine administration are changed or omitted (e.g., 
using a different room to inject nicotine and test responding), ani-
mals will show a loss of tolerance and exhibit the full dose effect of 
nicotine on pain sensitivity (Epstein et al. 1989). The development 
of tolerance to nicotine’s effects on decreasing milk intake 
(Caggiula et al. 1989) and on increasing corticosterone release 
(Caggiula et al. 1991) can also be disrupted if environmental cues 
(e.g., tones, odors) regularly paired with nicotine injections are 
subsequently omitted. Disruption of the development of acute 
tolerance to heart-rate effects of tobacco smoking has also been 
demonstrated in humans by changing auditory stimuli immedi-
ately preceding smoking (Epstein et al. 1991). Thus, nicotine’s ef-
facts under conditions commonly associated with its intake (e.g., 
smoking with coffee) may be slight, necessitating greater self-
administration to overcome conditioned tolerance and achieve 
the desired magnitude of effects. Conversely, omitting those con-
ditions (e.g., giving up coffee) may reduce conditioned tolerance. 
This reduction in tolerance would result in greater effects of nicot-
ine intake, requiring less exposure to achieve desired effects. Col-
lectively, this research stresses the importance of considering the 
role of stimuli paired with drug administration when assessing 
the effects of nicotine.
Instruction Set: Response Expectancies

The discussion above on conditioning highlights the importance learning can have for drug responses. Conditioning is assumed to result in associations between a cue for drug administration and drug responses, or between a cue for deprivation and withdrawal effects. Besides such conditioned effects, other cognitive variables may play an important role in mediating the effects of a drug. Constructs such as expectancies or instructional set have been shown to play an important role in mediating responses to other drugs, such as alcohol (Hull and Bond 1986).

Expectations regarding the effects of tobacco use can influence drug-seeking and drug-taking behavior. Adolescents who expect that tobacco use will result in positive effects such as pleasure are more likely to initiate tobacco use than are adolescents without such expectations (Bauman and Fisher 1985). Unfortunately, few studies have examined the influence of expectancy manipulations on nicotine’s effects. Since beliefs about drug effects usually develop with extended experience, it may be difficult to design studies aimed at manipulating such beliefs. Nevertheless, clinical research on the role of expectancies in withdrawal symptoms suggests that such instructional-set manipulations may alter behavioral responses (Tate et al. 1994). Before undergoing a period of tobacco abstinence, smokers were given varying instructions as to what withdrawal symptoms to expect while taking “nicotine gum.” The gum used was actually a placebo. Those who were told not to expect many symptoms reported fewer complaints (e.g., mood disturbances) than the no-expectancy controls. Those instructed to expect somatic, but not psychological, symptoms reported complaints consistent with the manipulation (Tate et al. 1994). Thus, manipulated expectancies appeared to have played a role in determining subjects responses to tobacco deprivation. Given this potential for expectancies to influence responses, the effects of nicotine may likely be influenced both by beliefs about the consequences of drug use obtained from a variety of sources and by direct behavioral experience with the effects of drug administration.

A number of other researchers have used some variant of the $2 \times 2$ balanced-placebo design (Marlatt and Rohsenow 1980),
whereby the effects of actual drug administration are separated from beliefs that one has received a drug administration (“told drug” versus “told placebo” is crossed with “given drug” versus “given placebo”). A study using the balanced placebo design found that the belief that one was receiving nicotine gum resulted in fewer withdrawal symptoms and better success during the first week of quitting regardless of the actual nicotine content of the gum (Gottlieb et al. 1987). Other work has confirmed the power of such expectancy manipulations (Hughes 1989). Furthermore, work by Hughes et al. (1989) suggested that instructional set may actually interact with the receipt of nicotine and modify the effects of the drug. In this study, smokers in a smoking cessation program were randomly assigned to one of six conditions in a $3 \times 2$ design that examined the effects of instructions (“told nicotine” versus “told placebo” versus “blind to dose assignment”) and the effects of nicotine (nicotine gum versus placebo gum). In addition to main effects of nicotine dose and instructions, some interesting interactions between drug assignment and instruction condition emerged. Actual receipt of nicotine rather than placebo improved abstinence rates and increased self-reported drug effects, but only in the “blind” conditions. Thus, subjects receiving nicotine did not differ from those receiving placebo in the “told nicotine” and “told placebo” conditions. In addition, subjects receiving nicotine tended to use more gum than subjects receiving placebo, but only in the “told nicotine” conditions. Subjects receiving nicotine in the “blind” and “told placebo” conditions actually used less gum than comparable subjects receiving placebo. Thus, instructions appeared to determine whether nicotine would act as a reinforcer (i.e., self-administration greater than placebo). This study suggests that under standard treatment conditions in which all patients are told they are receiving active nicotine gum, gum use may be higher but exert less of an effect relative to placebo, compared with gum use and effects under standard experimental conditions in which all subjects are blind to dose assignment. Collectively, this research suggests that cognitive constructs may play a role in determining drug seeking, drug use, and drug effects. Furthermore, attempting to alter smokers’ expectations about tobacco withdrawal and the efficacy of nicotine replacement may be particularly useful for smoking cessation treatments.
Summary

The central purpose of this chapter is to demonstrate how behavioral factors, in conjunction with pharmacological and individual difference factors, determine the observed effects of nicotine. In some cases we see that the same dose of nicotine can have opposite effects, depending on environmental circumstances. Furthermore, multiple nonpharmacological factors may interact to moderate the effects of the nicotine (Netter et al. 1998). Thus, nicotine does not necessarily have straightforward acute effects under all conditions that one can merely list. Given space limitations, we were not able to review all the behavioral factors that have been shown to influence responding to nicotine; instead, we highlighted specific examples. The selection of topics was not necessarily based on the amount of work done in an area or its relative importance, and the reader should be aware that a variety of other behavioral factors have been shown to mediate nicotine effects. In addition, we did not attempt to review any one area in depth. Rather, it is hoped that these selected examples will give the reader a broader perspective from which to view other work.

In closing, it is important to reiterate that many factors discussed in this chapter can be exploited in smoking cessation treatment. For example, manipulating the schedule and controllability of smoking before quitting may reduce reinforcement from smoking and aid in maintaining long-term abstinence (Cinciripini et al. 1995). Altering the instructions given to patients may help to increase the use and efficacy of nicotine replacement (Hughes et al. 1989) or to minimize the aversiveness of tobacco withdrawal (Tate et al. 1994). Providing cue exposure and response extinction treatment may reduce physiological and subjective responses to smoke stimuli (Niaura et al. 1988). Finally, providing some of the sensory effects of smoking without exposure to nicotine may help reduce tobacco withdrawal symptoms (Rose and Levin 1991).

References


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Addictive Capacity of Nicotine

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Introduction

Cigarettes are toxic, and cigarette smoking accounts for at least 20% of the mortality in the United States (Peto et al. 1992). It has only been in the past 10 years—through the development of nicotine polacrilex gum, the transdermal nicotine patch, and other nicotine replacement therapies—that the effects of nicotine have been separated from the effects of tobacco smoking. Although nicotine has an important role in maintaining smoking behavior, it is the other constituents of the cigarette and the products of its combustion that are most injurious. Tobacco cessation is an important public health goal. Toward this end, it is important to understand nicotine’s role in tobacco addiction.

Beginning with Langley and Dickinson’s (1889) original investigations of nicotine’s effects on autonomic ganglia and the discovery of neurotransmission, the action of nicotine on acetylcholinergic receptors has been used as a probe to better understand neural functioning. An exciting new consequence of this research has been to develop nicotine analogues for therapeutic use. Targeted therapies described in this book have many aims, including enhancing attention, memory, and cognition in illnesses of dementia such as Alzheimer’s disease, preventing or reversing the immobility associated with Parkinson’s disease, alleviating pain and depression, promoting weight loss, and assisting in smoking cessation. Risk-benefit analyses help determine the roles of new drugs in the pharmacological armamentarium. Assessing the ad-
dictive potential of nicotine and these agents is relevant in weighing their therapeutic actions against their side-effect profiles.

In this chapter we provide a foundation for understanding nicotine addiction and propose an array of methodologies for studying the addictive potential of newly developed nicotine analogues. The assumptions that form the basis of our knowledge are first explored. The current definition of addiction is critically examined, and some of the factors that make nicotine in cigarettes addicting are analyzed. Although preclinical concepts and studies are mentioned, the methodologies focus on human trials.

**Refining the Concept of Addiction**

**Current Definitions**

The definition of addiction is behaviorally based. The core elements of *The ICD-10 Classification of Mental and Behavioural Disorders* of the World Health Organization (World Health Organization 1992) and DSM-IV (American Psychiatric Association 1994) definitions can be best summed up as repeated use of a substance despite adverse consequences. This notion parallels the first step of Smokers Anonymous and other 12-step programs: “We admit that we are powerless over nicotine, and that our lives have become unmanageable.” (Smokers Anonymous World Services 1988). Smokers can be put in touch with their strong motivation and/or compulsion to smoke by asking them to recount the wildest thing they ever did to obtain a cigarette. Smoking outside buildings in the rain or cold and smoking despite the expression of family concern are only two examples of continued use despite social, psychological, financial, and physical harm.

Historically, *habituation* was used to describe repeated use of a substance that was not intoxicating and that perhaps caused damage to the individual user but not to society. In 1964, the World Health Organization recommended that the terms *addiction* and *habituation* be abandoned in favor of the term *dependence* in order to reduce the confusion between disorders, shift the focus away from the moral and social issues associated with addiction, and put more emphasis on behavioral aspects (U.S. Food and Drug Administration 1995). The World Health Organization first recognized that tobacco was
dependence-producing in 1974; however, tobacco was not included with other dependence-producing drugs until 1992, when the 10th edition of the International Classification of Diseases (ICD-10) was published (World Health Organization 1992). The dependence syndrome is typically a chronic and relapsing disorder (World Health Organization 1995). The ICD-10 (World Health Organization 1992) defines the dependence syndrome as

A cluster of physiological, behavioral, and cognitive phenomena in which the use of a substance or a class of substances takes on a much higher priority for a given individual than other behaviors that once had greater value. A central descriptive characteristic of the dependence syndrome is the desire (often strong, sometimes overpowering) to take psychoactive drugs (which may or may not have been medically prescribed), alcohol, or tobacco. There may be evidence that return to substance use after a period of abstinence leads to a more rapid reappearance of other features of the syndrome than occurs with nondependent individuals.

The American Psychiatric Association first recognized tobacco dependence in the third edition of the Diagnostic and Statistical Manual (DSM-III) (American Psychiatric Association 1980). Today, the seven diagnostic DSM-IV criteria for substance dependence, including nicotine dependence, include 1) tolerance, 2) withdrawal, 3) the substance is taken in larger amounts or over a longer period than was intended, 4) unsuccessful efforts to cut down or control substance use, 5) preoccupation (spending a great deal of time attaining or recovering from the substance), 6) important social, occupational, or recreational activities are given up or reduced because of use, and 7) use despite recurrent problems (American Psychiatric Association 1994, p. 181). In the absence of a more precise model, the criteria are given equal weight. Persons with a few or no symptoms in excess of those required for diagnosis are considered mildly dependent, and those with many additional symptoms are considered severely dependent.

**Assessment Tools**

Current definitions, measures, and models of nicotine addiction are limited in that they do not adequately explain or predict the various
degrees of nicotine dependence. Various associations of increased and/or decreased sensitivity to mood-altering drug effects, the development of acute and chronic tolerance, and the potential for withdrawal symptoms are theorized to underlie the pathophysiology of most chemical dependencies. However, scientists have not yet figured out the pieces of this puzzle. DSM-IV and other tools discussed below are the best measures currently available, but they are imprecise in assessing addiction severity.

The Addiction Severity Index (McLellan et al. 1985), like the DSM criteria, is based on symptomatology. However, it was developed for chemical dependencies other than nicotine. The index does not apply to nicotine addiction because, unlike the other drugs, nicotine is legal, and in its usual dose range it lacks acute intoxicant effects that interfere with social functioning. In addition, the use of nicotine has been socially acceptable during work and recreation.

Typologies such as the Horn-Waingrow Reasons for Smoking (RFS) scale (Ikard et al. 1969) are intuitively appealing in their aim toward differential and individualized treatment for smoking cessation. The six RFS motives and self-monitoring motive descriptions include stimulation, pleasure, sensorimotor manipulation, negative affect reduction, habit, and psychological addiction (craving). However, at best, there has been little agreement about the questionnaire’s validity coefficients (Tate and Stanton 1990), and its clinical utility remains unproved (Shiffman 1988).

We know that smokers tend to regulate their blood levels of nicotine. There have been attempts to correlate the severity of nicotine addiction with factors such as the duration of smoking, potency of cigarettes, puff frequency, puff duration, and inhalation volume. However, these items have only weakly correlated with biochemical measures, and they have not predicted the intensity and extent of withdrawal symptoms (Heatherton et al. 1991).

The Fagerström Tolerance Questionnaire (FTQ) (Fagerström 1978) was developed to measure the severity of nicotine dependence. It was developed from items based on clinical intuition. This questionnaire may be a valid measure of perceived or behavioral dependence in that it is predictive of the self-administration of nicotine and the inability to stop smoking (Hughes 1985). However, it is not a measure of physical dependence in that it has not correlated with symptoms of...
physiological tolerance (Lombardo et al. 1988) and has not been predictive of tobacco withdrawal (Hughes and Hatsukami 1986).

A revised Fagerström scale, the Fagerström Test for Nicotine Dependence (FTND) (Table 4–1) (Heatherton et al. 1991), was developed as a response to criticisms of the original questionnaire’s multifactorial structure, low levels of reliability, and poor item selection. Tolerance is no longer included in the name of the FTND. Of the six questions in the questionnaire, two correlate best with the biochemical levels of salivary cotinine, salivary nicotine, and expired carbon monoxide (time to first cigarette in the morning and number of cigarettes per day) (Heatherton et al. 1989). A revised scoring of these two items, which together make up the Heaviness of Smoking

| Table 4–1. Items and scoring for Fagerström Test for Nicotine Dependence (FTND) |
|-------------------------------|-------------------------------|----------------|
| Questions | Answers | Points |
| 1. How soon after you wake up do you smoke your first cigarette? | Within 5 minutes | 3 |
| | 6–30 minutes | 2 |
| | 31–60 minutes | 1 |
| | After 60 minutes | 0 |
| 2. Do you find it difficult to refrain from smoking in places where it is forbidden, e.g., in church, at the library, in cinema, etc.? | Yes | 1 |
| | No | 0 |
| 3. Which cigarette would you hate most to give up? | The first one in the morning | 1 |
| | All others | 0 |
| 4. How many cigarettes/day do you smoke? | 10 or less | 0 |
| | 11–20 | 1 |
| | 21–30 | 2 |
| | 31 or more | 3 |
| 5. Do you smoke more frequently during the first hours after waking than during the rest of the day? | Yes | 1 |
| | No | 0 |
| 6. Do you smoke if you are so ill that you are in bed most of the day? | Yes | 1 |
| | No | 0 |

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Index (HSI) subscale, improved the overall sensitivity of the FTND. The HIS accounts for the majority of the variance in the total FTND score. The time to first cigarette in the morning but not the number of cigarettes per day has been predictive of withdrawal discomfort (Hughes and Hatsukami 1986). To date, there is no proven relationship between the FTQ or FTND or HIS and the ability to achieve short- or long-term tobacco cessation. Further, the research is based on a sample of 254 adult visitors to the Ontario Science Center when the Canadian cigarette tax was substantial. The results may not extend to other cultures and populations.

**Nicotine Intake**

It can be speculated that the number of cigarettes smoked may become a more critical measure of nicotine dependence when each cigarette is smoked maximally. This may occur in Canada, where the price of a pack of cigarettes is high and it is less socially acceptable to smoke. Also, in Canada and in the United States, the nicotine content per cigarette is less than in Eastern Europe and many developing countries. These factors may explain the apparent contradictory results from previous studies such as those by Benowitz et al. (1983, 1986), which have shown that blood nicotine levels are determined more by the way smokers puff and inhale than by the nicotine yields or numbers of cigarettes they smoke.

In a chapter entitled “Nicotine Intake and Its Control Over Smoking,” Russell (1990) set forth the hypothesis that there is a more precise downregulation of nicotine intake, in order to avoid the undesirable effects of excessive blood levels, than there is a precise upregulation. On the basis of pharmacokinetic factors and acute tolerance, Russell characterized two profiles of inhaling smokers, based on the frequency of their cigarette consumption. “Peak seeker” smokers (Russell et al. 1976) tend to have prominent blood nicotine peaks, whereas “trough-maintainer” smokers (Russell and Feyerabend 1978) smoke more frequently and build up to a steady-state nicotine level. Trough-maintainer smokers take in less nicotine from each cigarette and have less prominent nicotine peaks. Unfortunately there are few data on the full profiles of various smokers. If smokers could be divided into two such populations and
these patterns were validated, many additional questions could be asked. One could see how the peak seeker and trough maintainer patterns correspond with the progression from sporadic tobacco use, with experimentation and enjoyment of smoking, to the development of tolerance, addiction, and avoidance of withdrawal. Then, transitioning from behavioral observation to molecular biology, one could hope to understand correlations between peak seeker and trough-maintainer smokers and their nicotinic receptor type, number, and activity, as well as circuitry, neuroregulation, and neuroadaptation.

In summary, the constellation of addictive behaviors may have diverse genetic and environmental etiologies and neurochemical alterations. Neuroscientists are beginning to investigate the structure and function relationships of receptor subunit composition, neuroanatomical location, and circuits that interact with other neurotransmitters, as well as the developmental and endocrinological regulation of these systems’ components. Scientists have speculated on ways in which these phenomena could lead to addiction through increased and/or decreased sensitivity to the desirable and/or aversive effects of nicotine, the development of acute and chronic tolerance, and the potential for withdrawal. However, this framework is incomplete. The DSM-IV behavioral criteria for addiction and the other assessment tools for tobacco use do not make it possible to deduce precise neurochemical correlates.

**Characteristics of Dependence-Producing Drugs**

In 1994, seven chief executives of tobacco companies testified under oath before a congressional subcommittee that nicotine was not addictive. In order to explain to newspaper reporters and the general public the ways in which tobacco use was similar to and also different from other drugs, Henningfield and Benowitz, basing their work on the detailed concepts presented in the 1988 Surgeon General’s Report (U.S. Department of Health and Human Services 1988), delineated several qualities common to addictive chemicals and rank-ordered the drugs according to these qualities (Hilts 1994). Because dosage form and route of administration vary among the substances, the rankings can be interpreted only as general guidelines. The char-
characteristics of addictive substances that Henningfield and Benowitz noted were 1) intoxication, 2) physical withdrawal, 3) reinforcement, 4) tolerance, and 5) difficulty achieving abstinence. Because Henningfield and Benowitz rank-ordered the drugs separately and, except for the tolerance criterion, had minor differences in their opinions, we have taken the liberty of adjusting and combining their results in the discussion below, with the exception of the discussion of tolerance.

Nicotine has a specific discriminative cue. This means that animals and humans can distinguish the subjective effects of nicotine from those of other drugs. In humans, nicotine’s mood-altering properties are subtle and user-regulated and range from stimulation to relaxation.

Intoxication refers to an extreme form of mood alteration, which is not characteristic of nicotine at its usual dose. Henningfield and Benowitz ranked six substances from most to least intoxicating as follows:

alcohol > heroin > cocaine > marijuana > nicotine = caffeine

(Hilts 1994). With respect to intoxication, persons smoking cigarettes are unlike persons drinking alcohol. For example, persons smoking cigarettes are not stopped by police for driving under the influence or driving while intoxicated, nor are smokers involved in smoking-associated brawls. Tobacco companies differ from the World Health Organization and other health agencies by focusing on the criterion of intoxication as key to their definition of addiction. If intoxication were the sole criterion of the definition of addiction, health professionals might agree that nicotine is not greatly addicting.

There are other important characteristics of dependence-producing chemicals. Chronic nicotine use produces an associated physical withdrawal syndrome. DSM-IV lists the symptoms of nicotine withdrawal as including 1) dysphoric or depressed mood, 2) insomnia, 3) irritability, frustration, or anger, 4) anxiety, 5) difficulty in concentrating, 6) restlessness, 7) decreased heart rate, and 8) increased appetite or weight gain. Severe alcohol withdrawal may result in delirium tremens, seizures, and hallucinations necessitating hospitalization. Nicotine withdrawal symptoms are uncomfortable,
but they do not require medical attention. According to withdrawal severity, one might rank these same substances as follows:

alcohol > heroin > nicotine > cocaine > caffeine > marijuana

Reinforcement is a third attribute of abused drugs. Reinforcement can be thought of “as a measure of the substance’s ability in human and animal tests, to get users to take it again and again, and in preference to other substances” (Hilts 1994). The Henningfield and Benowitz rankings for reinforcement based on models of animal self-administration are

cocaine > heroin > alcohol > nicotine > caffeine = marijuana

With cocaine, animals rapidly escalate their dose in preference to food until they die, whereas with heroin, animals more slowly escalate their dose, presumably by an increment that enables them to both feel a high and avoid withdrawal. In 1983, Victor DeNoble developed a rodent model of nicotine self-administration, which was withdrawn from publication in *Psychopharmacology* by Philip Morris Companies Inc. (Nowak 1994). With much difficulty, Corrigall and Coen (1989) were able to develop a rat model of nicotine self-administration. They needed to use a narrow nicotine dose to develop this model; no one has yet trained animals other than primates to smoke a cigarette. We (the authors of this chapter) believe that the rapidity of the “rush” caused by inhalation of the cigarette and the much higher levels of nicotine in arterial than in venous blood might alter the Henningfield and Benowitz ranking for humans smoking cigarettes.

Tolerance as defined by DSM-IV is either 1) the need for markedly increased amounts of the substance to achieve intoxication or the desired effect or 2) markedly diminished effect with continued use of the same amount of the substance (American Psychiatric Association 1994, p. 176). Without tolerance, persons smoking 20–40 cigarettes/day would become quite ill with symptoms of nicotine intoxication, ranging from nausea and headache to the potential for vision and hearing disturbances, diarrhea, confusion, and seizures. Surveillance data (U.S. Department of Health and Human Services 1988; U.S. Food and Drug Administration 1995) indicate that it takes from 3 to 4 years for many smokers to progress from sporadic low-dose smoking to daily use (subsequently stabilizing at a level of
1–2 packs/day). Dose escalations for the other drugs occur more rapidly. Tolerance occurs at different rates for different effects of each drug and may be incomplete. For example, tolerance of narcotic-induced respiratory depression is much more rapid than tolerance of the constipative effects of opiates. This may explain why Henningfield and Benowitz differ greatly from each other in ranking these substances (Hilts 1994). The rankings for tolerance according to Henningfield are

heroin > nicotine > alcohol > cocaine > caffeine > marijuana

and according to Benowitz are

cocaine > heroin > caffeine > alcohol = nicotine > marijuana

Nicotine appears to be addicting because of the high relapse rate when persons try to quit smoking. Regarding difficulty achieving abstinence despite adverse consequences, both Benowitz and Henningfield rated nicotine first among the drugs of abuse:

nicotine > heroin > cocaine > alcohol > caffeine > marijuana

Despite patients’ having myocardial infarctions, laryngectomies, chronic obstructive pulmonary disease, and other medical sequelae of smoking, 50% or more revert to smoking within days or weeks after leaving the hospital (U.S. Department of Health and Human Services 1988). Of young smokers, 70% regret having started smoking and 50% have at least one unsuccessful quit attempt by age 17 (George H. Gallup International Institute 1992). The long-term success rate for a single attempt at quitting smoking without assistance is about 5% (Cohen et al. 1989). Group and behavioral therapies increase the success rate to up to 20%, and the addition of the transdermal nicotine patch can double the 6-month abstinence rates (Hughes 1996). Most patients who make a serious attempt to quit will, even with good therapy, have to make 4–6 serious attempts to become abstinent (U.S. Food and Drug Administration 1995).

Hunt et al. (1971) compared relapse rates for clients discharged from opiate, alcohol, and tobacco dependence treatment programs and noted the remarkable similarity of relapse curves. Because the severity of addiction and the methods of treatment were not controlled, these curves are most important for their heuristic value.
They indicate that abstinence rates fall precipitously during the withdrawal and early posttreatment period; that most treated smokers, alcoholics, and heroin addicts relapse to at least a single use of their primary drug by the 3-month follow-up; and that those who have maintained abstinence for at least 6 months are much less likely to relapse. Even so, there are reports that 33% of successful quitters relapse after a full year of abstinence (U.S. Food and Drug Administration 1995).

During 1990, the inpatient chemical dependence units of the Medical College of Virginia, the Cleveland Clinic, the Minneapolis Veterans Affairs Medical Center, Gateway Rehabilitation Center in Pennsylvania, and CPC Parkwood Hospital in Georgia decided to integrate nicotine addiction treatment with therapy for other drug dependencies (Karan 1993). When they disallowed cigarettes entirely and considered smoking cigarettes to be a relapse, patient behaviors similar to those of other drug dependencies arose. Patients lined their suitcases to smuggle cigarettes into the unit. They stood atop toilets and surreptitiously blew smoke into the vents, and they created a black market with an elaborate distribution scheme to sell the cigarettes at an increased price. Patients risked losing their jobs and failing to graduate from the treatment programs by continuing to smoke. The unit milieu became so chaotic that each program soon declared cigarette amnesty and began to allow scheduled smoking breaks. Although the patients were in the action phase of quitting other drugs, they were not similarly prepared to quit a drug that had caused them fewer social or behavioral problems. Motivational programs to encourage future cessation are being devised. Because patients with alcohol and other drug dependencies have a more difficult time quitting cigarettes than quitting the other drugs, more intensive treatments are under development for the more severely addicted smoker.

Identifying the qualities of intoxication, physical withdrawal, reinforcement, tolerance, and difficulty achieving abstinence is a first step to understanding the similarities and differences between various drug dependencies. An improved understanding of the neurobiological basis of these characteristics can help us further refine DSM-IV and other current definitions of addiction. One aspect of drug addiction (e.g., intoxication) may involve specific receptors
and neurocircuits, which may overlap or be distinct from the receptors and neurocircuits responsible for other addictive drug aspects (e.g., physical withdrawal). Thus, further clarification of addictive qualities will be made possible in the future by advances in our knowledge of neurobiology, including more precise behavioral definitions based on neural mechanisms.

**Central Nervous System Effects**

Although what we know about nicotine’s actions on the brain is incomplete, significant advances in our understanding have taken place during the last decade. Early studies of tobacco use, including Horn’s Reasons for Smoking inventory, show that smokers smoke 1) for the “pleasurable-relaxing” effects, 2) for the stimulating effects, and 3) to “reduce negative feelings” or to “relieve anxiety” (Henningfield 1984). These effects are now attributed to nicotine’s pharmacological effects on the brain (U.S. Food and Drug Administration 1995).

It is believed that addictive drugs have common neural substrates and that nicotine’s release of dopamine in the mesolimbic pathways is central to its function as an addicting drug. Nicotine has been shown to stimulate local energy metabolism, as measured by 2-deoxyglucose autoradiography, and dopamine transmission, as estimated by brain microdialysis, in the shell of the nucleus accumbens (Pontieri et al. 1996). Fos-related protein expression in rats trained to self-administer intravenous nicotine and cocaine demonstrates overlapping patterns of activation in selected structures of the terminal fields of the mesocorticolimbic dopamine system (Pich et al. 1997). Corrigall et al. (1994) found that infusion of dihydro-β-erythroidine, a nicotinic antagonist, into the ventral tegmental area diminishes nicotine self-administration in rats. Additional supporting evidence for the role of the mesolimbic system in nicotine abuse is that both the administration of dopamine antagonists and lesions of the nucleus accumbens reduce nicotine self-administration in rats (Corrigall et al. 1992).

Whereas dopamine’s actions on the ventral tegmental area, the nucleus accumbens, and the prefrontal cortex have been thought to play a critical role in drug addiction through motivation and reward,
neuroscientists now believe that dopamine acts as an aid to learning by highlighting and drawing attention to certain “significant or surprising events” (Wickelgren 1997, p. 35). This new view of dopamine as an aid to learning can help explain why drug addicts continue to abuse drugs when the euphoric effects of the drug have worn off or even become distasteful. It may also provide a better understanding of the role of dopamine in schizophrenia and attention-deficit/hyperactivity disorder, in which dopamine may abnormally heighten attention to external events rather than causing pleasure.

Much of the neuroscience of nicotine has yet to be discovered. In addition to the mesolimbic pathway, there could be other pathways, directly and indirectly affected by nicotine, that contribute to its reinforcing effects and learned behaviors.

It is possible that, whereas nicotine-induced release of dopamine drives tobacco usage, inactivation of nicotinic acetylcholine receptors (nAChRs) by low levels of nicotine plays a role in the processes of tolerance and withdrawal (Dani and Heinemann 1996). With continued smoking, nicotine builds up to a low steady-state concentration that causes the nicotinic receptors to become desensitized or unresponsive to a nicotine agonist. With time, these receptors may undergo longer-term inactivation. After inactivation, there is less nicotinic receptor turnover, resulting in an increased number of these receptors (Peng et al. 1994). Under conditions of abstinence, a portion of the inactive nAChRs recover to a responsive state, and withdrawal is invoked by pathways that are hyperexcitable to synaptically released acetylcholine. This contributes to the drive for the next cigarette. Thus, with tolerance and withdrawal, smokers may be medicating themselves with nicotine to regulate the number of functional nAChRs in neurocircuits, which are most likely different from the mesolimbic dopaminergic system neurocircuit.

Factors Contributing to the Addictive Potential of Nicotine in Cigarettes

Given the framework of what is known about nicotine’s mechanisms of action and the characteristics of drug addiction, some of the reasons why cigarette smoking is so addicting are now explored.
Tobacco is frequently the first mood-altering substance an individual might regularly consume, excluding caffeine. This may occur passively in utero and/or through active consumption during early adolescence. Chronic tobacco use during these early and formative years may result in neurochemical perturbations, which may in turn predispose the individual to continued use in future years. The earlier the onset of use, the more difficulty in quitting tobacco.

Nicotine has rate-dependent activity that is useful in normalizing arousal states, as described by Grobe and Perkins (Chapter 3, this volume). Low-activity rats exposed to nicotine increase their activity, whereas the reverse occurs in high-activity rats (Rosecrans 1995). Subtle stimulation and/or relaxation effects may be thought beneficial by users who would like to fine-tune their dispositions at a given time. (Potential therapeutic uses of nicotine, such as treatment of attention-deficit/hyperactivity disorder [Levin et al. 1998], may take advantage of this quality [see also Levin et al., Chapter 9, this volume].)

Inhalation via the cigarette provides an extremely rapid drug delivery system. The nicotine is carried by tar particles into the small airways and alveoli of the lungs, where it is buffered to a physiological pH. Nicotine is rapidly absorbed from the large surface area of the lungs, which distribute it directly into the arterial system and to the brain (Zevin and Benowitz, Chapter 2, this volume). The more rapid the onset of mood alteration or “rush,” the more addicting the form of drug. Nicotine’s effects through a cigarette are more rapid than those of nicotine given intravenously, intranasally, orally, or transdermally. An analogy can be made between cigarettes and crack cocaine with respect to the rapidity of drug action: inhaling a cigarette is for nicotine what smoking crack is for cocaine. Additionally, ammonia and other constituents of the cigarette may increase the bioavailability of nicotine (Connolly 1997; Slade et al. 1995).

Individuals can self-titrate their nicotine intake to get their desired effect by adjusting the way they take puffs from a cigarette. They may also close the pores of the filter with their fingers to increase the tar and nicotine they receive (Kozlowski et al. 1989).

If each puff is considered a dose of nicotine, smokers give themselves a short interdose interval. An average smoker takes 10 puffs
from each cigarette. This corresponds to 200 puffs per day for the 1-pack/day smoker and 400 puffs per day for the 2-pack/day smoker. No other drug is dosed this frequently. Spread throughout a 15-hour day, a 1-pack/day smoker would average taking a puff every 4.5 minutes, and a 2-pack/day smoker would average taking a puff every 2.25 minutes.

Next, frequent nicotine dosing with its corresponding subtle mood alteration becomes intertwined with daily activities, for many years. Events from waking up in the morning, to talking on the telephone, driving one’s car, finishing a meal, taking a coffee break, watching television, having sex, combating fatigue, dealing with worries or concerns, and relaxing during stressful interactions all become enmeshed with the need for a cigarette. These conditioned cues trigger neurochemical events and craving that contribute tremendously to the difficulty smokers have in abstaining from cigarette smoking and relapsing once they have quit. Peripheral cues, such as the smell of flavorings and harsh sensations in the back of the throat, may serve to assure smokers of the upcoming discriminative cue, with its delicate effects on mood (Rose and Behm 1995).

Additional reasons why some persons smoke cigarettes include oral gratification, sensorimotor handling of the cigarette, weight loss, and the fear of weight gain (Gritz et al. 1996; see Westman and Rose, Chapter 10, this volume, for more on the sensorimotor effects of smoking). The cinema and advertising portray sexy, slender women and handsome, rugged men smoking. These images integrate into society and are internalized by smokers. Some successful behavioral cessation techniques involve counteracting these messages with the positive visualization of oneself as a nonsmoker.

In summary, many factors contribute to the profoundly addictive quality of nicotine in cigarettes: the early onset of drug use with neuroadaptation, the rapid onset of drug action, the capability of the drug to subtly stimulate or relax, its rapid onset of action, its ability to allow for self-titration, its short and frequent dosing interval, and its pairing to multiple conditioned cues intertwined with daily life events, in addition to oral gratification, sensorimotor handling, weight loss, and associated changes in self-image.
Assessing the Addictive Capacity of Nicotine Replacement Therapies and Newly Developed Nicotine Analogues

Nicotine replacement therapies (NRTs) and novel nicotinic analogues are being explored for their potential therapeutic actions on acetylcholinergic receptors and the neurocircuits involving these receptors. Assessing the addictive potential of these substances may be advantageous in determining benefits versus side-effect profile for a given drug. This assessment is important in both the general population and specific subsets of persons needing or using the drug, such as those with attention-deficit/hyperactivity disorder, Alzheimer’s disease, or inflammatory bowel disease. The following qualities may be useful in determining the addictive capacity of newly developed nicotine analogues as well as current and future nicotine replacement therapies.

Define Subjective Drug Effects

Because addictive drugs are used for their mood-altering properties, it is critical to discern subjective drug effects in assessing the addictive potential of new NRTs or nicotine analogues. Whereas in animals one might study locomotor activity and performance in various mazes, reports on human subjects are needed in order to qualify subjective effects. Rating scales of drug “liking,” dysphoria, stimulation, relaxation, and other such qualities are needed in addition to tests of concentration and achievement. For instance, Jasinski et al. (1984) found that nicotine elevated scores on the Liking and MBG scales of the Addiction Research Center Inventory similarly to morphine and Benzadrine. With regard to future drug development, to compare the effects of a new nicotine analogue with those of nicotine, it would be helpful to measure any changes in evoked potentials during alertness and alterations in electroencephalographic patterns during wakefulness and sleep.

Drug discrimination studies are possible in both animals and humans. One would want to discover whether the novel nicotine product generalizes to the same cue as does nicotine or amphetamine and determine its time course and its ED$_{50}$, the effective dose...
(or effective concentration) at which 50% of subjects respond. In comparing the mechanism of the new drug action with that of nicotine, one might investigate whether there is also antagonism by mecamylamine, a central nervous system acetylcholinergic antagonist, or other types of blockers. If the drug is a racemic mixture, both isomers should be assayed for their activity.

**Determine Other Desirable Drug Effects That Could Contribute to Abuse**

Some drugs have desirable effects other than for the therapeutic use for which they were designed. These desirable effects can contribute to drug abuse. For instance, there is some trepidation that adolescent girls and women will use over-the-counter NRTs to enhance and maintain weight loss. An understanding of any new drug’s effect on food intake and metabolism is important, as is discerning whether the new drug has additional qualities that may be sought after.

**Determine Pharmacokinetic and Pharmacodynamic Properties of the Drug and Its Active Metabolites**

The drug delivery system can dramatically affect the rate of onset of drug action, the ease of drug use, and the ability for self-titration. Mood-altering drugs that have a slower onset of action have a lesser risk of abuse. The onset of drug action is dependent on the drug’s route of administration, bioavailability, bioactivity, and dosage. Lipid solubility and means for crossing the blood-brain barrier are critical for central drug effects. Not only the drug itself but also its metabolites need to be checked for activity.

**Determine Mechanism(s) of Drug Action**

As nicotine’s actions on various receptor subtypes and neurocircuits are understood, it would be important to contrast and compare how similar these mechanisms are to the mechanisms of new analogues, or how different from them. If the new analogue had other nonnicotine activity, this activity would be important to define. Mechanisms of nonnicotine activity may be associated with a lesser risk of abuse for newly developed nicotine analogues.
**Determine Initial Sensitivity to Dose and Acute and Chronic Tolerance of Drug Effects**

Drugs may have both desirable and aversive effects. In addition to defining the subjective effects of a new NRT or nicotine-like drug, determining initial sensitivity and the rate of tolerance of these effects is helpful in determining whether a drug will be used, the rate of dose escalation of the drug, and the proportion of persons who will maintain use of the drug. One might presume that continued drug use will occur if the response to initial drug action is desirable and tolerance of aversive drug effects is rapid. It is not yet known for addictive substances whether tolerance of desired drug effects is preferentially slow or rapid.

**Determine Receptor Kinetics**

Receptor kinetics, including especially the rate of desensitization of the receptor, may be important in determining the duration of effect in novel nicotine analogues and products. Individual differences in desensitization may produce variation in both the duration of drug effect and the acquisition of tolerance of this effect. Understanding the basis for individual differences in receptor kinetics may be helpful in identifying subpopulations at risk for drug addiction.

**Test for Continuing Self-Administration of the Drug**

One might test the ease or lack of ease of developing an animal model for drug self-administration for different strains in animals. For instance, Sprague-Dawley rats self-administer nicotine more readily than do the genetically distinct Fischer rats. From this one might predict that nicotine by itself is less reinforcing than the other drugs and that there is a genetic basis for individual variation in susceptibility to drug use.

The less an animal will work for a drug, the less risk of abuse the drug is believed to have. Therefore, one could test for addiction potential by gradually increasing reinforcement ratios. The goal would be to determine the extent to which an animal will press a bar before drug-seeking behavior is extinguished. Additionally, tests of conditioned place preference can detect the rewarding effects of drugs.
Animal models that test dopamine release from the nucleus accumbens with drug self-administration can help determine whether the new nicotine analogues are similar to other drugs of abuse with respect to their actions on the mesolimbic pathway. Determining drug self-administration or conditioned place preference in knockout mice lacking specific subtypes of dopamine receptors may also provide useful information about the mechanism of drug action.

Tests for self-administration of new NRTs and nicotine analogues in humans can also be performed. Initial tests during phase 1 trials may be performed to get an initial evaluation of drug liking. Experimental paradigms in humans can also test the amount of work they will do to receive given drug doses. In humans it is important to test subpopulations for addiction susceptibility. Clinical trials can be performed in healthy volunteers, cigarette smokers, alcoholics, users of other street drugs, and persons with various comorbidities such as attention-deficit/hyperactivity disorder, depression, and schizophrenia. The drug development goal would be for persons who need a drug therapeutically to want to use the drug and for healthy volunteers not to want it.

In addition, postmarketing surveillance can determine the abuse potential of new agents when they become widely available. Rates of experimentation, patterns of use (e.g., binge, daily, escalating), and rates of continued use can be monitored. One might also ascertain whether the new nicotine analogues substitute for other abused drugs. Unlike the paradigm of drug discrimination, the substitution of one drug for another abused drug on the street may or may not be made with drugs of the same class: addicts frequently alternate between abusing heroin, cocaine, and other drugs. If the preferred substance becomes less available, another drug (often alcohol) can be substituted. This phenomenon should also be monitored during postmarketing surveillance.

**Determine Withdrawal After Acute and Chronic Drug Exposure**

Testing for physical withdrawal symptoms should occur after prolonged use of the NRT or new analogue. Tests to see whether the
withdrawal can be reversed with nicotine, clonidine, or other drug classes may be helpful in understanding the mechanisms of physical dependence of a new drug. Other testing methods include determining whether the new drug can combat withdrawal symptoms produced by chronic nicotine exposure and whether nicotine antagonists can precipitate withdrawal after chronic exposure to the new nicotine analogue.

Test for Relapse and/or Drug Craving Once the Drug Is Discontinued

Testing for relapse once the therapeutic indications for a drug no longer exist and the drug is tapered or otherwise properly discontinued can help to determine addiction liability. As part of this assessment, it may be helpful to ascertain whether physical withdrawal symptoms play a role in relapse and to determine the extent to which conditioned cues contribute to drug craving.

Weigh the Benefits of Increased Drug Accessibility Against the Risks of Abuse Liability to Determine Whether to Schedule the Drug

In evaluating the benefits of increased drug accessibility, the prevalence and severity of the disease and the benefit of drug therapy need to be taken into account. Then, against these factors should be weighed the prevalence and severity of intoxication, physical withdrawal, reinforcement, tolerance, and difficulty in achieving abstinence from the potentially abused substance.

Addiction may be less of an issue for drugs designed as maintenance therapy in Alzheimer’s and Parkinson’s diseases than for other drugs, because these illnesses are devastating and occur during the later stages of life. Addiction is more of an issue if a nicotine analogue is used to treat children and adolescents with a disorder such as attention-deficit/hyperactivity disorder because of increased potential for substance abuse in these subpopulations and the potential for long-term neurochemical changes.
Summary

Nicotine is problematic because of its role in causing continued tobacco use. In humans, nicotine causes short-term sympathetic effects and acute release of multiple hormones and may play a chronic role in accelerating atherosclerosis. In the developing fetus, nicotine may arrest neuronal replication and differentiation (Slotkin et al. 1987), and it may be associated with the sudden infant death syndrome. Despite concerns of cardiovascular toxicity and peptic ulcer disease, nicotine has not been found to have a major thrombotic effect nor to alter gastric mucosal thickness. Nicotine does not destroy the pulmonary parenchyma. It is unresolved whether the amount of nicotine-derived nitrosamines is sufficient to contribute to cancer (Society for Research on Nicotine and Tobacco 1995). Thus, although nicotine clearly has an important role in maintaining smoking behavior, it is the other constituents of the cigarette and products of its combustion that are injurious.

As discussed by Newhouse and Whitehouse (Chapter 7, this volume), nicotine can be used as a probe to enhance our understanding of brain function. Potential therapeutic applications for nicotine and its analogues include enhancing cognition in Alzheimer’s disease, preventing Parkinson’s disease, and improving symptoms in Tourette’s syndrome and ulcerative colitis. Nicotine may benefit persons with attention-deficit/hyperactivity disorder, schizophrenia, obesity, depression, anxiety, and sleep apnea. Although these applications are being investigated and the mechanisms for activity becoming understood, nicotine-related research needs to be fostered. Because of the role of nicotine in the morbidity associated with cigarette smoking, nicotine-related neurobiological research and future therapies are experiencing negative repercussions.

In usual therapeutic doses, nicotine can be addictive, but it is relatively safe and not intoxicating. A backlash against nicotine needs to be prevented in order to avoid impeding progress in understanding neurobiology, developing medication, and using future therapies.

Scientists are just beginning to understand the mechanisms of central drug action, tolerance, withdrawal, reward, and learning. Further understanding of these mechanisms and an improved understanding of nicotine’s action will help also in the analysis of the therapeutic and addictive potential of NRTs and new nicotine analogues.
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SECTION II

Clinical Applications
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The overarching theme of this book is the fact that nicotine is a drug with significant neuropharmacological properties. The increasing recognition of nicotine as a potent drug makes it extremely important to consider carefully the relationship between nicotine use and major mental disorders. Although the interest of medical researchers in tobacco smoking and its effects on health grew rapidly in the 1960s and 1970s, studies of the relationships between nicotine, smoking, and mental disorders are a much more recent phenomenon. In this chapter intriguing epidemiological findings are examined regarding the association between smoking and specific mental disorders. In addition, consideration is given to the underlying psychological and neurobiological mechanisms that may explain these relationships. Finally, certain issues regarding the treatment of nicotine dependence in psychiatric patients are reviewed.

The Epidemiology of Smoking and Mental Disorders

As awareness has grown regarding the carcinogenic effects of smoking and the addictive properties of nicotine, considerable attention has been given to tracking the epidemiology of smoking in the population of the United States. Typically, these analyses have focused on issues such as age, gender, educational background, and socioeco-
omic status. Links to medical disorders have focused primarily on the relationship to cardiopulmonary disease and cancer. These studies have emphasized the most prevalent form of tobacco use, cigarette smoking, and that is the focus of this chapter.

**Smoking in the General Population**

Although the cultivation and use of tobacco has been an intrinsic part of American culture since the founding of the country, it was the technological advances involved in the development of the cigarette that made widespread use of tobacco a 20th-century phenomenon. Detailed prevalence data regarding cigarette smoking have been maintained since 1965 via the National Health Interview Survey (Giovino et al. 1995). From 1965 to 1993 the prevalence of smoking among adults dropped from 42% to 25%. Over the same period, the prevalence of cessation (i.e., the discontinuation of smoking) increased from 24% to 50%. Overall, men have been more likely to smoke than women: 1993 prevalence rates were 28% and 22%, respectively. The declines in prevalence observed in recent decades have been greater among those who have attained higher educational levels, and higher prevalence is associated with poverty, blue-collar employment, being separated or divorced, and active military service.

Although the trends noted above are encouraging, the fact remains that approximately one-quarter of the adult population in the United States continues to smoke cigarettes. In addition, the gains of cessation programs are to a significant degree being offset by a steady stream of adolescents initiating cigarette smoking. The toll taken by tobacco use remains extremely high. Cigarette smoking is the single largest cause of preventable deaths in the United States: roughly 20% of deaths are attributable to a smoking-related illness (Bartecchi et al. 1994).

**The Epidemiology of Smoking in Relation to Specific Mental Disorders**

As noted above, detailed data have been available regarding smoking and the general population for more than 30 years. Although clinicians have long been anecdotally aware of an apparent high
prevalence of smoking among psychiatric patients, quantitative assessments have been made only recently.

**Population-based epidemiological studies.** The landmark Epidemiologic Catchment Area (ECA) study represented a major step forward in defining the prevalence of mental disorders in this country. The design of this study not only provided epidemiological data on the prevalence of individual disorders, but also allowed analysis of the comorbidity of these disorders with the abuse of alcohol and/or other drugs (Regier et al. 1990). Unfortunately, investigators at most sites did not gather information regarding cigarette smoking. Glassman et al. (1990) were able to analyze the ECA data from St. Louis with interesting results. The prevalence of depression was 6.6% among those who had ever smoked daily versus 2.9% among those who had never smoked. The same study showed no significantly increased prevalence of smoking among patients with dysthymia, phobias, agoraphobia, obsessive-compulsive disorder, or panic disorder when major depression did not coexist with these diagnoses. These researchers did note a significant increase in smoking among patients with alcohol abuse and dependence. The low number of subjects with schizophrenia did not allow meaningful conclusions regarding this disorder.

The National Comorbidity Survey (NCS) was conducted between 1990 and 1992 to examine comorbidity between drug use and dependence and other mental disorders. The data from this study are being analyzed, and reports have appeared in the literature (Warner et al. 1995). The initial NCS data regarding smoking in the general population are similar to those of other studies in that 24.1% of this study population ages 15–54 had developed tobacco dependence during their lifetime (Anthony et al. 1994). Further analyses of the database created by the NCS are in progress and should allow a more detailed examination of the links between tobacco dependence and other mental disorders.

Breslau and colleagues (Breslau 1995) made use of similar community-based sampling to explore the relationship between psychiatric disorders and tobacco use. In their sample of 1,007 young adults, 40.9% reported ever smoking and 20% had been dependent on nicotine at some point. Nicotine dependence in this study was posi-
tively associated with a history of major depression, anxiety disorder, early conduct problems, and abuse of alcohol and illicit drugs, but data regarding schizophrenia were not reported because of the sample size.

**Studies of selected patient groups.** Other investigators have focused on mixed populations made up entirely of psychiatric patients. Hughes et al. (1986) surveyed 277 outpatients coming to a general psychiatric clinic. Of the entire group, 52% were smokers. The percentages of smokers for specific diagnoses were 88% for schizophrenia, 70% for mania, 49% for major depression, 47% for anxiety disorders, 46% for personality disorders, and 45% for adjustment disorders. Hall et al. (1995) studied a group of 300 outpatients, the majority of whom were schizophrenic. Of their group, 56% were smokers. Lawrie et al. (1995) found a higher rate of smoking among 35 acutely hospitalized psychiatric inpatients. Eighty percent of the patients with schizophrenia were smokers, and 75% of those with affective disorders smoked. De Leon et al. (1995) found a very similar prevalence of 79% for smoking in a group of 360 psychiatric inpatients. In this group, 53% of the patients had schizophrenia. The prevalence of smoking for male schizophrenic patients was 93%, for male nonschizophrenic patients 78%, for female schizophrenic patients 70%, and for female nonschizophrenic patients 51%. The authors noted that the problem of polydipsia (excessive fluid consumption) was associated with heavy smoking in the patients with schizophrenia.

Several studies have focused exclusively on groups of patients with schizophrenia, confirming the high prevalence of smoking described above. In 1983, O’Farrell et al. noted a prevalence of smoking of 88% in schizophrenic patients. In 1984, Masterson and O’Shea studied 100 schizophrenic patients and found that 80% had a history of smoking for more than 16 years. Yet despite their smoking pattern, the patients did not display significantly higher rates of malignancies. A 1987 report from Munetz and Davies examined smoking in 72 schizophrenic outpatients and found that 72% were smokers. In 1991, Sandyk and Kay reported on 142 schizophrenic patients and noted that those who were smokers had a significantly earlier age at onset of schizophrenia. Goff et al. (1992) examined 78 schizophrenic patients; 74% were current smokers, 12% were former smokers, and
14% had never smoked. Smokers tended to be male and younger, with an earlier age at onset, more hospitalizations, and higher neuroleptic doses. A report by Sandyk and Awerbuch (1993) noted a lower prevalence of smoking in schizophrenic patients with late onset (15.4%) than in those with early onset (54.9%). Ziedonis et al. (1994) examined 265 outpatients with schizophrenia; 68% were current smokers, 7% were former smokers, and 24% had never smoked. These researchers also observed an earlier age at onset of schizophrenia in those who were smokers.

In summary, whereas the rate of smoking in the general population currently stands at about 25%, groups of individuals with various psychiatric disorders clearly display a much higher prevalence. For patients with schizophrenia, the reported prevalence has been as high as 93% in males, and every report shows a prevalence two to three times greater than that in the general population. For patients with major depression, the prevalence of smoking in most reports is roughly twice that observed in the general population. The data regarding other mental disorders are sparse, but the NCS data should provide more definitive answers regarding potential associations with anxiety disorders and other diagnostic categories.

**Associations between smoking, pharmacological treatment, and side effects.** The ability of cigarette smoking to alter drug metabolism, typically by accelerating it, is well known (Benowitz 1988). Given a large number of different components in cigarette smoke, it often is unclear which is responsible for the pharmacological alteration. In terms of commonly prescribed psychotropic drugs, smoking has been shown to increase the metabolism of imipramine but not nortriptyline, lorazepam, or diazepam. Although diazepam appears unaffected, there does appear to be accelerated metabolism of one of its active metabolites (Benowitz 1988).

Given the strong association between smoking and schizophrenia described above, it is especially pertinent to be aware of any interactions between smoking and the metabolism of antipsychotic drugs. It now has been well established that smoking has a significant effect on the metabolism of haloperidol; as a result, different dosing equations have been established for smokers than for non-smokers (Perry et al. 1993). These analyses have indicated that, in the
lower end of the desired therapeutic range of haloperidol blood concentrations, smokers may require doses as much as sevenfold higher than nonsmokers. Even in the upper limit of the therapeutic range, there is still a twofold difference between smokers and nonsmokers. Similar evidence of increased smoking-associated metabolism of neuroleptic drugs has been reported for other neuroleptics (Blumberg and Safran 1991).

Another interesting aspect of drug treatment in schizophrenic patients who are smokers has emerged. In studies of the atypical neuroleptic clozapine, patients have been observed to have a significant decrease in daily cigarette use when receiving clozapine as compared with standard neuroleptic drugs (George et al. 1995; McEvoy et al. 1995b).

In a series of studies, interesting observations have been made regarding smoking and neuroleptic side effects, especially parkinsonism and tardive dyskinesia. In 1987, Yassa et al. studied a group of chronic psychiatric outpatients and found a significantly higher prevalence of tardive dyskinesia in smokers than in nonsmokers. Binder et al. (1987) reported similar results in a study of 126 outpatients, again showing that the smokers were more likely to have tardive dyskinesia. Although the patients in the study by Yassa and colleagues showed higher doses of medication in the smoking group, the Japanese patients in the study by Binder and associates had relatively comparable doses of neuroleptics. A 1988 study by Wagner et al. examined parkinsonism in patients treated with neuroleptics. The data did not reveal any consistent relationship between extrapyramidal symptoms and smoking. Decina et al. (1990) studied 130 psychiatric inpatients who had received neuroleptic drugs. Although the smokers were receiving higher doses of neuroleptic medications before the study, they had significantly less parkinsonism than nonsmokers. Menza et al. (1991) studied 126 chronic psychiatric patients and evaluated tardive dyskinesia, parkinsonism, and akathisia. Once again, smokers received higher doses of neuroleptics. No difference was observed between smokers and nonsmokers with regard to tardive dyskinesia or parkinsonism; however, female smokers had more akathisia. Sandyk (1993), in examining 111 chronically institutionalized schizophrenic patients, observed a lower prevalence of parkinsonism in the smokers than in
the nonsmokers. It is interesting that the smokers also displayed significantly less cognitive impairment. In a study of 51 outpatients with schizophrenia, Zaretsky et al. (1993) noted no significant association between tardive dyskinesia and smoking. Finally, in 1994 Sachdev and Kruk studied a cohort of 100 consecutive inpatients regarding the development of acute akathisia and found no association between akathisia and smoking status.

In summary, intriguing questions have been raised regarding the possibility of some association between smoking and extrapyramidal disorders, especially the potential for an increase in tardive dyskinesia and a decrease in parkinsonism among smokers.

**Theoretical Considerations Regarding the Positive Association Between Smoking and Mental Disorders**

The data reviewed above provide a compelling argument that there is a strong positive association between smoking and both schizophrenia and depression. Similar positive associations may exist between smoking and other mental disorders, but the epidemiological data are not yet strong enough to confirm them. It is important to note that the positive associations identified are statistical associations, not conclusive causal links. It simply is not known whether the underlying neurobiology of the mental disorders in some way predisposes to smoking, whether smoking somehow increases the risk for developing a mental disorder, or whether the two are related through other indirect mechanisms. Nevertheless, it is of value to review some of the known facts regarding the psychological, neurobiological, and pharmacological effects of smoking in order to better understand why the association with mental disorders may exist. In Chapter 6 in this volume, Piasecki further examines the link between smoking and depression. The discussion below focuses on smoking and schizophrenia.

**Psychological Factors**

The psychological and behavioral effects of smoking are complex, and they appear to be dependent on the dose and timing of nicotine
use (Benowitz 1988; Grobe and Perkins, Chapter 3, this volume). Smoking (especially after a period of relative abstinence, as in the early morning) may be alerting and may improve cognitive processes, including attention and performance. There is a methodological problem in that most studies have been conducted with smokers who were allowed to smoke after a period of relative abstinence, raising the question of whether the performance improvement was due in part to the relief of withdrawal symptoms. There is evidence, however, that the performance enhancement accompanying arousal is a direct effect of nicotine. In addition to the arousing effects and positive enhancement of concentration and cognitive performance, there also is evidence that nicotine has direct effects on mood. Smoking is described as having calming effects, especially in stressful situations. Thus, depending on the context, nicotine self-administered through smoking has the ability to be associated with both alerting and calming effects. These rewarding effects are felt to have a key role in the development of tolerance to and dependence on nicotine in some individuals (Pomerleau et al. 1993).

Mental health clinicians can immediately recognize the susceptibility that individuals with various mental disorders might have to the rewarding effects of nicotine. In schizophrenia, the negative impact of the illness on cognitive performance, especially concentration and problem solving, is well understood; patients often show lower performance scores than verbal scores on intelligence testing. Although often less well recognized, many patients with schizophrenia also experience coexisting depression. The psychological benefits of a drug that improves both cognitive performance and mood would seem, in theory, to make the patient with schizophrenia very vulnerable to smoking.

**Neurobiological Factors**

As biobehavioral researchers are increasingly aware, it is difficult to separate the perceived psychological and behavioral effects of any drug from its underlying neurobiological activity (Pomerleau et al. 1993). The biological activity of nicotine is potent and complex. It binds to cholinergic receptors in the peripheral and central nervous system, acting as an agonist. This cholinergic activity may be linked
directly to the apparent cognitive-performance-enhancing properties of nicotine, insofar as the cholinergic system plays a key role in memory, attention, and related functions.

Recent studies also have elaborated a key role for a relationship between nicotine and dopaminergic systems. Nicotine stimulates dopamine release in the mesolimbocortical dopamine system (Nisell et al. 1995), which is a pathway central to reward mechanisms and to the modulation of motivational factors related to cognition. There also are data indicating that the acute effects of nicotine on dopamine release may differ from those resulting from chronic administration; thus the role of dopamine may differ in the initiation of smoking as contrasted with tobacco dependence (Kirch et al. 1987).

In addition to the effects of nicotine on acetylcholine and dopamine, studies also have demonstrated effects of nicotine on other monoamines, especially norepinephrine and serotonin, as well as a number of hormones, including vasopressin, growth hormone, and adrenocorticotropic hormone (ACTH) (Benowitz 1988; Pomerleau and Pomerleau 1984). The effects of nicotine are also dose dependent. In low to moderate doses, nicotine may stimulate the sympathetic nervous system, and there may be corresponding physiological responses such as increased blood pressure and tachycardia. At very high doses, however, nicotine may result in hypotension and bradycardia.

Additional intriguing information regarding the role of nicotine in the brain was provided by Fowler et al. (1996) in a study showing that smokers have a decrease in the brain level of monoamine oxidase B (MAO B) compared with nonsmokers. This enzyme plays a role in the degradation of dopamine; therefore, decreased MAO B activity may increase central nervous system dopamine levels, and it may also have indirect effects on norepinephrine, serotonin, and other neurotransmitters.

Potential links between the neurobiological properties of nicotine and the mental disorders with which it is associated should be apparent. In relation to schizophrenia, the dopaminergic effects of nicotine are especially intriguing. A number of recent studies of schizophrenia have raised the question of hypodopaminergic function in the prefrontal cortex, an area of the brain in which nicotine appears to stimulate dopamine metabolism. This raises the hypo-
theoretical possibility that individuals with schizophrenia may smoke in an effort to stimulate these dopamine projections (Glassman 1993; Lohr and Flynn 1992). The hypothesis that patients with schizophrenia may smoke in order to correct underlying neurobiological deficits is supported by another line of evidence. Adler et al. (1993) have shown that a neurophysiological deficit in schizophrenic patients—their failure to show normal sensory gating in response to auditory stimuli—is transiently corrected immediately after smoking. From animal studies, nicotinic cholinergic systems are known to be important in sensory gating, and sensory gating is also affected by dopamine and norepinephrine (Adler et al. 1993).

The observation by some, but not all, investigators that patients with schizophrenia who are smokers are also more likely to have tardive dyskinesia and less likely to display parkinsonism is also of neurobiological interest. Another neuropsychiatric disease involving abnormalities in dopamine, Parkinson’s disease, has been shown in numerous studies to be negatively associated with smoking. In most studies, smokers have approximately half the risk of developing Parkinson’s disease (Morens et al. 1995). Parkinson’s disease involves a decrease in dopamine activity in the nigrostriatal pathway, whereas tardive dyskinesia is thought to reflect dopaminergic supersensitivity in this same pathway. The possibility exists that either the acute release of dopamine caused by nicotine or a chronic effect of nicotine—increased dopamine receptor supersensitivity—may make smokers more at risk for neuroleptic-induced tardive dyskinesia (Kirch et al. 1988). If smokers are at less risk than are nonsmokers for parkinsonian side effects from neuroleptics, it may relate directly to the effects of nicotine on dopamine release or on cholinergic systems, or it may be an indirect effect of smoking: that of lowering neuroleptic blood levels.

**Pharmacotherapeutic Factors**

As described above, it is well known that smoking results in decreased blood levels in response to a given dose of many psychopharmacological agents. A corollary observation is that, especially in the case of treatment of schizophrenia with neuroleptic drugs, patients who are smokers are often given higher doses. The
neuroleptic drugs are commonly associated with side effects that trouble patients. It is conceivable that patients have discovered empirically (although perhaps not consciously) that smoking lowers the blood level of drugs and results in a diminution of side effects. In addition to neuroleptics, schizophrenic patients also are often treated with anticholinergic agents. Although these agents may help counteract the extrapyramidal side effects of neuroleptic medications, they also may be associated with some adverse anticholinergic effects, including cognitive blunting. Once again, it is conceivable that patients find that their cognitive function is improved by smoking—via the cholinergic agonist properties of nicotine.

Recent studies illustrate the potential complexity of the interactions between neuroleptics and nicotine. In a study of smokers with no medical or psychiatric disorder, Dawe et al. (1995) observed that the administration of oral haloperidol caused an increase in smoking by the subjects compared with their response to placebo. The authors attributed this to the blocking of dopaminergic reward pathways by haloperidol, for which the smokers attempted to compensate by increasing their nicotine intake in order to stimulate these pathways. In a similar vein, McEvoy et al. (1995a) observed that, after haloperidol was initiated in acutely ill patients with schizophrenia, their smoking increased.

**The Complexity of the Linkage Between Smoking and Mental Disorders**

This discussion highlights the probability that no simple, unidirectional link is likely to exist between smoking and any specific mental disorder. This probability certainly parallels the growing realization that the mental disorders themselves are likely to be a result of complex interactions between genetic and environmental factors and to involve multiple neurotransmitter and neurohormonal systems. Nevertheless, certain themes do stand out. In psychiatric patients, as well as in other individuals, nicotine has the ability to enhance both cognitive performance and mood. These functions are impaired in a broad range of psychiatric disorders. A key system involved in the neurobehavioral effects of nicotine is the dopaminergic reward pathway, a primary site of pharmacological activity for nicotine. Care must
be taken, however, not to reduce the issue simply to one of self-medication with nicotine by psychiatric patients. As in any case of drug use and dependence, the factors maintaining nicotine dependence may differ from those involved in the initiation of use of the drug.

Most important is that, whatever psychopharmacological benefits might accrue to patients from nicotine use, the cigarette remains deadly. Psychiatric patients should be assumed to be at equal risk for the negative medical effects of smoking. Our goal should be to better understand the biopsychosocial mechanisms underlying these patients’ smoking in order to better treat their mental disorders as well as to discover effective strategies for alleviating their nicotine dependence.

**Nicotine Use and Smoking Cessation in Relation to Psychiatric Treatment**

Although the positive association between smoking and several major mental disorders is irrefutable, as described above, the causal nature of this relationship remains ambiguous. Nevertheless, for the practicing clinician, the reality is that most patients treated for schizophrenia are also likely to be smokers who are dependent on nicotine. This is a form of comorbidity not nearly as widely recognized as that between mental disorders and the abuse of alcohol and illicit drugs (Regier et al. 1990). As a result, there is relatively little in the published literature to guide the clinician in the practical aspects of treating concomitant mental disorders and nicotine dependence. Some of the major clinical issues are outlined below.

**Approaching Smoking as a Treatment Issue**

Most clinicians have encountered the belief, in their patients, their colleagues, or themselves, that the stresses involved in experiencing a major mental disorder are such that it would unnecessarily complicate treatment to view smoking as an active therapeutic issue. A simplistic view of smoking as self-medication for the patient may reinforce this avoidance of smoking as a focus of treatment. From this perspective, the patient smokes in an attempt to alleviate psychic stress, and only when the mental disorder is effectively treated can
smoking be approached as a problem. Unfortunately, few clinicians who take this view ever get to the point of approaching smoking as a treatment issue. Often the mental disorder is chronic, especially in the case of schizophrenia, and no full remission is ever attained. In such cases, the patient’s smoking may not be addressed out of fear of further destabilization.

A better approach would seem to be that of directly dealing with the comorbidity. This does not necessarily mean that, in the midst of an acute psychiatric exacerbation, an attempt should be mounted simultaneously to achieve smoking cessation. It does mean that, when the patient is in a state of relative psychiatric stability, an attempt to deal with the nicotine dependence can be made. Given the greater susceptibility of psychiatric patients than of other individuals to nicotine dependence, it is unlikely that smoking reduction or cessation can be achieved through simple, unidimensional models such as self-directed use of nicotine gum or large-scale group cessation programs. A combined approach using pharmacological and behavioral techniques probably will be required for most patients with a psychiatric disorder. The clinician has been provided with a guide to the range of cessation techniques in the “Practice Guideline for the Treatment of Patients with Nicotine Dependence” from the American Psychiatric Association (1996). Overall, the research literature has indicated the superiority of combined pharmacological and behavioral therapy, compared with either modality alone, in achieving successful smoking cessation (Hughes 1993, 1995; Ziedonis and George 1997). For more information on behavioral treatments for smoking, see Antonuccio and Boutilier, Chapter 11, this volume.

The clinician should be especially vigilant about the possibility of an exacerbation of the psychiatric condition during an attempt at smoking cessation. Such an exacerbation, however, is not in and of itself an indication for the resumption of smoking. Often an intervention such as adjustment of the primary psychiatric medication can effectively support the patient in the smoking cessation effort.

**Smoking, Pharmacotherapy, and Side Effects**

The interactions between psychopharmacological agents and smoking call for special attention during periods of smoking reduction or
cessation, given that a large number of drugs show an increased blood level in response to smoking cessation. Obviously, patients may experience increased side effects if the dose of their primary psychotropic drug is not concomitantly decreased. Those side effects could be difficult to distinguish from nicotine withdrawal and/or symptoms of the primary psychiatric disorder complicating the treatment. For this reason, much closer pharmacological monitoring during smoking cessation would be advisable for any psychiatric patient.

**Instituting Smoke-Free Treatment Settings**

A particularly sensitive issue has arisen in psychiatric hospitals as a result of the national movement to create smoke-free environments. This was stimulated in part by assertive action of the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) and other organizations in establishing tobacco control standards for accredited institutions. A recent analysis of the compliance program (Longo et al. 1995) showed that nearly 96% of hospitals had met the JCAHO smoking ban criterion, yet psychiatric hospitals had a significantly lower (88%) rate of compliance. Several factors may be involved in the latter finding. The extended length of stay for some psychiatric patients (although decreasing), as well as restrictions on off-ward activities, may be factors thwarting the maintenance of smoking bans in psychiatric inpatient settings. Research is now emerging regarding the institution of smoking bans in psychiatric treatment settings. One analysis (Taylor et al. 1993) showed no significant increase in disruptive events or negative effect on staff morale after a smoking ban was instituted in a general psychiatry service. A study of patient reactions to a smoking ban in a community mental health center (Maiuro et al. 1989) showed only a slight decline in patient satisfaction, and in a follow-up survey it was seen that the negative reactions of smokers were minor and transitory. Resnick and Bosworth (1989) studied the effects of a smoking ban on an inpatient unit and found no significant change in the use of medications, seclusion, or restraint.

Thus, although psychiatric facilities appear to have lagged in instituting smoking bans, it is clearly feasible for these facilities to create such a policy without major adverse effects (Parks and Devine
1993). It is important for the clinicians on these units to be aware of the potential for the negative effects cited above, especially the ability of nicotine withdrawal to mimic psychiatric symptoms and the alteration of drug levels associated with a reduction in smoking.

**Future Considerations**

Despite the progress of recent years, we are only beginning to build an adequate knowledge base regarding smoking and major mental disorders. A number of important questions remain to be answered by researchers and clinicians, as described below. In addition, there are policy issues that increasingly merit the attention of clinicians and their patients.

**Epidemiological Questions**

It was highly significant that the defining study in psychiatric epidemiology, the ECA analysis, was limited to minimal data regarding smoking. It is a tribute to the growing awareness of smoking that the new NCS project focusing on the comorbidity of substance use in psychiatric disorders did include smoking questions for a significant portion of its data acquisition. The NCS study should provide key information regarding the association between smoking and psychiatric disorders. Given the observed associations with schizophrenia and depression, as well as preliminary data regarding other disorders, it is reasonable to expect that many psychiatric disorders are associated with an increased risk for smoking.

A related question that will be much more difficult to answer is the temporal relationship between smoking initiation and the onset of the psychiatric disorder. As exemplified by the recent evolution of neurodevelopmental theories of schizophrenia (which emphasize the potential combination of genetic predisposition, pre- and perinatal insults, and later developmental stresses), it is increasingly difficult to identify the onset of some psychiatric disorders. This difficulty in pinpointing the temporal onset of psychiatric disorders in relation to the initiation of smoking is only a problem, however, if one believes that there is a simple causal relationship: that smoking causes the mental disorder or that the mental disorder causes smok-
ing. It is likely that the relationship is much more complex, with genetic, environmental, and psychological factors that contribute both to the mental disorder and to the susceptibility to smoking.

**Inclusion of Smoking as a Relevant Variable in Neurobiological Studies and Clinical Trials**

The relative lack of attention to the high prevalence of smoking in psychiatric patients has extended even to carefully controlled research studies. Historically, few clinical research projects have identified the smoking status of the subjects. This would seem especially problematic in neurochemical studies focused on neurotransmitters and their metabolites. Given the significant effects of smoking on multiple neurotransmitter and hormonal systems, data in these studies may be complicated by a much higher rate of smoking among the patients compared with nonpatient control subjects. Future studies must control for this variable to ensure that smoking has not artifactually altered findings.

In a similar manner, the interactions between smoking and the levels of psychotropic drugs would indicate that all clinical drug trials should include smoking as a relevant variable. This would make possible some useful observations, such as the recent one that treatment with clozapine actually results in reduced smoking among schizophrenic patients.

**Policy Issues**

It is vitally important to state categorically that, although the association between smoking and mental disorders is intriguing from a neurobiological perspective, it in no way diminishes the responsibility of physicians to view the problem of nicotine dependence in their patients as a serious medical problem (American Psychiatric Association 1995). The cigarette is a highly evolved and potentially lethal nicotine delivery device. Even if psychiatric patients are in some manner self-medicating with nicotine, cigarette smoking remains highly likely to damage their longevity and quality of life. It is hoped that the growing awareness of the strong association between smoking and major mental disorders will spur researchers to explore further what this association may tell us about the complex neurobiology
of these disorders. One hopes as well that clinicians will be more cognizant of the nicotine dependence of their psychiatric patients and the need to aggressively support them in smoking cessation efforts.

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CHAPTER 6

Smoking, Nicotine, and Mood

Melissa Piasecki, M.D.

When loves grows cool, thy fire still warms me;
When friends are fled, thy presence charms me.
If thou art full, though purse be bare,
I smoke, and cast away all care!

German folk song

Alive With Pleasure!

Newport Cigarettes advertisement, 1987

Introduction

In 1990, the association between smoking and depression became the subject of a number of studies as well as an editorial in an issue of the *Journal of the American Medical Association*. In his comments, the editor stated, “At this point, it would be premature to recommend routine antidepressant treatment to assist smoking cessation for all smokers with a history of depression” (Glass 1990, p. 1584). Less than 7 years later, the *USA Today* news service proclaimed, “Pop a pill, kick the habit,” announcing the release of the drug bupropion-SR (an antidepressant) as a general smoking cessation aid (Levy 1997). This course of events reflects the research climate in two ways: first, that smoking cessation remains an active area for clinical research and practice, and second, that the nicotine-mood association is more rele-
vant than ever for both clinical and laboratory researchers. In this chapter, I review the various lines of research that converge on the nicotine-mood association to demonstrate what we know today and to suggest where we need to look for more answers. Only through a solid understanding of the role nicotine plays in mood can we effectively treat nicotine dependence in the general population.

**Epidemiology**

The association between nicotine and mood disorders has been examined in a number of different populations and by both cross-sectional and longitudinal designs in efforts to identify whether a causal relationship exists between smoking and mood problems. Glassman and colleagues analyzed a community-based survey (the 1980–1983 St. Louis Epidemiologic Catchment Area study) that tested the association between a lifetime diagnosis of depressive disorder and a history of cigarette smoking and smoking cessation failures. They found a 5.1% lifetime prevalence of major depression in their sample. Subjects who had never smoked had a 2.9% prevalence of depression, and those who had smoked daily for a month or more had a higher prevalence, 6.6%. They found that subjects with a history of depression not only were more likely to have smoked, but also were less likely to ever have successfully stopped smoking. Although in the general population more men smoke than women, the usual gender differences in smoking rates and smoking cessation rates disappeared in the subject population with a lifetime history of depression (Glassman et al. 1990).

Hughes et al. (1986) examined the prevalence of smoking in a clinical sample of psychiatric outpatients compared with the prevalence in a community control sample. Diagnostic interviews and smoking questionnaires revealed that the psychiatric patients had a consistently higher rate of prevalence of smoking (45%–88%). In the control population of Minnesotans, the prevalence of smoking was 30%, whereas in patients diagnosed with depression the prevalence was 49%, and in those with mania the prevalence was 70%.

Breslau et al. (1991) studied the association between mood and tobacco use and used DSM-III-R (American Psychiatric Association 1987) criteria to identify subjects who not only used tobacco but
were nicotine dependent. In a random sample of 1,007 young adults, they found a 20% lifetime prevalence for nicotine dependence. The researchers distinguished between mild and moderate dependence (there were no severely dependent subjects in her sample) and found significant positive associations between nicotine dependence and major depression. The mildly dependent subject group had a 19.2% lifetime prevalence of major depression, and the moderately dependent group had a 39.0% prevalence of the disorder, compared with a 10.1% prevalence in the non–nicotine-dependent group. In contrast to the very high prevalence of mania in smokers found by Hughes et al. (1986), Breslau et al. (1991) noted a lifetime prevalence of mania of 3.6% in non–nicotine-dependent subjects, 2.4% in mildly dependent subjects, and only 7.8% in moderately dependent subjects.

Although these three cross-sectional studies strongly suggest a positive association between smoking and depression, they do not have the type of longitudinal sampling that can better address questions of causality. In a prospective study, Breslau et al. (1993) interviewed 1,200 young adults (21–30 years old) and ascertained their smoking status, level of nicotine dependence, and lifetime psychiatric history. Approximately 14 months later, Breslau reinterviewed the subjects by phone, with a 99% follow-up completion rate.

With the follow-up data, Breslau was able to track the progression of nicotine dependence in this young adult population. The only statistically significant risk factor for progression to nicotine dependence was history of major depressive disorder: 37.7% of subjects with a positive history of major depression progressed in their level of nicotine dependence, compared to 22.8% of those with no major depressive disorder. In addition, Breslau tracked initiation of smoking in subjects who were nonsmokers at baseline. Although the number of new smokers was small (2.6% of the nonsmokers at baseline), the incidence of starting to smoke was greater in subjects with a history of depression. Examining the possibility of a depressant effect of nicotine, at the time of follow-up she measured the incidence of new onset or recurrent depression during the 14-month interval. In nicotine-dependent subjects the incidence was 13.6%, and in nondependent subjects it was 5.2% (Breslau et al. 1993). If Breslau’s work does not resolve the question of causality, her find-
ings do suggest that the positive association between smoking and depression noted by other researchers is true for young adults and may result from either self-medication with nicotine for depressed mood or a common predisposition to both nicotine dependence and depression. The longitudinal data suggest that the association is less likely to be due to a depressant effect of nicotine than to other factors.

Case Reports

Although case reports carry less import than studies of large sample populations, a number of case reports linking nicotine use to mood disorders are of interest. Five published reports detail severe new-onset or recurrent depression following abrupt nicotine withdrawal. Some patients’ mood disturbances resolved after a return to smoking; others’ responded to antidepressant medication. In addition, there are two case reports describing new-onset mania in patients who underwent abrupt smoking cessation. Ferry described two cases of atypical nicotine withdrawal with prolonged and severe dysphoria that responded to bupropion (Benazzi 1989; Benazzi and Mazzoli 1994; Ferry and Pettis 1995; Flanagan and Maany 1982; Labbate 1992).

Smoking Cessation and Depression

Consistent with the case reports, depression temporally associated with nicotine withdrawal has been well described (Hughes and Hatsukami 1986; West 1984). Depressed mood as a part of the syndrome of nicotine withdrawal is well established, reflected in DSM-IV (American Psychiatric Association 1994), which lists depression as a criterion for the diagnosis of nicotine withdrawal. As noted in the epidemiological studies, a history of depression is a risk factor for both relapse to smoking and a failure of cessation. This is evident as well in studies focusing on smoking cessation.

In 1988, Glassman and colleagues found a surprisingly high prevalence (61%) of a past diagnosis of major depression in smokers recruited for a smoking cessation study. All the subjects were euthymic at the time of entry into the study, but those with a past diagnosis of major depression had significantly poorer outcome. Whereas 57% of the patients with no history of depression achieved
a 4-week abstinence from smoking, only 33% of those with a history of depression had success with cessation. In addition to the overall outcome differences in cessation in this study, Glassman described 9 “psychiatric casualties” in another study of 300 smokers receiving clonidine or placebo. These were subjects with such extreme depressive features following cessation that all were advised to resume smoking and some received treatment with antidepressant medications (Glassman 1993; Glassman et al. 1988).

In an effort to examine more closely the phenomenon of major depression following smoking cessation, Covey et al. (1997) measured the frequency of major depression after smoking cessation in subjects who were not depressed at the time of quitting. Subjects were assessed 3 months after they completed a 10-week smoking cessation program. Of the 126 subjects, 9 developed major depression in the 3-month period. Of the subjects with no prior history of depression, 2% had an episode of depression. Of those with 1 prior episode of depression, 17% experienced depression in the 3 months following cessation; of the subjects with a past history of recurrent major depression, 30% had depression during the 3-month period. Risk factors for depression in addition to positive past history included female gender, an elevated score on the Beck Depression Inventory (BDI) at the end of the 10-week program, and increased number and severity of withdrawal symptoms.

In another study, Dalack et al. (1995) compared smokers who had a history of major depression with those who had never experienced a major depression, looking for subsyndromal differences in affect before smoking cessation. On a variety of measures, including the BDI and the Profile of Mood States (POMS), he found significant differences in all subscales between subject groups. Three weeks before the quit date, he treated the subjects who had a history of depression with fluoxetine, 20 or 40 mg. At the quit date, he noted that as a group, those treated with the antidepressant showed significant improvements not only on the BDI, but also on the depression, anger, and tension subscales of the POMS. He concluded that although 3 weeks may not be an adequate pretreatment time frame, some smokers with subsyndromal depression may respond to treatment with an antidepressant. Data about the outcome of the cessation trial are not available.
In May 1997, Glaxo Wellcome obtained U.S. Food and Drug Administration (FDA) approval for the use of the antidepressant bupropion-SR (sustained release) as a nonnicotine smoking cessation aid. The use of bupropion in smoking cessation is not, however, targeted to smokers with a history or symptoms of depression, even though this agent has been marketed as an antidepressant for several years. The mechanism by which bupropion acts to aid in smoking cessation is not yet known, but bupropion is hypothesized to act on the noradrenergic and dopaminergic systems, the same neurotransmitters that are thought to impart its antidepressant effects.

A placebo-controlled clinical trial of bupropion-SR for smoking cessation by Hurt et al. (1997) examined the efficacy, safety, and tolerability of this medication. The study included only non-depressed smokers (about 18% had a past history of major depression). They found that at 1 year, 23% of the subjects taking 300 mg/day of bupropion-SR were abstinent from nicotine, compared to 12% of the placebo group. Lower doses of bupropion yielded intermediate results. The medicated subjects did not have any differences in depression, as measured by the BDI, but they did show less weight gain than the placebo group. The use of bupropion-SR brings the nicotine and mood association full circle as the use of an antidepressant to treat nicotine dependence emphasizes the overlap between nicotine use and depression. The use of an antidepressant for nicotine dependence also raises the possibilities of overlapping neurochemical processes in these two disorders. This will be an important area for research in the next few years, and the findings may follow a pattern of discovery noted in other disorders: clues to the underlying neurochemical disturbances are found by examination of a medication that affects the disorder.

Before the use of bupropion-SR, all the pharmacological agents approved as aids in smoking cessation were forms of nicotine replacement. (See Zevin and Benowitz, Chapter 2, and Westman and Rose, Chapter 10, this volume, for further information on the specific types of nicotine replacement.) The mood effects of nicotine replacement therapy (in the form of nicotine gum) have been examined by a number of researchers (Fagerström et al. 1993; West 1984). In 1995, Kinnunen et al. studied smokers who received nicotine gum or placebo in addition to behavioral group treatment. In
contrast to the other cessation studies described, some of their subjects were identified, on the basis of a symptom scale, as currently depressed. These researchers found that the currently depressed subjects with nicotine gum achieved better 90-day cessation rates than nondepressed smokers with placebo gum, although this finding was not statistically significant (29.5% versus 24.1%). Among depressed smokers, those who received active gum did much better in terms of 90-day abstinence (29.5% versus 12.5%).

In a different approach to the treatment of depressed mood during smoking cessation, Hall et al. (1994) designed a cognitive-behavioral treatment (CBT) for mood management in a cessation study. Of their subjects, 31% had a history of major depression. The researchers found that standard treatment (behavioral groups with nicotine gum) plus a CBT component similar to that used in the treatment of depression increased abstinence rates for subjects with a history of depression. After 1 year, the CBT group had 34% abstinence, compared to 24% in the control group.

**Family Studies**

The associations between nicotine use and mood disorders provoke questions of causality. Some have questioned whether smoking causes depression by some effect of nicotine on the brain. Breslau’s longitudinal study (Breslau et al. 1993) with young adults helps clarify this question by showing past depression to be a risk factor for progression in nicotine use and dependence. Others have questioned how depression might lead to nicotine use. The epidemiological studies and smoking cessation research suggest that depressed individuals seek nicotine. Hughes has questioned whether there is a common element that predisposes certain individuals to depression and smoking, such as poor self-esteem, poor assertiveness skills, or a genetic link (Hughes 1988).

To look at possible genetic links, one may examine patterns of the two disorders in families. Hughes (1986) reviewed the literature on the genetics of smoking and concluded that both initiation and continuation of smoking are influenced by heredity. Likewise, there is a substantial literature to support the inheritability of major depression (Andreasen et al. 1987).
Kendler et al. (1993) examined the question of causality with a study of the association of smoking and major depression in twins. They studied both smoking history and lifetime diagnosis of depression in 1,566 twins, using the co-twin control method. Using a number of different statistical models, they found the best explanation (the best statistical “fit” for the data) to be a genetic factor that predisposes individuals to both smoking and depression.

**Adolescents**

Adolescents and children are of increasing interest to tobacco and nicotine researchers because they represent those in the earliest stages of nicotine addiction. Many researchers have focused on the factors that lead to youth tobacco use and nicotine addiction in the hope that decreasing smoking initiation will achieve the greater goal of decreased morbidity and mortality from smoking in a population. The link between smoking and depression appears to emerge in adolescence; information about this association will enhance our understanding about smoking behaviors.

Fergusson et al. (1996) documented the comorbidity between depression and smoking in a birth cohort of 947 New Zealand children. The researchers tracked the children from birth and prospectively measured risk factors, including family status, parental smoking, life events, conduct problems, and self-esteem. The researchers assessed the presence at age 16 of depressive disorders and nicotine dependence (defined as 5 or more cigarettes a day or presence of 2 or more withdrawal symptoms).

The 16-year-olds in this study demonstrated a positive correlation between depressive disorders and nicotine dependence; the odds of nicotine dependence were increased to 4.6:1 for those with a depressive disorder. This odds ratio was adjusted for risk factors common to or correlated with both disorders; after adjustment, the ratio was 2.3:1. Risk factors common to both disorders included affiliation with delinquent peers and lower self-esteem. The presence of common risk factors is consistent with the work with twins described earlier by Kendler et al. (1993), which suggested a model of common risk factors rather than a causal relationship between nicotine and depression. Kendler’s study emphasized genetic influences.
rather than the social and individual factors identified in Fergusson’s study.

Adolescents remain an important population for the study of earlier nicotine use and dependence. Fergusson’s work illustrates the presence of a mood disorder–nicotine dependence link as early as age 16, as well as common risk factors that are less clearly genetic than those suggested by Kendler.

**Laboratory Studies**

A number of researchers have explored the mood effects of nicotine in a controlled setting. One challenge in this type of research is to distinguish between mood changes that are a direct pharmacological effect of nicotine from those that are a response to relief from nicotine withdrawal. Pomerleau and Pomerleau (1992) examined the euphoriant effects of nicotine in the first two cigarettes of the day in overnight-abstinent smokers. Using a design that allowed their subjects to continuously report sensations of euphoria (defined as a “high, buzz or rush”) as they smoked, the Pomerleaus found that subjects reported euphoric sensations in a nicotine dose–related manner. Pomerleau and Pomerleau (1984) hypothesized that the positive mood effects were mediated by β-endorphin and other neuroregulators. These neurochemicals influenced by nicotine are thought to play an important role in the tenacity of the smoking habit. Endogenous opioids may improve mood and enhance pleasure. Such potential modulation of mood with nicotine may be particularly important in those who experience the psychological symptoms of major depression (or other negative-affect states such as anxiety).

Using intravenous nicotine with subjects who were smokers, Rosenberg et al. (1980) found that subjects reported a “pleasant” sensation and increased arousal. Using both iv and inhaled nicotine with smokers, Henningfield and Jasinski (1983) found that subjects had liking scores proportional to the dose of nicotine. The subject-rated liking scores were similar in magnitude to those reported with 25 mg of cocaine or 30 mg of morphine. These researchers also found elevated subject ratings on the Morphine Benzadrine Scale, measuring euphoria, with both inhaled and intravenous nicotine adminis-
tration. Intravenous nicotine was found to be positively reinforcing compared to saline. This reaction was attenuated by the nicotine antagonist mecamylamine—a finding that adds confirmation that these positive effects were specific to nicotine.

Not all laboratory researchers agree with the hypothesis that nicotine is a mood enhancer with effects mediated by endogenous neurochemicals. Gilbert et al. (1992) questioned whether the positive mood effects of nicotine are associated with modulation of endogenous opioids or are due to other factors. In two studies they measured the plasma levels of β-endorphin and cortisol in smokers who had had a minimum of 13 hours of smoking abstinence. They administered cigarettes of different nicotine strengths and noted that increases in serum β-endorphin and cortisol correlated with the subjects’ reports of distress, such as nausea and malaise, when smoking high-nicotine cigarettes. There was no significant increase in ratings of “pleasant” when subjects smoked cigarettes with nicotine compared to nicotine-free cigarettes. These researchers did not find an elevation in β-endorphin or cortisol after the subjects smoked “normal” cigarettes—only with the high-nicotine cigarettes, which made some subjects feel nauseated.

Meliska and Gilbert (1991) also examined the hormonal and subjective effects from the first five regular-strength cigarettes of the day. Smokers had all had 8 hours of confirmed abstinence. The subjects demonstrated a reduction in the morning decline in serum cortisol expected between 9:00 A.M. and noon (and thus increased cortisol levels compared with the control condition, a nicotine-free cigarette). Subjective arousal increased with cigarette use, as did malaise. The effects of nicotine on subjects’ report of positive-affect items (pleasantness, happiness) were very small. The plasma β-endorphin levels were higher after two cigarettes, but this increase disappeared after four or five cigarettes. The Meliska and Gilbert findings reflect, perhaps, the difference in sampling techniques for subjective effects and the duration of nicotine abstinence, compared to the Pomerleau studies. Alternatively, this research may disprove the findings of those who believe nicotine’s mood effects to be primary (not just relief from withdrawal) and to be mediated by β-endorphin.

In a different approach to researching the central nervous system effects of nicotine, Fowler et al. (1996) explored the neurophar-
macological actions of cigarette smoke with positron-emission tomography (PET) scans of active smokers, former smokers, and nonsmokers. These researchers found a 40% decrease in brain levels of monoamine oxidase B (MAO B), the enzyme that breaks down the monoamine neurotransmitters, in smokers with an abstinence range of 1.7–12 hours. Inhibition of this enzyme enhances the transmission of dopamine, which is implicated in mood regulation and in the reinforcement of behaviors. MAO B also influences the breakdown of other neurotransmitters implicated in mood disorders. The MAO B levels were comparable for nonsmokers and former smokers, suggesting that the differences noted in active smokers were indeed due to the effect of current smoking status and not another factor present in all who had ever smoked. Of note, this study did not consider nicotine independently from the many other substances found in cigarette smoke. There is evidence that components of tobacco smoke other than nicotine inhibit rat brain monoamine oxidase (Mendez-alvarez et al. 1997).

The relationship between nicotine and mood in the laboratory is inconclusive, although it does suggest a positive mood effect in some smokers. Further research with pharmacological probes and functional brain imaging will improve our understanding of the mood effects of nicotine.

In summary, research populations and methodologies ranging from epidemiology to functional brain imaging reflect an association between nicotine and mood. This body of research data brings to light important clinical and research implications.

Discussion

Although volumes of research and review have focused on smoking and nicotine over the decades, nicotine dependence and the morbidity and mortality resulting from smoking remain some of our most serious health problems both nationally and worldwide. We have far to go in making an impact on smoking behaviors and the health status of many patients who smoke. The studies reviewed above give us important information that will influence our future clinical and research efforts.
Clinical Implications

Clinical considerations of our research database involve both prevention of smoking and smoking cessation. The Breslau et al. (1993) study, which identifies an association between progression of nicotine dependence and depression, implies that young depressed people are at higher risk for nicotine dependence. Adolescents with major depression or with the identified risk factors of low self-esteem and delinquent peer associations may be targeted for primary prevention and early cessation; this would be an important area of research in primary prevention. Effective treatment of depression may decrease the risk of smoking initiation and enhance cessation efforts in all age groups. Women have twice the incidence of major depression that men have. Women who want to achieve “Virginia Slims” thinness are a particularly vulnerable group for smoking initiation and nicotine dependence. Gritz et al. (1996) discussed body image and other gender issues in smoking in a review.

Glassman and colleagues have made significant contributions to our understanding of relapse in smokers with a history of depression. Their studies (Glassman et al. 1988, 1990; Glassman 1993) make a strong case that any clinician helping smokers quit must be aware that smokers with a history of depression are at risk for more severe withdrawal symptoms, poorer cessation outcome, and relapse to a depressive episode in the 3 months following cessation. Thus, professionals in smoking cessation programs should ask their potential patients about a history of past major depression and possibly a family history of depression as well. Professionals working in these programs should be aware that there is the potential for psychiatric casualties, both early and late in the postcessation period. Clinicians and clinical researchers in cessation programs may want to implement long-term follow-up, inquiring not only about smoking status but also about mood. In addition, we need large, multisite clinical databases on cessation subjects to confirm the information found in smaller, single-site studies. It is hoped that ongoing research on Zyban subjects will provide such a database.

Although we do not know whether antidepressants improve outcome in patients with past depression histories, bupropion-SR is now FDA approved as a smoking cessation aid and has been shown
to improve depressed mood and increase abstinence during smoking cessation for subjects who were not depressed at baseline. Other antidepressants may prove to be helpful as well, such as nortriptyline, which in a 1998 trial of nondepressed smokers yielded a 6-month cessation rate of 14% (compared to a 3% rate with placebo) (Prochazka et al. 1998). To date there is little published evidence to support any agent other than bupropion-SR (one suspects that there are negative studies that have not been published) (Murphy et al. 1990).

Nicotine replacement therapies may also be used to decrease the risk of depression after cessation for vulnerable individuals. Other potential therapies may include extended periods of treatment with bupropion-SR and nicotine replacement or adjunctive antidepressant treatment such as cognitive-behavioral therapy in smoking cessation programs for high-risk individuals. Medications that modulate brain MAO B (such as the MAO inhibitors used in the treatment of depression and Parkinson’s disease) may have a role in smoking cessation treatment, as suggested by the PET scan findings of Fowler et al. (1996).

Additionally, there are clinical implications in the effects of nonsmoking inpatient units for psychiatric patients. Hughes has argued that, in severely ill psychiatric patients, nicotine withdrawal may complicate the treatment and cloud response to medications. Nicotine withdrawal can increase the anxiety, sleep disturbance, mood, and concentration difficulties of depressive and other psychiatric disorders (Hughes 1993). Ideally, either a psychiatrically ill patient would receive a nicotine replacement product during inpatient hospitalization, or nicotine withdrawal would be timed for when the patient is more stable. Alternatively, the structure and support of a nonsmoking inpatient setting may be helpful for certain patients who want to stop smoking and cannot achieve abstinence in a less structured environment. Such an environment prevents short-term relapse and provides maximum support for patients who are severely nicotine dependent and who have failed in less structured cessation attempts. Inpatient detoxification might also be indicated for patients who are at risk for psychiatric sequelae but have an urgent medical need to stop smoking (Hurt et al. 1992).
Research Implications

Clearly, research studies in smoking cessation from this point on will need to control for current and past histories of depression (as well as other psychiatric diagnoses). Similarly, studies of treatments for depression will need to control for smoking, because subjects may be able to modulate negative affect with nicotine and because smoking decreases blood levels of some medications. Laboratory researchers examining the acute mood effects of nicotine need to measure any existing withdrawal symptoms before administering nicotine. Baseline withdrawal measurements and standard abstinence periods will help make “primary” mood changes from nicotine distinguishable from the “secondary” phenomenon of relief from withdrawal. The use of non–nicotine-dependent smokers would also be helpful in making this distinction. In addition, novel research designs, such as the “delayed quitter” control group suggested by Gilbert (1997), may decrease methodological confounds and improve the validity of research data concerning the mood effects of nicotine.

Many research questions await study. Will other antidepressants be found helpful in smoking cessation? Will we see the development of nicotine-like drugs for the treatment of depression in smokers and/or nonsmokers? Will the neurochemical basis for depression and nicotine dependence be clarified? Will family histories of depression and nicotine dependence be useful in identifying individuals at risk for depression after smoking cessation? As smoking cessation programs attempt to treat nicotine-dependent individuals with the increasing armamentarium of cessation aids, and as researchers refine the understanding of the acute and chronic effects of nicotine on the brain, some of these questions may find answers. Undoubtedly, these are areas for fruitful research in the near future.

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Introduction

In this chapter we provide an overview of the evidence for nicotinic involvement in degenerative neurological diseases, and we review studies from our laboratories and others that examined the effects of nicotinic agonists and antagonists on cognitive functioning in Alzheimer’s disease (AD) and Parkinson’s disease (PD). We then discuss the potential effect of a nicotinic treatment on cognitive functioning in AD and PD and suggest a particular therapeutic target: attentional deficits in these two diseases. We review the nature of such deficits in AD and PD (and briefly provide an overview of similar problems in other neuropsychiatric conditions) and discuss the potential benefits of a nicotinic treatment for such cognitive impairments. We examine evidence for cytoprotective effects of nicotinic stimulation and consider whether prophylactic use of nicotinic agonists may be justified. Finally, we review the current state of the treatment of cortical dementias, and we attempt to place potential nicotinic therapies in the context of these approaches and the future development of other therapeutic options.

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Advances in the understanding of the structure, function, and distribution of central nervous system (CNS) nicotinic receptors have provided the impetus for new studies examining the role or roles that these receptors and associated processes may play in CNS functions. Further motivation has come from the realization that such receptors must be involved in maintenance of cigarette smoking and from clues discovered in studies of degenerative neurological diseases such as AD and PD in which the loss of nicotinic receptors has been described (Nordberg 1994). Ongoing investigations of the molecular substructure of CNS nicotinic receptors and their pharmacology have begun to open up new possibilities for novel CNS therapeutics with nicotinic agents (Arneric et al. 1995b; Arneric, Chapter 1, this volume). Exploiting these possibilities will require understanding of the role or roles that these receptor systems play in human cognitive, behavioral, motor, and sensory functioning. Clues from careful studies of human cognition are beginning to emerge and will provide direction for studies of potentially therapeutic novel nicotinic agents. In spite of promising studies of acute treatment with nicotine or nicotinic drugs in dementing disorders, there has been a dearth of chronic-treatment studies. This leads to uncertainty as to whether chronic nicotinic treatment will provide long-term cognitive or behavioral benefit. However, there is considerable evidence for the involvement of CNS nicotinic cholinergic receptors in a variety of cognitive, motor, and behavioral systems. Modulation of these receptors with the ultimate goal of producing therapeutic benefits is the goal of these investigations and of related drug development.

**Cognitive Effects of Nicotine in Humans**

Studies in humans have spanned several decades and mostly consist of experiments using cigarettes to administer nicotine, usually to smokers deprived of cigarettes for some period of time. Such studies have been reviewed extensively by Levin (1992) and by Spillich et al. (1992) and critically by Heishman et al. (1994). In general, the use of the deprivation model presents problems of interpretation. Although nicotine may “improve” performance in deprived smokers, it appears that this improvement is usually limited to restoring
predeprivation performance, which clearly declines during cigarette withdrawal (Snyder and Henningfield 1989). It has not been established whether deprivation-induced impairment of performance returns to predeprivation level and what is the time course of recovery to baseline without nicotine replacement.

Enhancement with nicotine of normal nondeprived smokers and nonsmokers has been more difficult to demonstrate. However, several studies with careful experimental designs have found such effects. Provost and Woodward (1991) showed that nicotine administration to nonsmokers enhances the Stroop effect, an attentional conflict phenomenon in which color naming is impaired if the word for one color—for example, the word red—appears in another color—for example, blue. Provost and Woodward’s finding suggested nicotine effects on selective attention. Le Houezec et al. (1994) showed that nicotine administration appears to shorten information processing time on harder stimuli in a choice-reaction time task and improves reaction time. Rusted et al. (1994) showed that nicotine administered via cigarettes to nondeprived smokers enhances recognition memory, especially in light smokers. Wesnes and Revell (1984) showed that nicotine may act to prevent fatigue-induced deficits in vigilance and long-term performance tasks. However, Newhouse et al. (1992a) were able to note only small, short-lived improvements in an attentionally and cognitively demanding vigilance task with intravenous nicotine administration after prolonged total sleep deprivation. It appears that improvement of “normal” performance with nicotine is more likely in tasks that are attentionally and/or cognitively demanding and in tasks that have a large ceiling or for which baseline performance is relatively low. However, performance enhancement in cognitively impaired subjects may be more realistic under real-world conditions.

Dementing Disorders and Nicotinic Cholinergic Mechanisms

Alzheimer’s Disease

The cellular and molecular derangements underlying the development of this disease have been the subject of intense investigation
over the past decade, and substantial progress has been made in understanding the nature of the underlying defects (Selkoe 1997). However, if therapeutic strategies are to be intelligently designed, it will be necessary to understand what neurochemical and cognitive system deficits are produced by cellular derangements in AD. Although treatments aimed at the basic cellular deficits in AD may be helpful in preventing disease progression, it is unlikely that these treatments will eliminate the need for direct treatment of the cognitive failings in AD, which will probably require agents directly interacting with specific neurotransmitter systems. Further, understanding of how damaged neurotransmitter systems in AD produce impaired cognitive functioning will increase knowledge of how complex cognitive operations take place in the brain.

Although a myriad of neurochemical deficits have been described in AD, explanation of the nature of the cognitive disturbances has been most closely focused on the cholinergic hypothesis, which implicates disturbances in central muscarinic cholinergic mechanisms in disorders of memory function (Bartus et al. 1982; Drachman and Leavitt 1974). Evidence supporting this hypothesis includes significant reductions in choline acetyltransferase (Corkin 1981) and in cholinergic cell number in autopsy-confirmed AD (Whitehouse et al. 1982). Antimuscarinic drugs such as scopolamine disrupt some cognitive functions in normal individuals (Peterson 1977) and have been proposed as a model of the cognitive deficits in AD (Caine et al. 1981; Sitaram et al. 1978).

There is a large literature showing learning impairment following administration of antimuscarinic anticholinergics in animals. Studies of young humans without cognitive disorders that examined the cognitive dysfunction brought about by muscarinic cholinergic blockade showed that such blockade significantly impairs several cognitive processes (Drachman and Leavitt 1974; Ghoneim and Mewaldt 1977; Peterson 1977). These studies were extended to examine aspects of the learning dysfunction produced by administering scopolamine to AD patients, elderly persons without AD, and elderly depressed patients (Newhouse et al. 1988a; Sunderland et al. 1986). However, these studies and others in humans suggest that scopolamine models some aspects of dementia (e.g., impaired vigilance and discrimination) but does not fully re-
produce others, such as the deficit in acquisition of verbal or visual information or the high rate of intrusion errors on verbal learning tasks (Beatty et al. 1986; Grober et al. 1988). It has been argued that muscarinic blockade with scopolamine may produce a deficit in retrieval rather than a true acquisition or learning deficit (Callaway et al. 1985; Dunne and Hartley 1985).

Nicotinic mechanisms may be important in explaining the pathophysiology of AD and in designing treatments for it (James and Nordberg 1995). Patients with AD have a marked reduction in cortical nicotinic cholinergic receptor binding compared to that in age-matched controls (Aubert et al. 1992; Flynn and Mash 1986; Whitehouse et al. 1986). Aged subjects without AD show an age-related decline in cortical nicotinic binding (Flynn and Mash 1986). Perry et al. (1996) showed that the entorhinal cortex (important in memory formation), rich in nicotinic binding, appears particularly vulnerable to amyloid plaque–induced loss of receptors. More generally, Perry et al. (1995) showed that nicotine receptor loss seems tightly linked to the primary pathology in the dementias—that is, linked to dopaminergic cell loss in PD and Lewy body dementia, and linked to amyloid plaques and tangles in hippocampal and parahippocampal areas in AD. These investigators also theorize that downregulation of the nicotinic receptors in entorhinal cortex that gate Ca\(^{+2}\) may play a specific role in AD-type cognitive pathology.

In humans, nicotine is reported to increase arousal and attention as well as to decrease reaction time and prevent decline in efficiency over time (Wesnes and Warburton 1983, 1985). In both animals and humans, nicotine improves the subject’s ability to withhold responses to inappropriate stimuli (Myrsten et al. 1972; Newhouse et al. 1988b; Wesnes and Warburton 1983). This may be relevant to AD, because a cardinal feature of the cognitive disorder of AD and a possible marker of cholinergic dysfunction (Fuld et al. 1982) is the difficulty that patients with dementia have in inhibiting inappropriate responses or in withholding responses to inappropriate stimuli. This difficulty in response selection and/or suppression is one explanation of the liberal response bias seen in AD. Nicotine reverses abnormal behavioral effects in the nucleus basalis lesion model of Alzheimer’s disease (Ksir and Benson 1983). Gray et al. (1996)
showed that nicotine enhances hippocampal synaptic transmission, which may be critical to the occurrence of new learning.

Evidence from studies of cerebral blood flow (CBF) also suggests an important nicotinic component of AD. AD is associated with a marked perfusion deficit in parietotemporal cortex in addition to the global decrease in cerebral perfusion. This focal deficit is seen even in early stages of the disease and appears to be specific to AD (Prohovnik et al. 1988). Although the pathophysiology of this deficit is incompletely understood, attempts have been made to model these changes with pharmacological agents. It is of interest that the nicotinic antagonist mecamylamine reliably reproduces this abnormal cerebral blood flow pattern (in volunteers without AD), whereas the muscarinic antagonist scopolamine does not (Gitelman and Prohovnik 1992). Studies in animals suggest that cerebral blood flow may be in part controlled by basal forebrain cholinergic neurons (Linville and Arneric 1991), and nicotine reliably augments the enhancement in CBF produced by electrically stimulating this region (Arneric 1989), suggesting an underlying nicotinic mechanism. Since the basal forebrain cholinergic neurons are heavily damaged in AD, changes in observed CBF may be secondary to damage to nicotinic systems. Presumably, the inability to autoregulate CBF impairs cognitive functioning.

Neuroimaging studies also support the involvement of nicotinic cholinergic systems in AD. Nordberg (1993a), using positron-emission tomography (PET), showed a significant correlation between the change in temporal cortex labeling of $^{11}$C nicotine and cognitive function scores in AD patients. This result was bolstered by further work from these investigators (Nordberg et al. 1995) in which a kinetic model was developed to quantify the loss of nicotinic receptor binding in vivo in AD patients. With PET, significant correlations were shown in these patients between cognitive dysfunction and the loss of nicotinic receptor binding in temporal and frontal cortices and hippocampus. Nordberg (1993b), using PET, also examined the effects of treatment with the anticholinesterase tacrine on AD patients and showed that brain nicotinic receptor binding of $^{11}$C nicotine increased along with cerebral blood flow after 3 weeks of treatment.

One other aspect of AD suggests a connection to nicotinic mechanisms. Epidemiological studies of AD that assess risk factors show
that, as is the case in PD, smokers are at a lower risk of developing AD than are nonsmokers, even when other factors are controlled for. Lee (1994) performed a meta-analysis of these studies and calculated a relative risk of 0.64 for smokers to develop AD. A recent study by Van Duijn et al. (1995) examined the risk of early-onset AD in subjects as a function of their Apo E gene status and family history. The protective effect of smoking was even larger (odds ratio = 7), especially for subjects positive for Apo E4 and with a family history of early-onset disease. Whether the protective effects of smoking are secondary to nicotine is unclear, but in vitro data suggesting a neuroprotective effect of nicotine are consistent with this possibility (Arneric et al. 1995a).

**Parkinson’s Disease**

In addition to AD, changes in CNS cholinergic systems have also been shown to occur in the brains of patients with PD. In particular, a loss of cholinergic cells in the basal forebrain nuclei similar to that occurring in AD has been described in PD (Whitehouse et al. 1983). The loss of cholinergic markers in the cortex (Perry et al. 1995) that may occur in PD may be related to lesions in these nuclei and other cholinergic projections to the cortex (Whitehouse et al. 1988). In PD patients with dementia, the loss of cortical cholinergic markers has been shown to be of greater magnitude and more extensive than that of PD patients without dementia (Perry et al. 1985). Studies have shown that, as with AD, a roughly linear relationship exists between the loss of cortical (particularly temporal) cholinergic markers (choline acetyltransferase and acetylcholinesterase) and the degree of cognitive impairment before death (Ruberg et al. 1982). PD patients have also been shown to have an exaggerated sensitivity to the cognition-impairing effects of scopolamine, as is true for patients with AD (Dubois et al. 1987).

Studies have shown a marked reduction in cortical nicotinic receptor binding that parallels the degree of dementia in PD and in increasing age (Aubert et al. 1992; Whitehouse et al. 1988). There is similarity between the cortical nicotinic binding site loss in PD and that occurring in AD, and there are similar changes in other
cholinergic markers. The loss of presynaptic cortical nicotinic receptors (Schwartz et al. 1984) may reflect degeneration of cortical projections from subcortical structures, notably the nucleus basalis, pedunculopontine, and lateral-dorsal tegmental nuclei.

A number of studies have shown that smokers have a lower than expected incidence of PD, suggesting a protective effect of nicotine (Baron 1986, 1994; Baumann et al. 1980). These studies have been carefully reviewed by Morens et al. (1995). Their conclusion that the association is not artifactual was based on several findings: 1) more than 35 studies have found this association in varying sites, with both prospective and case-control designs, 2) dose-response effects exist in a number of studies (i.e., relative protection increases with the amount smoked), 3) relative protection appears to be afforded even in patients who have stopped smoking (i.e., their risk of developing PD appears intermediate between that of those who have never smoked and that of current smokers), 4) neither confounding variables nor study biases can explain the association, and 5) there is a similar association between smoking history and a reduced incidence of AD. Although epidemiological studies do not confirm that nicotine is the protective agent, it remains the best candidate constituent of tobacco smoke. Nicotine was examined as a treatment for postencephalitic PD as early as the 1920s (Moll 1926). In mice, nicotine was also shown to counteract the locomotor effects of lesions induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a putative model for PD (Sershen et al. 1987).

Studies of the cognitive deficits seen in PD suggest that cholinergic mechanisms may play a substantial role, particularly in producing so-called subcorticofrontal deficits (Dubois et al. 1990; Reid et al. 1990). A recent study of the relationship between regional CBF and motor learning performance in early-treated PD patients revealed that when performance on a motor learning task was equated with that of control subjects, the CBF pattern in PD patients showed activation that was absent in the control subjects (Nakamura et al. 1999). Taken together, these results suggest that loss of nicotinic receptors and their associated source and/or target cells may play an important role in the cognitive deficits seen in this disorder.
Studies of Nicotinic Antagonists and Agonists in Alzheimer’s Disease

Antagonist Studies

One approach to the question of the importance of CNS nicotinic mechanisms for cognitive functioning is to use a nicotinic antagonist to produce a temporary chemical “lesion.” Antagonist studies are often more productive in humans without cognitive disorders than are agonist studies because of the lack of ceiling effects. Newhouse et al. have studied the effects of mecamylamine, a centrally active non-competitive nicotinic antagonist and ganglionic blocker, on cognitive functioning (Newhouse et al. 1992b, 1993, 1994) in young and elderly individuals without cognitive disorders and in patients with AD and PD. These studies attempted to establish that nicotinic blockade produced cognitive impairment in humans and examined whether there might be age- or disease-related changes in sensitivity to nicotinic blockade, which might be indicated by shifts in dose-response curves between groups.

Mecamylamine administration produced dose-related impairment of the acquisition of new information, with group differences in sensitivity. Young subjects without cognitive disorders showed significant cognitive impairment errors after the highest dose. By contrast, elderly subjects without cognitive disorders showed significant impairment after the middle and high doses, and the subjects with AD showed impairment after all three active doses. This pattern was seen in both verbal and nonverbal learning tasks.

In the AD patients, the learning rate actually became negative at 10 and 20 mg of mecamylamine—that is, they were actually getting worse with increasing trials. It is interesting that, in the elderly subjects without cognitive disorders, mecamylamine produced a dose-related change in response bias with a significant liberal shift after the high dose, which has been seen in AD patients. This did not occur with the young subjects without cognitive disorders. Regarding psychomotor speed, mecamylamine produced dose-related slowing in a number of tasks that measured reaction time. These included increases in reaction time for the Choice Reaction Time test and the Manikin task (a mental spatial rotation task). Older subjects
tended to show proportionately greater increases in reaction time than the younger subjects did. By contrast, there were minimal behavioral effects.

These results suggest that the deficits produced by mecamylamine resemble in several respects those seen in AD and to a lesser extent PD. Deficits in short- and long-term memory, impaired attention, liberal response bias, and decreases in reaction time are hallmarks of the dementing picture seen in these disorders. The age-related nature of some of the findings suggest that the decline in nicotinic receptors with age produces increased vulnerability to the effects of nicotinic blockade.

**Agonist Studies**

Initial studies by Newhouse et al. examined the effects of intravenous nicotine on cognitive, behavioral, and physiological functioning in both nonsmokers without AD and patients with AD (Newhouse et al. 1988b, 1993, 1996). Analysis of the cognitive effects of nicotine in the AD group showed that there was a significant dose-related decrease in verbal learning errors, with a U-shaped dose-response curve. A similar improvement pattern was seen in long-term verbal recall. Neuroendocrine measures (Newhouse et al. 1990) tended to confirm that the doses used were active at CNS nicotinic receptors.

Newhouse et al. (1996) recently reexamined the effects of intravenous nicotine in AD, but with particular attention to tasks that are affected by mecamylamine. Results showed that nicotine produced improvements in attentionally driven tasks, with improved reaction time, hits, and false alarms on a continuous performance task. Throughput (speed-accuracy product) was improved as well. Small improvements were seen also in verbal memory tasks, but no improvement was seen in the Repeated Acquisition Task (RAT), a serial nonverbal learning and retrieval task, which was impaired by mecamylamine.

These findings of the beneficial results of acute nicotinic stimulation in AD have been supported by the studies of Sahakian and colleagues (Jones et al. 1992; Sahakian and Coull 1994), who showed that subcutaneous nicotine administration in AD patients produced
improvements in attentional functioning. This group found that nicotine produced a highly significant improvement in accuracy on a sustained visual attention task (which involved the detection of number sequences). It is important that there was no speed-accuracy tradeoff—that is, patients did not become slower, even though they became more accurate. Further, these studies showed that the AD subjects improved in a dose-dependent manner on attentional aspects of a visual short-term memory and attention task. Katayama et al. (1995) showed that nicotine improved performance in dementia patients, as measured by the use of event-related potentials. Further support is provided by Parks et al. (1994), who showed that nicotine improves retrieval from long-term semantic memory and increases CBF in patients with AD. More chronic administration of nicotine to patients with AD has also shown promise. Wilson et al. (1995) administered nicotine by patch to 6 AD patients for 8 days. Compared to the placebo patch condition, there were significantly fewer errors on a nonverbal learning task while subjects were receiving nicotine. This effect persisted for at least a week after withdrawal. However, Snaedal et al. (1996) were unable to find a significant effect on memory of 4 weeks of transdermal nicotine administration in 18 AD patients.

The acute effects of the novel nicotinic agonist ABT-418 on cognitive functioning in AD have recently been examined (Potter et al. 1999). Subjects showed significant dose-related improvements in verbal learning and memory on the Selective Reminding Task, as reflected by improved total recall and a decline in recall failure. Similar though not as robust improvements were seen in nonverbal learning tasks such as spatial learning and memory and repeated acquisition. Positive dose-related effects on reaction time were also seen. No significant behavioral effects, vital-sign effects, or physical side effects were seen. Preliminary results from a study of acute and subchronic administration of nicotine in early PD patients (Kelton et al. 1999) suggest beneficial effects on both cognitive and motor functioning.

Taken together, these studies represent significant evidence that stimulation of nicotinic receptors can improve the acquisition and retention of verbal (declarative) and nonverbal information in humans. Previously, it has been difficult to demonstrate that stimulation of nicotinic receptors produces true learning or memory
improvement effects in those without cognitive disorders (Heishman and Henningfield 1994). The role of attentional effects of nicotinic stimulation has been stressed by Sahakian and Coull (1994) and is reviewed in detail below. However, as has been suggested by Warburton and Rusted (1993), nicotine’s effects are most often seen in tasks that have a large attentional load. For example, the verbal learning tasks that showed improvement in the AD patients after acute administration of ABT-418 required focused attention and significant cognitive effort. It also may be the case that any cognition-enhancing effects of nicotinic stimulation are more clearly manifest in cognitively impaired individuals. Preclinical studies of other novel nicotinic agonists have also showed promise. Aged rats showed improved learning when treated with the nicotinic agonist GTS-21 (Arendash et al. 1995), and SIB-1508 may improve motor and cognitive functioning in lesioned animals (Cosford et al. 1996).

Newhouse et al. (1998) recently began to examine the quantitative effects of nicotine in PD patients. Subjects with mild to moderate PD received dose-ranging infusions of intravenous nicotine up to 1.25 µg/kg/min, followed by chronic administration of nicotine by transdermal patch, with doses ranging up to 14 mg/day for 2 weeks. Testing occurred both during drug administration and up to 2 months after drug cessation to look for prolonged effects. Nicotine appeared to acutely improve attention/arousal in PD patients as measured by the Critical Flicker Fusion (CFF) and the Choice Reaction Time tests. Mecamylamine preadministration antagonized the improvement, suggesting a specific effect on nicotinic receptors. Because PD patients have been noted to have defects in attention, this effect suggests that stimulation of nicotinic receptors may have salutary effects on attentional systems in these patients. Optimal nicotinic stimulation appears to improve performance, but beyond that, performance worsens.

During the chronic phase of administration by transdermal patch, nicotine appeared to improve performance speed in standard clinical motor performance tasks. In most cases, improvement appeared to persist after drug withdrawal, although there was some evidence for the beginning of a return toward baseline values at the session 2 weeks after drug withdrawal. For the computerized performance tasks, subjects showed improvement on the motor por-
tions of certain tasks at day 14, but by 2 weeks postdrug, they had returned almost to baseline values. These effects are consistent with the possibility that a sustained evoked increase in the release of dopamine in nigrostriatal pathways may be occurring as a result of presynaptic nicotinic receptor stimulation. Studies such as these provide optimism that nicotinic stimulation may be a fruitful strategy for PD treatment, by using nicotinic agonists either as monotherapy in early-stage disease or as dopa-augmenters or dopa-sparing drugs in later-stage disease.

**Potential Therapeutic Targets in Alzheimer’s Disease**

**Cytoprotection**

Intriguing evidence has been developed that suggests that nicotine and nicotinic drugs may have cytoprotective effects (Brioni et al. 1996). Above, we have reviewed studies suggesting a protective effect of cigarette smoking on the development of AD and PD. At this point there are several other possible mechanisms whereby tobacco smoke might be neuroprotective, including MAO inhibition (Fowler et al. 1996) and smoking-associated inhibition of free-radical damage, potentially mediated through carbon monoxide (Morens et al. 1995). However, in vitro work with nicotine and related compounds provides the most direct evidence supporting the belief that nicotine is an important factor in neuroprotection.

In vitro studies have shown that nicotine can protect against the excitotoxic effects of glutamate when it is administered before, but not during, exposure to glutamate or N-methyl-D-aspartate (NMDA) (Shimohama et al. 1996), perhaps mediated through the inhibition of nitric oxide formation. Nicotine also prevents the neuronal degeneration that occurs after destruction of the basal forebrain by neurotoxins (Owman et al. 1989). Other nicotinic agonists such as ABT-418 and GTS-21 have also shown neuroprotective effects in cell culture studies (Arneric et al. 1995a; Marin et al. 1994). These neuroprotective effects may be mediated by stimulation of the α7 nicotinic receptor, because agents that block this receptor, such as α-bungarotoxin, attenuate the
cytoprotective effects of nicotinic agonists. The α7 receptor appears to be involved in calcium flux (Seguela et al. 1993), and its interaction with glutamate-induced neurotoxicity is perhaps not surprising. Nicotine receptor activation may also be linked to neurotrophin production (Freedman et al. 1993). Yamashita and Nakamura (1996) showed that nicotine prevents cell death in PC-12 cells after withdrawal of growth factors. This effect appears to be mediated through nicotinic receptors and is blocked by nicotinic receptor antagonists. Recently, it has been shown that nicotine may act to inhibit the deposition of β-amyloid in vitro (Salomon et al. 1996) by impairing the aggregation of β1-42 peptide into β-pleated sheets. It appears that nicotine may bind to and stabilize the α-helical structure of the β-peptide. However, Monteggia et al. (1994) examined the effects of chronic nicotine administration in aged rats on amyloid precursor protein splicing, but failed to find a significant effect on the relative proportion of gene transcripts.

These studies, in conjunction with the epidemiological data, suggest the possibility that chronic treatment with nicotine or other nicotinic agonists might delay or prevent the clinical onset of AD. It is not necessary to prevent completely the onset of a disease such as AD in order to produce a significant impact on individual patients, families, and health care costs. The ability to delay the clinical manifestations of AD by a long period with a protective agent would mark a significant step forward in the treatment of this disorder. Such strategies are under active investigation with agents such as estrogen and antioxidants. The evidence for the neuroprotective effect of nicotine is at least as strong as that for some of the other classes of agents under investigation. The use of nicotine as a chronic protective agent may raise more complex issues than other compounds such as antioxidants: the potential for other chronic adverse effects (e.g., cardiovascular) or dependence. However, even after patients become symptomatic, chronic nicotine (and/or muscarinic) stimulation may slow disease progression and prolong the period of less impaired functioning. Such a strategy is worth considering, particularly for high-risk groups, such as 1) individuals who have a strong family history of AD and/or who are positive for the Apo E4 allele or 2) individuals who appear, on the basis of cognitive or clinical assessment, to be either questionably impaired or in the very earliest
stages of dementia. Along with the assessment of other potential protective agents, large-scale prevention trials with nicotine or other nicotinic agonists should be considered.

**Attentional Systems**

**Cholinergic regulation of attentional processes.** Studies of animals with central cholinergic lesions produced either by pharmacological inhibition of choline uptake or by direct excitotoxic lesions of basal forebrain cholinergic neurons have shown highly specific attentional deficits (Muir et al. 1992; Robbins et al. 1989). These animals show deficits that might be predicted from studies of humans with AD: increased response latency and increased responsiveness to irrelevant sensory stimuli. Studies by Vidal (1994a) showed that administration of a nicotinic antagonist in rat prefrontal cortex impairs performance of spatial working memory tasks, which requires the rat to suppress its preferred alternation strategy. This result suggests interference with inhibitory mechanisms, since the animal must inhibit its normal practice of alternating locations in order to complete the task successfully. Vidal (1994b) has correlated this behavioral result with nicotinic effects on prefrontal glutamatergic synapses. Nicotine appears to increase release of glutamate in rat prefrontal cortex as measured by in vivo microdialysis and to increase the amplitude of excitatory postsynaptic potentials from the same region. Presynaptic nicotinic receptors may then modulate glutamatergic activity via their presence on thalamocortical afferents (Vidal 1994b).

Studies of the role of central cholinergic systems and attention in humans suggest that these systems appear to help constrain the focus of attention (for example, Callaway et al. 1992). Wesnes and Warburton (1983) showed that nicotine improves sustained attention and vigilance performance, particularly over long intervals. Most interestingly, they showed that nicotine appeared to reduce the Stroop effect. The results found by Wesnes and Warburton most strongly argue for an effect on inhibitory mechanisms, since reducing the Stroop effect requires improving the ability to selectively suppress attention to word reading over color naming. This result was confirmed in nonsmokers by Provost and Woodward (1991), who showed that there was a robust effect of nicotine in this para-
digm. Parrott and Craig (1992) showed positive effects of nicotine on visual selective attention: rapid information processing showed improvement, and increased speed and accuracy were seen in other tasks, including letter cancellation.

Warburton and Rusted (1993) summarized the effects of cholinergic, particularly nicotinic, systems on cognition by suggesting that the data support a role for such systems in regulating the functional state of the cortex and the central executive mechanism (or supervisory attentional system). They further conclude that nicotine’s most robust memory effects are seen in tasks that have a high attentional requirement—and that therefore, memory enhancement may be a consequence of improved attentional functioning.

**Attentional deficits in Alzheimer’s disease.** Patients with AD have a wide range of cognitive deficits that can be broadly characterized as problems with acquisition, retention, retrieval, access to previously acquired knowledge, decisional processes, and processing capacity. These deficits have been in part ascribed to deficits in attentional functioning (Parasuraman and Haxby 1993). In a review of studies of attention in AD, Parasuraman and Haxby (1993) concluded that attentional impairment represents the first cognitive indication of cortical dysfunction. They noted marked deficits in attentional shifting, in divided attention, and in sustained attentional functioning. Brazzelli et al. (1994) confirmed that AD patients show significant deficits in vigilance and sustained attention. Deficits in spatial attention shifting in AD appear to correlate with the degree of parietal hypometabolism (Parasuraman et al. 1992), and Parasuraman et al. (1992) found that the reduced cholinergic activity seen in AD is associated with an increased cost of incorrect spatial cues (i.e., impaired shifting of attention). This is consistent with data from Parasuraman et al. (1992) suggesting that this impairment correlates with the decline in parietal blood flow, which may be under nicotinic modulation (Linville and Arneric 1991).

Studies of the deficits seen in early AD also suggest significant deficits in the central executive component of the working memory model of Baddeley (Baddeley et al. 1991). This has been seen in studies that highlight mechanisms involved in allocating attentional resources by using dual tasks and requiring divided attention. On
divided-attention tasks, AD patients show a greater degree of impairment than those without AD, even when performance on individual tasks is equivalent (Baddeley et al. 1991). Baddeley et al. (1986) and others (Cossa et al. 1989) have argued that the inability to allocate and direct attention appropriately may be one of the principal deficits observed in AD. Impaired inhibitory mechanisms appear to be an important element of those attentional deficits. Impairment in divided attention in AD appears to be linked to dysfunction of the right frontal lobe (Nestor et al. 1991).

Further, a characteristic change seen in AD on memory tasks is a liberalization of response bias (Snodgrass and Corwin 1988). It has been noted that AD subjects show high numbers of intrusion errors on recognition memory tasks (Fuld et al. 1982), a result that suggests failure of the inhibitory response selection mechanism. This failure may result either from a reduced inhibition of inappropriate information in working memory or from reduced cholinergic constraint on information processing (Callaway et al. 1992). The nicotinic antagonist mecamylamine appears to reproduce this effect, whereas nicotine antagonizes it.

**Attentional deficits in Parkinson’s disease.** Multiple studies of the cognitive deficits in PD have suggested that there is difficulty with selective attentional functioning (Brown and Marsden 1990; Dalrymple-Alford et al. 1994; Goldenberg et al. 1990; Stam et al. 1993). There appears to be considerable agreement that cognitive impairment in PD may reflect impairment of prefrontal cortex—that is, that PD patients appear “hypofrontal” (Reading 1991; Taylor et al. 1986). More specifically, the loss of inhibitory attentional processes may be a general mechanism responsible in part for the impairment seen early in this disease (Downes et al. 1993). Attentional deficits in PD may be secondary to impaired inhibitional functioning of the central executive component of working memory, which may be secondary to damage to the prefrontal and/or parietal cortex and/or to known basal ganglia, thalamic, or frontal circuits. Although PD and AD have different underlying cellular pathology and macropathology, a shared loss appears to be cholinergic cell and subsequent nicotinic receptor loss. Although the anatomy of the deficits is incompletely understood, especially in AD, this shared damage to cholinergic systems
may be responsible for qualitatively similar attentional deficits. This deficiency may present an attractive therapeutic target for nicotinic stimulation (see also Piasecki, Chapter 6, this volume).

**A Nicotinic Model of Cognitive Impairment in Alzheimer’s Disease and Parkinson’s Disease**

The loss of or alterations to nicotinic receptors and/or their associated processes may be responsible for some of the cognitive changes and blood flow alterations seen in AD and other neuropsychiatric disorders. Nicotinic systems appear important to normal learning and memory, but effects may be in part mediated through effects on certain aspects of attentional functioning. Effects of nicotinic receptor activation may be mediated through presynaptic regulation of catecholaminergic, cholinergic, and/or glutamatergic transmitter mechanisms in widespread projections to prefrontal and/or parietal cortex and basal ganglia–thalamic–prefrontal loops. What subtypes of nicotinic receptors might mediate these effects is unclear. Stimulation of nicotinic receptors with nicotine and/or novel nicotinic agonists may produce significant improvement in attentional functioning in AD and PD (Lawrence and Sahakian 1995), with significant therapeutic benefit.

This model, like other models of cholinergic dysfunction, is not intended to explain all the cognitive deficits in AD. Data suggest that nicotinic systems and/or receptors are modulatory of the release of acetylcholine, dopamine, and other neurotransmitters to their receptors. Therefore, there are probably limits to the actions of this system, and the loss of these receptors may result in the loss of a degree of control of cognitive processes rather than the loss of the underlying basic cognitive function itself. Certain cognitive processes affected in AD may not be under nicotinic modulation or influence. It appears more likely that nicotinic systems act to modulate or control the “front end” of memory processing—for example, control and partitioning of attentional resources that are critical to the appropriate encoding of memories. Further, these mechanisms may help to control the flow of information into and out of working memory, from the outside or from long-term store, inhibiting irrelevant infor-
mation and augmenting salient information. Although stimulation of this system is unlikely to restore full function, it may augment remaining cell connections, increasing information (signal) traffic, and may therefore improve cognitive function.

The Potential Role of Nicotinic Treatment in Alzheimer’s and Parkinson’s Diseases

From the studies presented in this chapter, it appears possible that nicotinic compounds may have an important role in the treatment of AD and/or PD in the future. This role may lie either in improving cognitive symptoms or in slowing the progression of the disease. The question is how these nicotinic approaches fit other developments in both AD and PD treatment. In this section we review these considerations by 1) reviewing current treatments for AD, 2) describing efforts to improve these therapies, which may bear fruit in the future, and finally 3) offering some comments about the relationship between Alzheimer’s disease and Parkinson’s disease relevant to drug development.

Current Treatment of Alzheimer’s Disease

The treatment of AD can be divided into symptomatic and disease course–altering approaches. The only medications to treat the cognitive impairment that have been approved in the United States are the acetylcholinesterase inhibitors tacrine and donepezil. Although of some value in the treatment of AD, such agents are problematic because of a number of difficulties in clinical use, including dose-related gastrointestinal side effects such as nausea, abdominal pain, and diarrhea related to nonspecific cholinergic effects. Studies of acetylcholinesterase inhibitors suggest that there may be a ceiling of improvement with such nonselective compounds. In other countries, concerns about the cost and efficacy of these medications have limited their use.

Any new therapeutic must undergo scrutiny to demonstrate its value in pharmacoeconomic studies. Three other acetylcholinesterase inhibitors have been submitted to the U.S. Food and Drug Ad-
ministration for approval. The first, submitted in March 1998, was revastigmine (Novartis). Sustained-release physostigmine (Forest Labs) and metrifonate (Bayer) have also been submitted. The efficacy of these compounds is quite similar, and their success in the market will depend on marketing strategies, as well as subtle differences in side-effect and use profiles.

Future efforts to treat the cognitive symptoms of AD will probably continue with drugs that enhance cholinergic function. In addition to the new acetylcholinesterase inhibitors in late stages of development, a number of muscarinic agonists are also under clinical study (Bodick et al. 1996; Fisher and Barak 1994; Hoover 1994; Schwarz et al. 1994). The hope of researchers of muscarinic agonists is to develop a drug that has more effects on enhancing cognition and fewer side effects. At the moment, however, it appears that the muscarinic agonists are having difficulty in achieving that target of greater clinical specificity. The search has focused on drugs that stimulate M₁ postsynaptic muscarinic receptors and perhaps antagonize the actions of the inhibitory presynaptic muscarinic type 2 receptors. However, it remains to be seen whether any of these muscarinic agonists can improve on the risk-benefit ratio of the cholinesterase inhibitors. Nicotinic agonists may directly release neurotransmitters by direct presynaptic stimulation, potentially augmenting the effects of cholinesterase inhibitors.

Other therapies for AD focus on other neurotransmitter systems that may play a role in cognition. Drugs to enhance adrenergic, serotonergic, and glutamatergic function are under examination. Once again, these are in early stages of development, and it remains to be seen whether these drugs are any better than cholinergic drugs. Combinations of agents or agents that have effects on multiple neurotransmitters are also under investigation. The treatment of the noncognitive symptoms will also continue to improve in the future with the FDA approval of a variety of other antidepressants and novel neuroleptics. The clinician will be looking for drugs with better risk-benefit ratios, particularly those that have the fewest side effects affecting confusion and extrapyramidal symptoms.

Most of the excitement for the future lies in developing more effective interventions for slowing the progression of disease. As mentioned above, antioxidant and hormonal therapies are under active
clinical examination. Another approach, which is also being tested clinically, is the use of anti-inflammatory agents (McGeer et al. 1996). For some time it has become clear that atypical inflammatory changes occur in the brains of patients with AD. Preliminary clinical trials and epidemiological studies suggest that exposure to nonsteroidal anti-inflammatory agents may either delay the onset of the disease or slow the course of the illness. Studies of nonsteroidal anti-inflammatory agents and steroids themselves are under way. Nicotinic agonists may have a role in decreasing amyloid deposition or in cytoprotection.

In the long term, other therapeutic approaches are designed to modify the basic pathogenetic mechanisms of AD. Principal attention has been paid to the deposition of amyloid. Amyloid occurs in the center of senile plaques and is thought to be toxic to nerve cells, particularly when in the fibrillar state. Thus, researchers are trying to develop drugs that block the formation of the β-amyloid protein or prevent its accumulation in these amorphous and insoluble plaques (Selkoe 1996). Other strategies are focusing on the process of formation of neurofibrillary tangles. Hyperphosphorylated tau is thought to be one of the principal constituents of neurofibrillary tangles occurring early in the formation of this intracellular feature of the disease. Since phosphorylation of tau may play an important role, attempts to affect the protein kinases and other enzymes involved in the formulation of tau have been made. In the case of attempts to develop therapies to dissolve amyloid or prevent the formation of neurofibrillary tangles, no clinical trials are under way, although animal models have been developed that may allow testing of these therapies.

Summary

The potential usefulness of nicotinic agonists can be summarized as follows: first, many dementias are characterized by loss of cholinergic neurons and nicotinic receptors, including the two most common degenerative diseases, AD and PD (Kalaria et al. 1994; Whitehouse et al. 1988). Second, nicotinic compounds appear to act on the attentional mechanisms affected by these disorders. In the view of many clinicians, these attentional impairments are even
more important in producing impairment of activities of daily living and function than are memory problems. Finally, nicotinic compounds offer the promise in one molecule of providing cognitive benefit as well as an effect on slowing the course of disease. A major problem with nicotinic compounds relates to side effects. Can a compound be developed that is selective in producing improvement in cognition but does not cause significant side effects? The critical issue is whether a more receptor-specific compound with an improved risk-benefit ratio can be developed.

Further Research Directions

Future directions for research include specific testing of the atten-
tional hypotheses proposed above. Attempting to replicate the atten-
tional impairments of AD and/or PD with nicotinic antagonists will help establish the relevance of nicotinic mechanisms to these impair-
ments. The development of novel centrally acting and/or competi-
tive nicotinic antagonists will also further our understanding of the role of nicotinic receptors. Studies of functional brain imaging will continue to define the anatomical substrate or substrates of the cog-
nitive effects of nicotinic agents. Therapeutic trials of nicotine and novel nicotinic agonists will assess the realistic likelihood of long-term improvements in functioning. Future clinical studies will involve early trials of novel nicotinic agonists such as ABT-418, GTS-21, RJR-2403, SIB-1508, and SIB-1553A for AD and PD. ABT-418 is a promising selective nicotinic agonist for clinical and research in-
vestigations (Arneric et al. 1994). RJR-2403 (Lippiello et al. 1996) ap-
pears to be a highly selective ligand for the $\alpha_4\beta_2$ subtype of nicotinic receptor and may be a useful agent for investigating the clinical and cognitive effects of stimulating this receptor subtype. The novel nico-
tinic agonist SIB-1765F appears to augment L-dopa effects on loco-
motion in reserpine-treated rats (Menzaghi et al. 1997a) and spontaneously increases motor activity in untreated rats (Menzaghi et al. 1997b), suggesting potential activity in PD. The related com-
pound SIB-1508 (Cosford et al. 1996) is a promising selective agonist with prominent motor properties and cognitive effects in preclinical studies. SIB-1553A is a novel nicotinic agonist with selectivity for re-
ceptor subtypes containing β4 subunits and is highly effective in releasing acetylcholine. This suggests that it may have effectiveness in AD, which shows a relative cholinergic deficit (Lloyd et al. 1998).

Preliminary evidence suggests that, although attentional effects can be manifested very rapidly with nicotinic agonists, significant learning and memory effects may take longer administration or exposure to nicotinic agonists than can be provided for by a single bolus injection. An intriguing preclinical study by Riekkinen and Riekkinen (1995) suggests that the loss of serotonergic functioning may affect the ability of nicotine to improve cognitive functioning. The combination of nicotinic stimulation with serotonergic augmentation may produce supra-additive effects on cognitive performance. Also deserving investigation are the effects of nicotinic augmentation on motor functioning and cognitive performance in PD, as well as in other dementing disorders with known cholinergic lesions, such as Lewy body dementia.

For maximum advantage of the effects of nicotinic agents on cognitive functioning, it may be necessary to design cognitive treatment programs that integrate drug treatment with cognitive training and/or rehabilitative strategies for both patients and their families. In this way, rehabilitative strategies can take advantage of the known properties of nicotinic agents in various cognitive domains. It should be possible to design strategies to teach caregivers how to take advantage of gains produced by these cognition-enhancing drugs for optimal outcome. Such integrative drug-rehabilitation strategies should represent the next phase of cognition-enhancing treatment development.

The evidence that nicotine and other nicotinic agonists have cytoprotective effects, coupled with the evidence that smoking is protective against the development of AD and PD, suggests that it may be worthwhile to consider whether chronic nicotine or nicotinic agonist administration may be a useful strategy for delaying or preventing the clinical onset of the disease. High-risk individuals—identified by gene status (e.g., Apo E), family history, or cognitive profile—may represent a promising subject group in testing whether chronic nicotinic stimulation can significantly delay the onset of a dementing disorder.
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Introduction

In this chapter we review the literature involving the relationship between smoking and various neurological movement disorders. We also review the evidence demonstrating the utility of nicotine as a therapeutic agent in the treatment of certain movement disorders. We begin with a short introduction to the behavioral pharmacology of nicotine in animals.

Behavioral Pharmacology of Nicotine

Depending on dose and previous exposure, nicotine can produce either increases or decreases in the spontaneous locomotor activity of animals (Ksir et al. 1987). For example, many studies have consistently reported that high doses of nicotine (at or above 0.5 mg/kg base weight) generally produce decreases in locomotor activity, especially in rats tested in a novel environment (Clarke and Kumar 1983; Kita et al. 1986; Morrison and Stephenson 1972; Stolerman et al.
On the other hand, increases in locomotor behavior are typically seen at lower doses, especially in rats that have had previous exposure to nicotine and/or the testing environment (Battig et al. 1976; Clarke and Kumar 1983; Geyer et al. 1986; Ksir et al. 1985, 1987; Morrison and Stephenson 1972; Reavill et al. 1990). With repeated intermittent exposure (usually once daily), tolerance develops to the depressant effects of high doses (Morrison and Stephenson 1972; Stolerman et al. 1973), and sensitization or reverse tolerance occurs with the stimulant effects of low doses (Ksir et al. 1985, 1987). The behavioral effects of nicotine are also rate dependent. For example, rats selected for high levels of spontaneous activity displayed a reduced locomotor response to nicotine, whereas rats with low levels of activity displayed a stimulant response to nicotine (Rosecrans 1995). (For more information on the situational and behavioral effects of nicotine, see Grobe and Perkins, Chapter 3, this volume.) Because nicotine-induced hyperactivity is attenuated by the selective dopamine receptor antagonists (O’Neill et al. 1991), several investigators have hypothesized that the dopamine system plays an important role in mediating the locomotor response to nicotine (Balfour et al. 1991; Benwell and Balfour 1992; Clarke 1990; Clarke et al. 1988).

The form of administration is also important in determining the locomotor response to nicotine. Although a bolus injection of nicotine can cause a locomotor stimulant response in rats (Ksir et al. 1985, 1987), continuous delivery of nicotine via osmotic mini-pumps fails to do so at similar concentrations. In fact, the latter form of administration has been shown to actually prevent a stimulant locomotor response to a bolus injection of nicotine (Benwell et al. 1994). Nicotine has complex neuropharmacological actions, acting initially as a rapid agonist at nicotinic acetylcholine receptors (nAChRs), followed by a prolonged inactivation of these receptors shortly thereafter (Ochoa et al. 1989). It has been proposed that the predominant effect of nicotine on many nAChR subtypes over time (its time-averaged effect) is that of an antagonist (Hulihan-Giblin et al. 1989). On the basis of this evidence, bolus forms of nicotine administration (e.g., cigarette smoking and nicotine gum) should have a more acute agonist effect on nAChRs, whereas continuous forms of administration (e.g., transdermal nicotine patches) should have an overall antagonist effect on nAChRs (Shytle et al. 1996a, 1996b). This would be consistent with
the different behavioral responses to each of these two forms of nicotine administration in rats (Benwell et al. 1994).

**Smoking, Nicotine, and Parkinson’s Disease**

Parkinsonism is a clinical syndrome characterized by lack of or poverty of movement (akinesia), slowness and fatiguing (bradykinesia), rigidity, resting tremor, and postural instability. When this syndrome is thought to result from a specific degenerative process, it is called Parkinson’s disease; when it is thought to arise from other definable diseases, it is called secondary or symptomatic parkinsonism. Although the etiology of Parkinson’s disease is unknown and probably heterogeneous, the symptoms of Parkinson’s disease are thought to be caused by a loss of dopamine-producing neurons in the pars compacta of the substantia nigra and in the ventral tegmentum area (VTA) of the brain. These changes result in the denervation of the nigrostriatal and VTA-mesocortical dopaminergic pathways and a subsequent loss of dopamine release at their terminal regions. Although denervation may begin at an early age, the clinical symptoms begin to surface only when there is approximately 80% depletion of striatal dopamine levels.

Numerous epidemiological studies have suggested that cigarette smoking is negatively associated with the incidence of Parkinson’s disease. Baron (1986) reviewed these studies and found odds ratios ranging from 0.3:1 to 0.7:1. The most powerful study yet to assess this association was the Honolulu heart cohort study (Grandinetti et al. 1994). Eight thousand men were categorized as nonsmokers, current smokers, or ex-smokers and followed for 26 years. The relative risk for developing Parkinson’s disease for smokers versus nonsmokers was 0.39 (95% confidence interval: 0.22–0.70). In addition, an inclusive review of 46 published reports covering 35 independent epidemiological studies (Morens et al. 1995) found that 34 of the studies had findings supporting an inverse relationship between cigarette smoking and the occurrence of Parkinson’s disease.

Several hypotheses have been suggested to explain the inverse relationship between smoking and the development of Parkinson’s disease. It is possible that those predisposed to Parkinson’s disease
do not enjoy smoking. This possibility could reflect a genetic predisposition to have Parkinson’s disease and not to smoke, or it could involve early degeneration of mesolimbic dopaminergic pathways thought to be critically important to the establishment of nicotine self-administration (Paulson 1992). However, Morens et al. (1995) found evidence for direct protective roles for nicotine and/or smoking in reducing the risk of Parkinson’s disease.

**Direct Pharmacological Effect of Nicotine**

As noted earlier, nicotine has the ability to induce the release of dopamine from synaptic terminals of dopaminergic neurons in the striatum and other terminal regions. In addition, there have been studies of the use of nicotine in the alleviation of parkinsonian symptoms. Moll (1926) administered nicotine subcutaneously to 13 patients with parkinsonism associated with encephalitis lethargica. According to his observations, 9 of the 13 showed short-lived improvement in rigidity but no change in tremor. Marshall and Schnieden (1966) studied the effects of several compounds, including nicotine, on different types of tremor and observed a reduction of tremor in 6 patients given 6 mg of nicotine tartrate intravenously. However, 1 patient received only 3 mg and experienced an increase in tremor. Fagerström et al. (1994), using a double-blind, crossover trial of 2 patients, recently reported that a combination of nicotine gum and transdermal nicotine may relieve the symptoms of Parkinson’s disease. A study of 6 cases of juvenile parkinsonism revealed that cigarette smoking reduced symptoms in the short term but that tolerance to the effects occurred with the second or third cigarette, possibly due to nAChR inactivation. Nicotine gum also helped, but it was not as effective as cigarette smoking (Ishikawa and Miyatake 1993). More recently, Clemens et al. (1995) examined the short-term effects of acute nicotine gum chewing in 48 patients with Parkinson’s disease in a randomized double-blind, placebo-controlled trial. They used the unified Parkinson’s disease rating scale to assess tremor, rigidity, and bradykinesia, and they found no statistically significant improvements between the two groups. However, these investigators stated that further studies are needed to assess repeated long-term treatment with nicotine, and they noted that even an early
study with acute L-dopa administration (now a standard treatment for the disease) found that there was no improvement in Parkinson’s disease symptoms (Fehling 1966). Newhouse et al. (1997) found preliminarily acute and chronic improvements in motor functioning in Parkinson’s disease patients who received nicotine administration.

**Direct Neuroprotective Effect of Nicotine**

Several studies using a partial unilateral transaction of the ascending mesocortical dopamine pathway in rats have shown that nicotine has neuroprotective properties (Fuxe 1990; Fuxe et al. 1994; Janson et al. 1988; Owman et al. 1989). In this experimental model of Parkinson’s disease, chronic infusion of nicotine blocked retrograde and anterograde degeneration of dopaminergic neurons (Janson et al. 1988), reversed the decrease of striatal dopamine, and eliminated asymmetry in striatal glucose utilization (Janson et al. 1991; Owman et al. 1989). These researchers hypothesized that chronic continuous infusion of nicotine causes nAChRs located on dopaminergic neurons to become inactivated, resulting in decreased release and utilization of dopamine and less energy expenditure by these neurons. In a study on aging, Prasad et al. (1994) found that chronic oral nicotine administration in rats reversed normal age-related losses of nigrostriatal dopamine (D₁) and D₂ receptor sites and also reversed normal age-related changes in behavior. Although Janson et al. (1992) determined that acute intermittent nicotine administration partially protected against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)–induced neurotoxicity in the black mouse, similar studies have also reported negative results (Behmand and Harik 1992; Fung et al. 1991).

**Neuroprotective Effect of Cigarette Smoke**

Monoamine oxidase (MAO) is an important enzyme involved in the degradation of the monoamine neurotransmitters dopamine, serotonin, and norepinephrine. It has also been suggested that this oxidative process may play an important role in the production of free radicals responsible for the neurodegeneration of dopaminergic neurons in Parkinson’s disease. In addition, it has been known for some time that smokers have lower platelet MAO activity than do
nonsmokers (Oreland et al. 1981). This effect on MAO is not due to a pharmacological effect of nicotine but rather involves some compound or compounds found in tobacco smoke (Fowler et al. 1996). Berlin et al. (1995) found that this smoking-related effect occurs primarily with MAO B, the enzyme involved in the breakdown of dopamine. Likewise, Fowler et al. (1996), using sophisticated neuroimaging techniques, demonstrated that brains of living smokers show a 40% greater decrease in the level of MAO B than the decrease shown in nonsmokers or former smokers. Since MAO B inhibition is associated with an enhanced activity of dopamine, as well as with decreased production of free-radical metabolites, it is possible that a reduction of MAO B activity may synergize with nicotine to reduce or even partially reverse the degeneration of dopaminergic neurons characteristic of Parkinson’s disease.

Smoking, Nicotine, and Neuroleptic-Induced Movement Disorders

Schizophrenia, a psychiatric disorder involving hyperdopaminergic tone, is most often treated with neuroleptics. Surveys of schizophrenic patients have demonstrated rates of smoking between 74% and 92%, compared to 35%–54% for all psychiatric patients and 30%–35% for the general population (Leon et al. 1995). This relationship between schizophrenia and smoking is found even when confounding factors like marital status, alcohol use, and socioeconomic class are controlled (Leon et al. 1995). Given the health risks of smoking, many psychiatric inpatient units have increasingly adopted no-smoking policies. As a result, the need to understand why people with schizophrenia smoke so heavily is an important issue, particularly with regard to the consequences of cigarette abstinence (Polgar et al. 1996). It has been speculated that cigarette smoking may improve underlying psychopathology by enhancing concentration and reducing anxiety from hyperarousal (Gopalaswamy and Morgan 1986). Subsequently, Glynn and Sussman (1990) surveyed 59 patients with schizophrenia and found that smoking produced relaxation and reduced anxiety in most patients and that many patients reported that smoking reduced medication side effects.
Cigarette smoking may decrease neuroleptic side effects through a pharmacokinetic interaction. Cigarette smoke, but not nicotine, stimulates hepatic microsomal enzyme activity (Jusko 1979), resulting in increased catabolic metabolism of neuroleptics and decreased plasma levels (Jann et al. 1986). This may explain why individuals with schizophrenia who smoke receive higher neuroleptic doses (Goff et al. 1992). In addition, nicotine may have some role to play in reducing the cognitive deficits associated with schizophrenia and neuroleptic treatment. Cigarette smoking has been found to normalize sensory gating deficits in schizophrenic patients (Adler et al. 1993), and a double-blind, placebo-controlled trial (Levin et al. 1996b) found that transdermal nicotine reversed some of the adverse cognitive effects of the neuroleptic haloperidol and improved cognitive performance in general for schizophrenic patients (see Newhouse and Whitehouse, Chapter 7, this volume).

The relationship between smoking and neuroleptic-induced motoric side effects is less clear. The primary action of typical neuroleptics is thought to be their ability to block dopamine receptors. As a result of dopamine receptor blockade, neuroleptics can mimic all the behavioral features of Parkinson’s disease (this reaction is called neuroleptic-induced parkinsonism, or NIP). Decina et al. (1990) evaluated 130 psychiatric inpatients and found significantly less NIP in smokers than in nonsmokers, and Wagner et al. (1988) found this effect only in people with schizophrenia with a duration of illness less than 7 years. Yassa et al. (1987) did not find a relationship between NIP and smoking, but only 11 patients with NIP were identified in their sample of 154 chronic psychiatric patients. Goff et al. (1992) examined 78 schizophrenic outpatients and found that current smokers displayed significantly less NIP but more akathisia. Although Menza et al. (1991) found no relationship between smoking and NIP, they did find significantly more akathisia among female smokers.

Two epidemiological studies have reported an increased incidence of tardive dyskinesia (TD) in psychiatric patients who smoke (Binder et al. 1987; Yassa et al. 1987). Since TD is thought to result from supersensitive dopamine receptors, Kirch et al. (1988) hypothesized that individuals who are given neuroleptics and who are smokers may develop a greater degree of dopamine receptor supersensitivity.
as a result of combined receptor blockade by neuroleptics and a
decrease in central nervous system dopamine turnover caused by
chronic nicotine exposure, resulting in an increased prevalence of
TD. Although animal research conducted by this group did find that
chronic nicotine reduced striatal dopamine turnover (Kirch et al.
1987), similar follow-up studies found no parallel alterations in
dopaminergic receptor binding parameters (Kirch et al. 1992). More-
over, three additional epidemiological studies found no relationship
between smoking and TD (Goff et al. 1992; Menza et al. 1991; Youssef
and Waddinton 1987). Although one study did quantitatively dem-
onstrate more spontaneous orofacial dyskinesias in neuroleptic-
treated patients who were current smokers (May et al. 1983), such a
finding is complicated by the association of dyskinesia with chronic
obstructive pulmonary disease, which may be a consequence of
smoking itself (Campbell et al. 1983).

Nicotine and Tourette’s Syndrome

Tourette’s syndrome (TS) is a hyperkinetic movement disorder char-
acterized largely by the expression of sudden, rapid, brief, recurrent,
nonrhythmic, stereotyped motor movements (motor tics) or sounds
(vocal tics), which are experienced as irresistible but can be suppressed for varying lengths of time (Shytle et al. 1995; Tourette Syn-
drome Classification Study Group 1993). The symptoms usually
begin in childhood and range from relatively mild to very severe
over the course of a patient’s lifetime (Bruun and Pukdman 1992;
Robertson 1989). Many TS patients also exhibit other neuropsychiat-
ric abnormalities, including obsessive-compulsive disorder (Pauls et
al. 1986), attention-deficit/hyperactivity disorder (ADHD) (Comings
and Comings 1988), and visual-motor deficits (Silver and Hagin
1990). TS is frequently treated with the neuroleptic haloperidol,
which is effective in about 70% of cases (Erenberg et al. 1987; Shapiro
and Shapiro 1988). Other neuroleptics such as pimozide can be
used to treat this disorder, but it appears that haloperidol is more ef-
efective and shows no appreciable difference in adverse effects
(Shapiro et al. 1989b). As alluded to earlier, neuroleptics can pro-
duce adverse side effects, including reduced cognitive functioning,
sedation, weight gain, acute dystonic reaction, akathisia, parkin-
sonism, and (with long-term treatment) tardive dyskinesia (Shapiro and Shapiro 1989).

Unlike Parkinson’s disease, which found its link to nicotine through epidemiology, the story of the therapeutic use of nicotine in the treatment of TS has its roots in the laboratory. Following findings that acute nicotine administration augmented reserpine-induced catalepsy in rats (Montgomery et al. 1985, Moss et al. 1989), it was later determined that low doses of nicotine could also potentiate haloperidol-induced catalepsy as well as reduced locomotor activity (Emerich et al. 1991a, 1991b). The findings from these preclinical experiments suggested that nicotine may have some potential benefit in the treatment of TS. Although the pathogenesis of TS is still not known, excessive striatal dopamine has been proposed (Singer et al. 1982, 1991). This possibility is based largely on the therapeutic effectiveness of neuroleptics that block D2 receptors (Shapiro and Shapiro 1988; Shapiro et al. 1989) and on recent imaging findings from single photon emission computed tomography (SPECT) showing differences in D2 receptor binding in the striatum of monozygotic twins discordant for TS (Wolf et al. 1996). Thus, it has been suggested that striatal dopamine excess or receptor hypersensitivity may play a role in the etiology of this disorder.

In the first open trial, 10 TS patients concurrently treated with haloperidol chewed nicotine gum three times daily. Decrease in tic frequency and severity was noted, as well as subjective improvement in concentration and attention in 8 of the 10 subjects (Sanberg et al. 1989). A second study of 10 additional patients receiving haloperidol revealed a quantitative reduction in tic frequency following nicotine gum chewing. This reduction occurred both during the 30-minute period of gum chewing and at 1 hour after administration (McConville et al. 1991). A subsequent controlled trial also yielded similar results: nicotine gum plus haloperidol reduced both tic severity and tic frequency, nicotine gum alone reduced only tic frequency, and placebo gum alone had no effect on tic severity (McConville et al. 1992).

Because of gastrointestinal side effects of nicotine gum and its short duration of action, Silver et al. (1995) examined the effects of the transdermal nicotine patch (TNP) (7 mg/24 h) in 11 TS patients who were not responding to current neuroleptic treatment. Using a
video camera to record tics at baseline and at 3 hours after application, they noted a 47% reduction in tic frequency and a 34% reduction in tic severity following patch application. Surprisingly, in 2 patients, the effect of a single nicotine patch persisted for a variable length of time after patch removal. Similar long-term benefits of the TNP in 5 TS patients were reported by Dursan et al. (1994), who found that applying two consecutive 10-mg TNPs, each TNP given for 24 h, reduced Yale Global Tic Severity Scale (YGTSS) scores significantly for 4, but not 16, weeks after TNP removal.

To further investigate the putative long-term therapeutic response to the TNP, 20 TS patients were followed for various lengths of time after the application of 2 TNPs. Of these patients, 16 were children or adolescents receiving concurrent neuroleptic treatment (Silver et al. 1996), and the additional 4 patients differed in that two were free of neuroleptics at the time of TNP application and the other 2 were adults (Shytle et al. 1996b). Following a baseline evaluation, each patient received a single TNP (each 7 mg/24 hours) and was told to return for a follow-up evaluation when he/she felt that symptoms were beginning to return. At that point a decision was made as to whether a second TNP was needed. At each observation point, the frequency and severity of TS symptoms were quantified on the YGTSS (Leckman et al. 1989). Although there was a broad range in individual response, application of the first TNP produced a significant 35% reduction in the mean YGTSS score over baseline at an average duration of 10 ± 2 days after application. Although 3 patients did not receive a second TNP, for the remaining 17 who did, a significant 45% reduction in the mean YGTSS score over baseline was achieved at an average duration of 13 ± 3 days after application. For reasons unknown, possibly severe concomitant emotional stress (Silver et al. 1996), 3 patients did not respond at all to either the first or second TNP. Interestingly, both patients who were free of other medication at the time of TNP treatment also exhibited a beneficial response to TNP exposure. As found with nicotine gum (Sanberg et al. 1989), improved handwriting was documented in patients receiving the TNP. Side effects, including itching at the site of application, nausea, and occasional headache and sedation, were for the most part transient. However, no evidence was found for nicotine dependence occurring in patients treated with the TNP.
Here again the paradoxical nature of nicotine comes forth. Originally, it was proposed that the therapeutic mechanism was due to a nicotine-induced release of acetylcholine in the striatum, reestablishing the competing balance between dopamine and acetylcholine. However, as discussed earlier, nicotine is able to increase striatal concentrations of several neurotransmitters, one of which is dopamine. In contrast to the putative therapeutic actions of nicotine in Parkinson’s disease (an increased level of dopamine in the striatum), the potentiation of haloperidol would require a relative decrease in dopamine release. Although both an agonist and an antagonist role for nicotine may be involved in the total therapeutic response to transdermal nicotine found in TS, the available evidence from animal studies suggests that a prolonged inactivation of nAChRs following exposure to transdermal nicotine may be responsible for the long-term therapeutic response seen in some TS patients (Sanberg et al. 1997; Shytle et al. 1996b). Thus, the difference in duration of action between nicotine gum and transdermal nicotine can be attributed to a difference in length of nAChR inactivation.

Unfortunately, no epidemiological studies have examined the relationship between TS and smoking. Tobacco use is, however, much higher in neuropsychiatric populations (Glassman 1993; Newhouse and Hughes 1991), in whom symptoms of inattention are often present, especially in people with schizophrenia (Glassman 1993), major depression (Breslau et al. 1991), and ADHD (Pomerleau et al. 1995). Thus, because many TS patients have problems in concentrating and poor visual motor function, one might predict that smoking would be more frequent in this population. In addition, nicotine has been shown to enhance cognitive functioning in ADHD (Conners et al. 1996; Levin et al. 1996a), a comorbid disorder often present in TS patients. (For more information on nicotine and ADHD, see Levin et al., Chapter 9, this volume.)

Dimitsopulos and Kurlan (1993) published a case report of a 22-year-old female TS patient who also responded to the nicotine patch in the absence of a neuroleptic, the standard treatment for TS. Although her tic symptom severity had not required tic-suppressive drug therapy since she had been 15 years old, within 3 days of abruptly quitting a 7-year tobacco smoking habit (1.5 packs/day), she experienced a dramatic worsening of tic severity to the point that
they were occurring at a nearly constant rate. Her symptoms returned to baseline after wearing daily nicotine patches (14 mg/day) for 2 weeks. Her symptoms did not recur on discontinuation. In addition, Devor and Isenberg (1989) reported a 21-year-old male TS patient whose symptoms had improved while smoking tobacco (1 pack/day) in the absence of neuroleptics, with TS symptoms reappearing in a milder form on discontinuation of tobacco smoking.

**Conclusions**

Depending on several factors, nicotine has the ability to cause either increases or decreases in the spontaneous activity of animals. Dose, previous exposure to nicotine, the baseline activity of the animal, and form of nicotine administration are all important in determining behavioral response to nicotine.

Epidemiological evidence has implied a negative association between the neurodegenerative disorder Parkinson’s disease and smoking. The exact cause of this association is unclear at present, but the available evidence suggests that nicotine and/or MAO B inhibition from cigarette smoke may have neuroprotective effects on the dopaminergic neurons of the nigrostriatal pathway. Scattered clinical trials showing therapeutic effects of nicotine in Parkinson’s disease are consistent with nicotine’s influencing the release and turnover of dopamine in the striatum.

Cigarette smoking is very frequent among psychiatric patients, particularly those with schizophrenia. The available evidence suggests that nicotine improves cognitive functioning, reduces anxiety, and decreases the side effects of neuroleptic drugs in patients with schizophrenia. Cigarette smoking has been found to reduce neuroleptic-induced parkinsonian symptoms. However, there is some evidence that nicotine may increase the occurrence of neuroleptic-induced akathisia. The relationship between tardive dyskinesia and smoking is even less clear, but the bulk of the evidence does not support a causal relationship.

Research with transdermal nicotine shows promise as a therapeutic adjunct to neuroleptic treatment of Tourette’s syndrome, a hyperkinetic movement disorder. Although one can only speculate about the mechanism of action, the available evidence suggests that
transdermal nicotine may be acting as a functional antagonist of nAChRs, leading to a long-term receptor inactivation and a restoration of the dopamine-acetylcholine balance in the striatum. Dystonia is another movement disorder in which the therapeutic effects of nicotine should be further investigated. For example, one case study suggests that nicotine alleviated the motoric symptoms of hemidystonia (Lees 1984).

Undoubtedly, we need further characterization of the actions of nicotine on a variety of neuronal nicotinic receptor subtypes, as well as an understanding of the broad neuropharmacological consequences of different forms of nicotine administration. It is hoped that novel ligands specific for receptor subtypes will aid in elucidating the role and therapeutic potential of nicotinic receptor modulation in disorders of movement.

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CHAPTER 9

Nicotine Effects and Attention-Deficit/Hyperactivity Disorder

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Introduction

Nicotine has been shown to improve attention significantly in dependent smokers, nondependent smokers, and nonsmokers. Attentional improvements are also seen in clinical groups with attention deficits, including patients with Alzheimer’s disease and schizophrenia and adults with attention-deficit/hyperactivity disorder (ADHD). Nicotine delivered via nicotine skin patches and novel nicotinic agonists holds promise for inducing attentional improvement.

Nicotine and Attention

Nicotine is best known as the primary psychoactive chemical in tobacco, and as such, nicotine serves to a large degree as the basis for smoking dependence. In this regard nicotine has been viewed in a largely negative light. However, like all drugs, nicotine has a spectrum of effects; it is not purely an addictive drug. Like morphine and caffeine, two other dependence-producing drugs, nicotine has effects that may be therapeutically useful (Levin 1992, 1993; Levin and Rosecrans 1994; Levin et al. 1993, 1996a, 1996b, 1998). In this chapter
we present data concerning the possibility of nicotinic therapy for attentional deficits. Nicotinic treatment has been proposed for the treatment of ADHD (Barkley 1977; Conners et al. 1996; Levin et al. 1996b; Milberger et al. 1997; Pomerleau et al. 1995a, 1995b; Wender et al. 1985, 1991).

Nicotine skin patches were developed by Rose and associates beginning in 1985 (Rose 1986; Rose et al. 1984, 1985, 1990, 1994). They have proved useful in helping people to quit smoking (Daughton et al. 1991; Hughes and Glaser 1993; Levin et al. 1994; Palmer et al. 1992; Rose et al. 1990, 1994, 1995; Russell et al. 1993; Westman et al. 1993). However, nicotine skin patches may also be useful in administering nicotine for other therapeutic reasons. Because nicotine is administered without the 4,000 other compounds present in the tar and gaseous components of tobacco smoke, nicotine patches appear to be safer than smoking and to have little likelihood of abuse (Pickworth et al. 1994). Thus, nicotine skin patches may be a therapeutic means for administering nicotine relatively safely. In addition, a variety of pharmaceutical companies and academic laboratories are exploring the effects of novel nicotinic ligands to determine whether some of the therapeutically useful effects of nicotine can be obtained with low side-effect profiles.

Nicotine has long been reported by smokers to improve attentiveness. This effect has been documented in formal studies of attentional performance with and without cigarette smoking (Peeke and Peeke 1984; Wesnes and Warburton 1983). However, because smoking withdrawal includes a demonstrable cognitive impairment (Hatsukami et al. 1989), there is concern about the degree to which nicotine-induced attentional improvements may merely reflect an attenuation of an attentional deficit induced by nicotine withdrawal. Recently, this issue has been resolved. It has been demonstrated that nicotine improves attentiveness in nondeprived smokers and *chippers*, who are smokers who only smoke occasionally and do not show pronounced withdrawal symptoms (Warburton and Arnall 1994). We have found that nicotine administered via skin patches significantly improved choice accuracy and reduced response speed variability in normal nonsmoking subjects (Levin et al. 1998). Thus, nicotine seems to have attention-improving effects apart from alleviation of withdrawal symptoms.
Nicotine and Attentional Disorders

Attention-Deficit/Hyperactivity Disorder

Nicotine may be useful for the treatment of ADHD. This idea evolved from three different lines of evidence:

- First was the attention-improving effects of nicotine in smokers, described above.
- Second was the finding that nicotine potently stimulated the release of dopamine (Wonnacott et al. 1989), a primary mechanism of action of the stimulants, such as methylphenidate and amphetamine, currently used to treat ADHD (Hoffman and Lefkowitz 1996).
- Third was the finding that adults with ADHD showed a smoking rate about twice the societal background rate (Pomerleau et al. 1995b). These adults with ADHD may be self-medicating with nicotine to attenuate symptoms of ADHD.

We conducted a study of adults with ADHD to determine, with a placebo-controlled, double-blind design, whether nicotine administered via skin patches would acutely attenuate ADHD symptoms in this population (Conners et al. 1996; Levin et al. 1996b). Nicotine treatment significantly diminished clinical symptoms of ADHD, as assessed by the blind clinical global assessment (see Figure 9–1). It is important that this improvement was seen even when only the nonsmokers were considered. Thus it did not seem to be merely the nicotine skin patches that attenuated the effects of smoking withdrawal. A study of the chronic effects of nicotine in comparison with methylphenidate is currently under way.

The improvement in attentiveness was also discernible in terms of performance consistency on the Conners’ Continuous Performance Test (CPT), an attentional task (Conners 1995). The smokers showed a significant reduction in variability of reaction time over blocks of the test session; nonsmokers had a nearly significant reduction in variability of reaction time across different interstimulus intervals (Levin et al. 1996b). On the Profile of Mood States (POMS) scale (McNair et al. 1981), the smokers but not the nonsmokers re-
ported significant self-perceived reductions of difficulty in concentrating. Both smokers and nonsmokers reported significant nicotine-induced increases in self-perceived vigor on the POMS scale.

Figure 9–1. Study of nicotine treatment of adults with attention-deficit/hyperactivity disorder: global clinical assessment. Nicotine effect: all subjects, $P < .025$; nonsmokers only, $P < .005$. 
Nicotine’s positive effects on memory in subjects with ADHD are best seen in the maintenance of consistency of attention as measured by the variance in response time on the CPT. We have found that nicotine skin patches reduce the standard error of reaction time over blocks of trials within a session or across the different interstimulus intervals (Levin et al. 1996b).

Potential application of nicotine treatment for ADHD at least in adults seems promising. However, there are other disorders with attentional deficits that may be addressed by nicotine, such as schizophrenia and Alzheimer’s disease.

**Alzheimer’s Disease**

In Alzheimer’s disease patients, attentional performance has been found to be significantly improved with nicotine (Jones et al. 1992; Sahakian and Jones 1991; Sahakian et al. 1989;). Recently, we studied the use of a chronic nicotine patch in this population during four weeks of nicotine administration. Nicotine caused a significant reduction in errors of omission in the Conners’ CPT (White and Levin 1999). This reduction in errors of omission was not at the expense of increased errors of commission—a finding that supports a nicotine-induced improvement in attention. Thus, the nicotine effect did not seem to be a mere increase in response rate. Rather, a true increase in response accuracy seemed to be caused by nicotine treatment. The consistency of attention seemed to be improved by nicotine as well. In the Alzheimer’s disease patients, nicotine caused a significant reduction in variability of response speed on the Conners’ CPT. (For more information on nicotine and Alzheimer’s disease, see Chapter 5, this volume.)

**Schizophrenia**

Nicotine-induced attentional improvement has recently been described in individuals with schizophrenia (Levin et al. 1996a). Regardless of the dose of the antipsychotic medication (haloperidol), nicotine caused a significant dose-related reduction in variability of response time on the Conners’ CPT (Figure 9–2; Levin et al. 1996a). This contrasted with nicotine-induced improvements in short-term memory and mental processing speed, which appeared to be an at-
tenuation of deficits caused by moderate or high doses of haloperidol (see also Chapter 6, this volume).

**Prenatal Exposure to Nicotine**

Paradoxically, although nicotine administration in adults seems to improve attentiveness, prenatal nicotine exposure has been associated with attentional impairment. The children of women who smoke during pregnancy are more likely to develop cognitive and learning deficits (Butler and Goldstein 1973; Dunn and McBurney

![Figure 9–2. Nicotine skin patch effects on Conners’ Continuous Performance Test in patients with schizophrenia. Nicotine effect: *P* < 0.05 versus 0-mg patch, all haloperidol groups. Adapted from Levin et al. 1996a.](image-url)
1977; Gueguen et al. 1995; Naeye and Peters 1984; Rantakallio 1983). These include ADHD (Denson et al. 1975; Fried et al. 1992), impaired attention and orientation (Jacobson et al. 1984; Landesman-Dwyer and Emanuel 1979; Picone et al. 1982a, 1982b; Streissguth et al. 1984) and poor impulse control (Kristjansson et al. 1989).

Long-lasting deficits in cognitive function after maternal smoking during pregnancy have been seen in most studies (Hardy and Mellits 1972; Lefkowitz 1981). Fried (1989) found that maternal cigarette smoking during pregnancy was significantly correlated with impaired performance on the McCarthy Scale of Children’s Abilities at 3 years of age. Streissguth et al. (1984) found impaired orientation and attentiveness in 4-year-old children. Kristjansson et al. (1989) found hyperactivity, impaired vigilance, and poor impulse control in 4- to 7-year-olds. These long-lasting effects of developmental nicotine exposure may go undetected until they affect school performance. Difficulties with attentional behavior were still noted at 4–7 years of age in the offspring of women who smoked during pregnancy, as assessed by auditory and visual vigilance tasks. There was an increased activity level during the tasks and an increased incidence of errors of commission in both auditory and visual tasks compared to the same factors in the offspring of women who did not smoke. This combination of results suggests that the deficits in attention may reflect impulsive responding and increased overall activity (Kristjansson et al. 1989). It is important that in the 6-year-old children there was a demonstrable dose-response relationship between the magnitude of prenatal exposure and 1) impulsive behavior (as manifested in a response inhibition task) and 2) increased errors of commission on a sustained vigilance task. Performance on a series of memory tasks, particularly those requiring verbal recall, was also impaired with maternal cigarette use during pregnancy (Fried et al. 1992). Thus, maternal smoking during pregnancy has an impact on the affected individuals and on society far beyond the more well-known and well-publicized immediate perinatal consequences.

**Summary**

There is strong evidence showing that attentional improvements are produced by nicotine in subjects without attentional deficits, as well
as in those with attentional deficits associated with ADHD, Alzheimer’s disease, and schizophrenia. Paradoxically, nicotine exposure during the prenatal period has been associated with attentional deficits later in life. This may produce a cycle of impairment if women exposed prenatally are more likely to take up smoking (possibly as self-medication) and expose their own offspring. Nicotine administered via a skin patch appears to be safer than smoking in that it does not contain the components of tar and the gas phase of a cigarette. The dependence liability for the nicotine skin patch appears to be lower than that for smoking. Although nicotine skin patches are currently approved only to aid in smoking cessation, additional evaluation may demonstrate safety and efficacy for other indications, including attentional impairment. The research thus far holds promise for the usefulness of nicotine skin patches as a treatment for ADHD and other disorders characterized by attentional deficits. Other nicotinic agonists under development may have better efficacy and a larger therapeutic index (see Chapters 1 and 5, this volume).

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Introduction

Cigarette smoking is a complex process based on pharmacological and behavioral dependencies. To address these dependencies, most comprehensive smoking cessation programs include nicotine replacement and behavioral counseling. Nicotine replacement is a substitute for the pharmacological need for nicotine, and individual or group counseling helps in understanding and managing the associations between situational cues and smoking. In spite of the advances in this treatment approach, the success of comprehensive treatment programs at 1 year is only about 10%–20% (Russell et al. 1993; Silagy et al. 1996; Transdermal Nicotine Study Group 1991).

Although nicotine may be a necessary component of smoking addiction, there are also important behavioral aspects of cigarette smoking, such as expected sensations, accustomed movements, and social facilitation. Although nicotine replacement has advanced the treatment of nicotine addiction tremendously, an understanding of

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Why people smoke is important to the future of smoking cessation therapy beyond nicotine replacement. In this chapter, we review nicotine replacement therapies in the context of a comprehensive model of smoking behavior.

Why Do People Smoke?

One needs a model of smoking to understand what nicotine replacement might be expected to do as a smoking cessation aid, and what it would be expected not to do. For example, nicotine replacement would be expected to relieve the craving for a cigarette associated with smoking withdrawal, but nicotine replacement would not be expected to stop the involuntary reaching into a pocket for a cigarette when an emotionally stimulating situation arises—for example, receiving an upsetting telephone call.

Because an individual smoker may smoke for many different reasons throughout the day, it has been difficult simply to classify smokers into categories such as relaxation smokers or stimulation smokers. Furthermore, most classifications have been made by eliciting responses from the smokers themselves, which assumes that a smoker has an adequate understanding of why he or she smokes.

Several analyses of smoking motives have supported the model of pharmacological and nonpharmacological reasons for smoking. Ikard et al. (1969) proposed six types of smoking: habitual, addictive, negative affect reduction, pleasurable relaxation, stimulation, and sensorimotor manipulation. Russell et al. (1974) proposed a model consisting of the following types of smoking: Stimulation, Indulgent, Psychosocial, Sensorimotor, Addictive, and Automatic. Tate et al. (1994) found that two smoking motivation factors were apparent: one factor consisting of Addictive, Sedative, Automatic, and Stimulation rewards, and the other factor consisting of Psychosocial, Indulgent, and Sensorimotor rewards.

These models of smoking behavior divide the reasons for smoking into two domains: a nicotine effect and a nonnicotine effect. The nonnicotine effect includes psychosocial and sensorimotor factors. In the Tate model, the Indulgent factor—which consisted of three items, including “I smoke for the pleasure of having something to put in my mouth”—may represent a sensory effect in that question-
The classification of motives based on these two domains is complicated in that nicotine itself has significant sensory effects. The airway sensations produced by high-nicotine cigarettes are more intense than those of low-nicotine cigarettes having equal tar delivery (Rose et al. 1993), and nicotine antagonists such as mecamylamine (a central and peripheral antagonist) and hexamethonium (a peripheral nicotine antagonist) attenuate the sensory effects of inhaled nicotine (Rose et al. 1989). Additionally, these peripheral sensory effects may be coupled with central nervous system (CNS) effects.

In Figure 10–1, we propose a revised model of smoking motives based on nicotine effects, sensory effects, and social effects. The nicotine effects include what is currently understood to represent CNS effects of nicotine: mood regulation, pleasurable relaxation, addiction, or stimulation smoking. Sensory effects, which are less well studied, include the peripheral nervous system effects of nicotine and other components of cigarette smoking, including the hand, mouth, and lung sensations derived from smoking (Rose 1988). Social effects include the social rewards from the ritual of smoking while interacting with other people. This model will provide the basis for understanding the benefits and limitations of nicotine replacement therapy.

Although these three components of reward are clearly important for the perpetuation of smoking, how they interact in a given smoker may explain the difficulty in classifying the smoking behav-

![Figure 10–1](image-url)
ior: is it possible that an individual smoker could be dependent on the nicotine, the sensory, and the social effects of smoking? Most experts, however, agree that the single unifying feature to explain why people smoke is nicotine addiction or dependence (U.S. Department of Health and Human Services 1988).

**Nicotine Dependence**

Smoking meets the definition of an addictive behavior because there is a highly controlled or compulsive pattern of use, there are psychoactive or mood-altering effects, nicotine functions as a reinforcer to strengthen the behavior, and withdrawal symptoms occur on discontinuation of smoking. (See Karan and Rosecrans, Chapter 4, this volume, for an in-depth discussion of nicotine and addiction.)

Another line of evidence supporting the addiction model derives from the observation that smokers titrate their nicotine plasma levels throughout the day—beginning to smoke when the levels decrease beneath a certain threshold, then discontinuing smoking when the level exceeds a certain threshold (Fisher et al. 1993). Several studies have shown that this regulation of nicotine levels is not precise because if nicotine is administered by means other than smoking, smokers are not able to maintain the same nicotine level. In several studies in which smokers were allowed to smoke while receiving other forms of nicotine (via skin patch or intravenously), smokers did not reduce their smoking as much as would be expected on the basis of the theory of nicotine regulation alone (Benowitz and Jacob 1990; Foulds et al. 1992). These studies suggest that nicotine levels are not the only factor determining smoking behavior.

Another interpretation of the immediate rewards of smoking regards smoking as a responsive and effective coping strategy (Pomerleau and Pomerleau 1987). Certainly there are many immediate rewards from smoking, including pleasurable sensations, heightened arousal and attention, reduced hunger, and anxiety relief. In this model, these rewards constitute a successful coping mechanism that influences the smoker to continue smoking.

The two competing hypotheses as to why people smoke, based on the addiction model, are that 1) smoking is maintained to reduce withdrawal symptoms and 2) smoking is reinforced by the positive
effects of nicotine, including enhanced coping ability. If the reason for smoking derived totally from relief of withdrawal symptoms, then one would expect nicotine replacement to decrease all kinds of withdrawal symptoms (nicotine craving, dysphoria, irritability, anxiety, difficulty in concentrating, restlessness, insomnia, and increased appetite or weight gain). Several nicotine replacement studies have reported partial but not total withdrawal symptom relief (see below).

**Nicotine Self-Medication Theories**

Along the same line of thinking as the positive-effect theory, is it possible that certain smokers are medicating themselves with cigarettes to feel more normal or to alleviate side effects of other medications? This self-medication theory of smoking stemmed from the observation that many patients with established psychiatric disorders also smoke cigarettes.

This theory leads to an important expansion in understanding the role of nicotine replacement in people’s lives. If nicotine replacement is also substituting as a medication for an underlying psychiatric disorder, and that psychiatric disorder is not treated after the nicotine therapy is discontinued, a patient may be more likely to relapse to smoking because of worsening symptoms of that disorder. This understanding leads to the possibility that smokers with psychiatric conditions may need new medication or medication adjustment after they quit smoking.

**Nonnicotine Reasons for Smoking**

In the same way that intravenous alcohol cannot provide the same taste as drinking an alcoholic beverage, nicotine replacement cannot provide the enjoyable sensations of smoking a cigarette, including taste, olfactory, and airway sensations. If nicotine replacement is provided without the usual sensations, smokers may not appreciate that they are receiving nicotine and may relapse to smoking to receive the sensations that they have come to associate with the nicotine effect.
Rationale of Nicotine Replacement Therapy for Smoking Cessation

The rationale for nicotine replacement therapy is to allow smokers to break their dependence on smoking in two stages. First, while receiving nicotine replacement, the smoker breaks the conditioned association between environmental cues and the act of smoking. Nicotine replacement decreases withdrawal symptoms during this period of time, enabling the smoker to remain abstinent from smoking. Then the smoker is weaned from the nicotine replacement.

Efficacy of Nicotine Replacement Therapy for Smoking Cessation

Several meta-analyses of randomized controlled trials using nicotine replacement therapy (NRT) for smoking have concluded that NRT is an effective and cost-effective treatment for smoking cessation (Fiore et al. 1992; Fiscella and Franks 1996; Silagy et al. 1996). Each of these studies also provided the smoker with a quit date and included some kind of smoking cessation counseling: self-help materials, brief counseling, or intensive group counseling.

Nicotine Gum

Approved by the U.S. Food and Drug Administration (FDA) in 1984 for prescription use, 2-mg nicotine gum (polacrilex [Nicorette] gum) was the first nicotine replacement therapy available for smoking cessation. In spring 1996, 2-mg and 4-mg nicotine gum were approved for over-the-counter use for smoking cessation.

The technique of using nicotine gum is more like chewing tobacco than like chewing gum. When nicotine gum is chewed and placed in contact with the buccal mucosa, nicotine is absorbed systemically. The absorption of nicotine is slower than if a cigarette were smoked, but nicotine gum can provide effective nicotine replacement if enough pieces of gum are chewed. In typical clinical circumstances, the percentage of baseline nicotine replacement relative to smoking baseline is approximately 33% for 2-mg nicotine gum and 66% for 4-mg gum (Fagerström 1988).
The 2-mg nicotine gum has been studied in more than 50 placebo-controlled clinical trials of smoking cessation (Silagy et al. 1996). A meta-analysis of these studies shows that nicotine gum increased the odds of abstinence at 12 months by 1.7 when compared to placebo. The absolute rates of smoking cessation were 18% for nicotine gum and 11% for placebo gum. Studies using the higher dose 4-mg nicotine gum suggested that it provides a greater degree of nicotine replacement for highly dependent smokers and significantly increases smoking cessation rates as compared to the 2-mg gum (Glover et al. 1996; Sachs 1995; Tonnesen et al. 1988). Nicotine gum, however, is difficult to tolerate for many smokers because of its side effects of bad taste, jaw soreness, heartburn, and hiccups.

Although it is assumed that nicotine gum works by relieving withdrawal symptoms, the effect of 2-mg nicotine gum on withdrawal symptoms was not as uniform as expected (Fagerström 1988). Across four studies, nicotine gum consistently reduced irritability and impatience but less consistently reduced depression, sleepiness, urges to smoke, anxiety, difficulty in concentrating, and restlessness. In one study, nicotine gum appeared to relieve craving and urges to smoke in smokers who scored high on baseline Stimulant and Dependent smoking motivation scales (West et al. 1986). The relief of craving by nicotine gum was not correlated with baseline Sedative, Indulgent, or Automatic smoking scores.

**Nicotine Patch**

The second form of nicotine replacement available for smoking cessation, approved in 1991, was transdermal nicotine, or the nicotine patch. In spring 1996, several nicotine patches were approved for over-the-counter use for smoking cessation.

Four different brands of nicotine patches are available, and these deliver either 21 mg/24 h or 15 mg/16 h. The nicotine patch typically produces plasma nicotine levels in venous blood of 10–20 ng/mL, comparable to the trough (lowest) plasma levels of nicotine in smokers before smoking a cigarette. In doses that are approved for clinical use, the nicotine patches replace approximately 50% of baseline nicotine levels (Tonnesen et al. 1991). The 21-mg/24 h and 15-mg/16 h nicotine patches have been studied in 17 placebo-controlled clinical
trials of smoking cessation (Table 10–1) (for review of the trials, see Fiore et al. 1996). A meta-analysis of these studies showed that the nicotine patch increased the odds of abstinence at 6 months by 2.0 when compared to placebo. The absolute rates of smoking cessation were 22% for the nicotine patch and 9% for the placebo patch. The nicotine patch is well tolerated, and compliance with treatment is excellent. The most common problem is skin irritation, which rarely leads to discontinuation of the medication.

Like nicotine gum, the nicotine patch did not alleviate all kinds of withdrawal symptoms in these studies. The nicotine patch effectively relieved the drowsiness (decreased arousal) associated with smoking withdrawal, but it only partially relieved symptoms of craving and irritability (Rose et al. 1990; Westman et al. 1993). In these studies, the nicotine patch did not relieve the symptoms of habit withdrawal or increased appetite.

Nicotine Nasal Spray

The third form of nicotine replacement available for smoking cessation, approved by the FDA in 1996 for prescription use, was the nicotine nasal spray (Table 10–1).

The nicotine nasal spray delivers a nicotine solution directly to the nasal mucosa for systemic absorption. One dose has been defined as two sprays, one spray in each nostril. This dose provides approximately 1 mg of nicotine, similar to the amount of nicotine provided by smoking a cigarette. The recommended dosing of nicotine spray is 8–40 mg/day of nicotine for 3 months.

There have been four placebo-controlled trials of nicotine nasal spray combined with behavioral counseling for smoking cessation (Hjalmarson et al. 1994; Leischow et al. 1996; Schneider et al. 1995; Sutherland et al. 1992). Again, the nasal spray appeared to double the smoking abstinence rates over an active placebo spray. The absolute smoking cessation rates at 3 months were 30%–45% for nicotine nasal spray and 10%–20% for placebo spray. In one study the 6-month smoking cessation rates were 21% for the active spray and 6% for the placebo spray. The nasal spray provided nicotine replacement ranging from 33% to 72% of baseline levels. Higher replacement was probably a result of more intensive instruction in the spray.
Table 10–1. Summary of placebo-controlled trials of nicotine replacement for smoking cessation

<table>
<thead>
<tr>
<th>Formulation</th>
<th>No. of trials</th>
<th>Setting</th>
<th>Dosage</th>
<th>Duration</th>
<th>Improvement in abstinence</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine gum</td>
<td>50</td>
<td>All types</td>
<td>2 mg: up to 30 pcs/day; 4 mg: up to 20 pcs/day</td>
<td>3–52 wks</td>
<td>1.6 (18% vs. 11%)(^a)</td>
<td>Mouth/jaw soreness, heartburn, hiccups</td>
</tr>
<tr>
<td>Nicotine patch</td>
<td>17</td>
<td>All types</td>
<td>21 mg/24 h or 15 mg/16 h: 1 patch/day of either dose</td>
<td>6–18 wks</td>
<td>2.3 (22% vs. 9%)(^a)</td>
<td>Skin irritation</td>
</tr>
<tr>
<td>Nicotine spray</td>
<td>4</td>
<td>Volunteers</td>
<td>1 dose = 1 spray in each nostril = 1 mg; 1–2 doses/h, up to 5 doses/h</td>
<td>12 wks</td>
<td>2.3 (45% vs. 20%)(^b)</td>
<td>Nose/throat irritation, cough</td>
</tr>
<tr>
<td>Nicotine inhaler</td>
<td>4</td>
<td>Volunteers</td>
<td>10 puffs = 1 puff of cigarette used ad lib</td>
<td>12 wks</td>
<td>2.2 (24% vs. 11%)</td>
<td>Cough</td>
</tr>
</tbody>
</table>

Note. pcs = pieces; wks = weeks.
\(^a\)Abstinence at 6 months. \(^b\)Abstinence at 3 months.
use. Nearly everyone using the nicotine spray had nasal irritation and cough, but these symptoms were not severe enough to cause discontinuation of the spray.

**Nicotine Inhaler**

The fourth type of nicotine replacement therapy available for use in smoking cessation is the nicotine vapor inhaler, or nicotine inhaler (Molander et al. 1996).

The nicotine inhaler is a plastic cigarette-shaped tube containing a perforated plastic plug impregnated with 10 mg of nicotine (and an additive to lessen the harshness of the nicotine). The smoker draws air through the tube in much the same way as one draws smoke from a cigarette. The inhaler is not a metered dose inhaler; there is no propellant in the inhaler. The dose of nicotine delivered per inhaler puff is approximately one-tenth of a puff from a typical cigarette.

The nicotine inhaler was shown to be effective compared to a placebo inhaler (which contained the additive only) in four randomized, double-blind clinical trials (Hjalmarson et al. 1997; Leischow et al. 1996; Schneider et al. 1996b; Tonnesen et al. 1993). The combined 6-month smoking abstinence rate was 24% for the nicotine inhaler, as contrasted with 11% for the placebo inhaler. The nicotine inhaler provided approximately 40% of baseline nicotine levels. The main side effects of the nicotine inhaler were mouth and throat irritation and coughing, occurring in about 50% of subjects.

Although there is little information regarding the effects of the nicotine spray or inhaler on smoking withdrawal symptoms in the clinical setting, there are theoretically some advantages to these modalities: they provide the ability to self-titrate the nicotine dose, and they address smokers’ needs for the sensory and social aspects of smoking.

**What Is Not Provided by Nicotine Replacement?**

**Total Nicotine Replacement**

The failure of nicotine replacement to be the panacea for smoking cessation has been attributed to the lack of total nicotine replacement
when compared to baseline smoking levels. If the goal of nicotine replacement is to provide the same levels of nicotine as smoking, most smokers are currently underdosed by the current use of nicotine replacement. Because of the underdosing, some of the expected relief of withdrawal symptoms might not be experienced. One study showed that there was an improvement in short-term smoking abstinence when the dose of nicotine patch was increased after 1 week of patch therapy if significant craving was present (Russell et al. 1993).

Future research will address whether tailoring the dose of the nicotine replacement to individual characteristics will improve smoking abstinence. Whether this individualization of treatment should be based on baseline number of cigarettes smoked per day, exhaled carbon monoxide, therapeutic drug monitoring (saliva or urine cotinine), or other characteristics is not clear.

**Rapid Nicotine Delivery**

The partial success of nicotine replacement for smoking cessation can be attributed to the slowness of nicotine delivery in these products. Cigarette smoking provides rapid plasma peaks of nicotine, and it has been theorized that these rapid nicotine peaks are particularly important in the maintenance of nicotine addiction (Russell and Feyerabend 1978).

None of the current formulations of nicotine replacement provides the rapid increase in nicotine levels of smoking a cigarette (Schneider et al. 1996a). Although it would seem that the nicotine inhaler would have the greatest potential to provide similar rapid delivery, the inhaler is unable to fully simulate a cigarette, because most of the nicotine vapor is deposited in the mouth and throat, not inhaled into the lungs (Bergstrom et al. 1995).

**Immediate Sensory Cues**

Nicotine replacement cannot provide all the immediate sensory cues provided by the other components of cigarette smoking, including taste, aroma, and flavor. These other aspects of smoking have been shown to reduce symptoms of smoking withdrawal (Westman et al. 1996a). In a laboratory setting using denicotinized cigarettes, the sensations of inhaled cigarette smoke without nico-
tine provided immediate craving reduction, enjoyment, calming, and irritability reduction. These findings suggest that the calming effect of smoking may not entirely depend on the delivery of nicotine to the CNS.

**Social Needs**

If the social reward provided by smoking is independent of the nicotine effect, then nicotine replacement alone would not be expected to meet this need for smoking. Some of these social needs may be fulfilled by allowing a smoker to use a nicotine delivery system similar in behavioral aspects to cigarette smoking or by giving the smoker something to do instead of smoking that is socially rewarding.

**NRT as the Foundation of Smoking Cessation Treatment**

Because a smoker may have different reasons for smoking throughout the day, the ideal smoking cessation program should address the nicotine effects, sensory effects, and social effects that smoking provides. Viewed in this way, nicotine replacement is just one component of a successful program.

**Combination of Several Types of NRT**

If most smokers who relapse while using nicotine replacement do so because they are underdosed, combining several types of NRT may enhance success because of an increase in percentage of nicotine replacement. Several studies have shown that the combination of the nicotine patch and nicotine gum is more effective than the nicotine patch or the gum alone (Fagerström 1994; Fagerström et al. 1993). These combinations improved abstinence rates from 25% to 35%, but they still have not entirely solved the problem of smoking cessation.

**NRT and Nicotine Blockade Therapy**

Even if all of the reasons for smoking are addressed by replacement therapies, one would still expect smokers to use cigarettes
because of the extensive history of reinforcement for smoking beha-
vior. Therefore, replacement therapy alone may have intrinsic
limitations because it does not affect the learned connection be-
tween smoking and reward. An analogy may be drawn with the
extinction of fears or phobias. A fear-eliciting stimulus does not
lose its potency when an individual merely avoids the stimulus. If
extinction is to take place, it is necessary for the patient to be ex-
posed to the stimulus without the occurrence of the anticipated
consequence. Similarly, avoidance of smoking, in itself, does not
reduce the reinforcing value of cigarette-related cues. It may be
important to engage in the act of smoking without experiencing
the anticipated rewarding effects. Blockade therapy, using nico-
tinic receptor antagonists, has the potential to break this associa-
tion between the act of smoking and reward; it thus addresses an
important aspect of dependence not addressed by conventional
nicotine replacement techniques. Engaging in the act of smoking
when the reward is blocked should lead to a gradual extinction of
the behavior.

Mecamylamine, a nicotinic antagonist, has been shown to
block many of the rewarding effects of nicotine and thus has poten-
tial therapeutic application in smoking cessation treatment. When
first studied as a single treatment modality, mecamylamine was
not well tolerated in doses of 25–40 mg/day (Tennant et al. 1984).
On the basis of a theoretical model of receptor activation and block-
ade, it was postulated that lower doses of mecamylamine used in
combination with nicotine would work together to enhance smok-
ing cessation treatment (Rose and Levin 1991). This prediction was
based on the view that activation of some nicotinic receptors could
relieve withdrawal symptoms, whereas blockade of other recep-
tors would attenuate the rewarding effects of smoking and pro-
mote its extinction.

In several laboratory studies and clinical studies, the combina-
tion of nicotine and lower doses of mecamylamine has reduced crav-
ing and improved smoking cessation (Rose et al. 1994a, 1994b). In
two studies, the combination of nicotine and mecamylamine pro-
duced a two- to threefold increase in continuous smoking abstinence
rates beyond nicotine patch treatment alone. The 6-month abstinence
rates were approximately 40% for nicotine-mecamylamine, com-
pared to 10%–20% for the nicotine patch alone (Rose et al. 1996). Moreover, initiating combination treatment before the subject’s target quit date was noted to have important consequences, as expected from the extinction hypothesis. At a mecamylamine dose of 5 mg twice a day, the main side effect was constipation, which was relieved by milk of magnesia or a dosage reduction.

**Nicotine Replacement Therapy and Airway Sensory Replacement**

The traditional approach to smoking may have reached its limit of success because it does not adequately address many of the other behavioral reasons for smoking, including the airway sensations (Ashton and Stepney 1982; Rose 1988). From the smoker’s perspective, the perception of smoke in the airways may be more important initially in the relief of craving than nicotine itself.

Several different kinds of inhaled substances have been shown to reduce craving and smoking behavior (Levin et al. 1993; Rose and Behm 1994; Rose and Hickman 1987). One randomized, double-blind clinical trial involving 100 subjects assessed a combination of citric acid inhaler and nicotine patch versus a combination of placebo inhaler and nicotine patch (Westman et al. 1995). In addition to standard nicotine patch treatment, subjects were allowed to use these nonnicotine inhalers as desired. Smoking abstinence at the end of the 10-week treatment period was 19.5% for the citric acid inhaler group versus 6.8% for the lactose group. Relief of craving and short-term abstinence increased as airway sensations from the inhaler also increased. Sensory replacement through inhalers may be useful for the 60%–80% of smokers who report that they like the airway sensations or find themselves smoking without remembering lighting up the cigarette.

The nicotine inhaler may be useful as a sensory replacement even though by itself it does not provide high levels of nicotine replacement. Since nicotine vapor is irritating, the upper-airway sensations derived from using the nicotine inhaler are fairly close in character and intensity to cigarette sensations. Preliminary sensory comparison studies suggest that the inhaler may deliver enough sensory impact to reduce craving (Westman et al. 1996b).
Bupropion

Bupropion in a sustained-release form has recently been shown to be an effective treatment for smoking cessation (Hurt et al. 1997). The mechanism of action of bupropion for smoking cessation is not known, and preliminary evidence suggests that combining bupropion with the nicotine patch might not increase the efficacy of bupropion alone (Jorenby et al. 1999). The lack of additive effect suggests that bupropion may have a mechanism similar to that of nicotine replacement. Also, initiation of bupropion treatment before the quit date may be an important part of its mechanism of action.

Conclusion

Nicotine replacement is an important, effective therapy for smoking cessation. The currently available types of nicotine replacement therapy include nicotine gum, nicotine patch, and nicotine nasal spray. The use of nicotine replacement may be improved in the future by combining several types of nicotine replacement, by the addition of bupropion, or by individualized dosing based either on percentage of nicotine replacement or on relief of craving.

If there is more to smoking than nicotine, there is more to smoking cessation than nicotine replacement. Future successful smoking cessation treatments will use nicotine replacement as the foundation of the program and will continue to combine nicotine replacement with treatments targeted at other parts of dependence, including sensory components, social needs, and the history of association between smoking and reinforcement.

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CHAPTER 11

Behavioral Treatment of Cigarette Smoking and Nicotine Dependence

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Lynn R. Boutilier, Ph.D.

Introduction

In this chapter we primarily provide a brief overview of behavioral theory and a practical guide to empirically validated behavior therapy interventions for smoking. These interventions include self-control strategies, nicotine fading, contingency management, partner support, hypnosis, aversive procedures, cognitive strategies, and relapse prevention (Antonuccio et al. 1992). Secondarily, we discuss adding nicotine replacement to behavioral interventions.

Epidemiology of Tobacco Use

Currently, about 26% of adult Americans smoke cigarettes (Centers for Disease Control and Prevention 1994). Somewhere between 2% and 9% of adult Americans use smokeless tobacco (Centers for Disease Control and Prevention 1993), a practice that has been on the rise. Smoking prevalence has declined steadily since 1974, leading to the projection that 22% of the adult population will smoke by the year 2000 (Pierce et al. 1989). At that time, less than 10% of college graduates will smoke, and more than 30% of those who have not gone beyond high school will smoke.
About 44% of all adult Americans who had ever smoked have become former smokers, and about 1.3 million Americans quit smoking each year. About 1 million people, mostly teenagers, take up smoking for the first time each year.

It should be noted that whereas smoking rates in the United States are declining, they are increasing in developing countries like China, where half the global increase in tobacco use occurred from 1976 to 1986 (Yu et al. 1990). Current smoking patterns in China are similar to those in the United States during the 1950s. About 61% of Chinese males over age 15 currently smoke, and it is estimated that by 2025, 2 million Chinese men will die annually from smoking. An American Medical Association review of worldwide smoking reported that the use of tobacco had increased worldwide by almost 75% over the previous 20 years (Council on Scientific Affairs 1990). In 1986, an estimated 1 billion people smoked more than 5 trillion cigarettes.

**Consequences of Smoking and Nicotine Use**

The detrimental health effects of smoking have been well documented. Worldwide, an estimated 2.5 million premature deaths (about 5% of all deaths) per year are directly attributable to tobacco consumption (Council on Scientific Affairs 1990). Risk is correlated with the number of cigarettes smoked, but even smoking as few as 1–4 cigarettes per day can substantially increase risk (Willett et al. 1987).

The smoker is not the only person exposed to the hazards of tobacco smoke. Environmental tobacco smoke is estimated to kill 53,000 people per year in the United States (Glantz and Parmley 1991). Information about the hazards of secondhand smoke has been reaching smokers: as many as 72% have indicated awareness that sidestream smoke is a lung cancer risk factor (Price and Everett 1994). Although we could find no data about the impact of this awareness, clinically this awareness does seem to motivate some smokers to consider quitting in order to help lower the risks to family members, if not friends. Recent evidence suggests that smoking during pregnancy increases the risk for attention-deficit/hyperactivity disorder and reduces childhood IQ scores (Milberger et al. 1996).
Every recent report of the U.S. Surgeon General has identified smoking as the primary cause of preventable morbidity and mortality in the United States. Smoking is one of the leading causes of cancer in the United States (U.S. Department of Health and Human Services 1992), including lung, laryngeal, oral, esophageal, pancreatic, and bladder cancer. Smoking accounts for 30% of all cancer-related deaths (Bartecchi et al. 1994). Smoking is also the most important modifiable risk factor for the development of coronary artery disease, stroke, and peripheral vascular disease (U.S. Department of Health and Human Services 1992). Some of the cardiotoxic effects of smoking are attributable to nicotine; others are caused by various components of cigarette smoke. Nicotine has sympathomimetic effects that lead to an increase in heart rate and blood pressure and cause coronary vasoconstriction (Joseph et al. 1996). Nicotine may also contribute to endothelial cell injury (Davis 1990; Pittilo and Woolf 1993).

According to the 1990 Surgeon General’s Report (U.S. Department of Health and Human Services 1990), the individual smoker who quits may expect to benefit in many ways. Smokers who quit before the age of 50 have half the risk of dying in the subsequent 15 years that continuing smokers have. This decrease in risk of dying is due in turn to decreased risks of cancer, coronary disease, stroke, pulmonary disease, arterial disease, and peptic ulcer. These benefits have been shown to be present regardless of age or presence of smoking-related illness. Therefore, programs aimed at helping smokers quit should not be restricted to the young nor to patients who have not developed a smoking-related illness.

**Behavior Therapies**

The most prevalent smoking cessation programs have employed behavioral principles in concert with other strategies (Lichtenstein 1982). Typical behavioral treatment programs focus on antecedents and consequences of smoking and include cognitive techniques that promote coping during and after treatment (Lichtenstein and Mermelstein 1985). The behavioral perspective is that smoking is a learned behavior, originally initiated by psychosocial variables (e.g., adult modeling, curiosity, peer pressure, availability, rebelliousness).
and maintained by physiological dependence on nicotine in combination with conditioned environmental stimuli that elicit the urge to smoke once the behavior has been firmly established (Lichtenstein 1982). In this sense, smoking is a highly overlearned behavior. An average pack-a-day smoker puffs an estimated 160 times each day (Lichtenstein and Antonuccio 1981), providing ample opportunity for internal cues (e.g., anxiety, hunger) and environmental cues (e.g., drinking coffee, talking on the phone) to become associated with the urge to smoke. The act of smoking can also be heavily reinforced operantly by consequences both internal (e.g., pleasure, craving reduction) and external (e.g., social approval from other smokers, handling the cigarette) (Lichtenstein and Brown 1980).

The aversiveness of withdrawal from nicotine must be considered in any model of smoking behavior. Self-monitoring has revealed that coughing, craving for tobacco, feelings of aggression, increased appetite, irritability, nervousness, and restlessness increase in severity during the first week after quitting, followed by a decrease in severity thereafter (Lawrence et al. 1982). For 6 weeks after quitting, constipation and craving for sweets are at higher levels than baseline. Other symptoms show no clear trends. Patients who maintain abstinence for 6 weeks experience fewer symptoms during the initial 2 weeks after quitting than those who do not maintain abstinence for 6 weeks. Additionally, at 6 weeks all abstinent patients experience symptoms at baseline or lower levels of severity. Clearly, many individuals experience the act of quitting smoking as aversive. The role of expectations in the experience of withdrawal symptoms has yet to be adequately evaluated.

A comprehensive biobehavioral theory of smoking must include biological factors as well. Pomerleau and Pomerleau (1985) specified several biological factors that help to maintain smoking behavior. They hypothesized that smokers smoke to cause temporary improvements in performance and affect. They identified a periodic pattern of arousal and alertness during smoking, followed by calming and tension reduction after smoking. They showed that smoking stimulates the production of β-endorphins and vasopressin. These neurotransmitters are known to reduce pain, increase tolerance to stress, improve memory, increase concentration, and speed up information processing. Therefore, as Pinto and Morrell (1988)
have pointed out, smoking is maintained by powerful negative (e.g., reduction of craving) and also positive inducements. There may even be an inherited predisposition to being susceptible to these inducements (Hughes 1986; Pomerleau et al. 1993).

Cognitive-behavioral methods often use strategies designed to counteract these negative and positive inducements to smoke. These interventions include 1) aversive strategies such as smoke holding, rapid smoking, and noxious imagery, 2) nicotine fading and controlled smoking techniques, 3) self-control and self-monitoring strategies that help smokers identify and modify situations, cognitions, feelings, and other cues that promote the urge to smoke, and 4) relapse prevention strategies (Antonuccio et al. 1992). Reports from behavioral programs regarding initial cessation have given rates ranging from 50% to 100%, with relapse rates of 70% to 80% among studies that provided 3-month follow-up data (Marlatt and Gordon 1985). This dramatic decline from initial cessation to immediate relapse among the majority of smokers has caused a shift in emphasis toward relapse prevention among researchers.

In a selective review of controlled studies conducted between 1977 and 1987, Glasgow and Lichtenstein (1987) concluded that behavioral approaches have generally been found to be superior to control conditions. These researchers concluded that all successful treatment approaches, including behavioral interventions, are more successful with light smokers and result in abstinence rates ranging between 25% and 33%. In his comprehensive review, Lichtenstein (1982) observed that at 6- and 12-month follow-ups, the average participant in the average smoking control program has a 20% chance of being abstinent. Lichtenstein suggested that involvement in one of the more successful programs may increase these odds to between 30% and 40%. It should be noted that most smokers quit without the help of an organized program (Cohen et al. 1989), perhaps leaving the programs to deal with the smokers who have the most difficulty quitting.

The Typical Behavioral Treatment Program

The Stop Smoking Program at the Reno Department of Veterans Affairs Medical Center uses a structured format (Antonuccio 1993a,
1993b; Graybar et al. 1993) and typifies a behavioral smoking cessation program. Participants in the program have an average smoking history of 27 cigarettes per day for 35 years. About 58% of participants quit smoking initially, and 20% are abstinent at long-term follow-up (mean, 27 months) (Graybar et al. 1993). The program is psycho-educational in nature and is structured to reflect the natural stages of quitting (DiClemente et al. 1991), which include the precontemplation, contemplation, preparation, action, and maintenance stages. Everyone who attends a smoking cessation class is presumed to be at least in the contemplation stage. Contemplators are interested in gathering information about smoking and how to quit. Therefore, session 1 is designed to provide information about the class, to assess motivation and readiness to quit, and to enhance motivation to proceed into the preparation stage. Patients are given the Reasons for Quitting Scale (Curry et al. 1990) to evaluate intrinsic and extrinsic motivation. The Therapeutic Reactance Scale (Dowd et al. 1991) is used to evaluate resistance to instruction. The Partner Interaction Questionnaire (Mermelstein et al. 1983) evaluates the impact of the smoker’s partner. The Fagerström Nicotine Dependence Scale (Fagerström 1978) can help determine the strength of the smoker’s addiction. These questionnaires help the therapist tailor information, feedback, and interventions to an individual smoker’s needs.

During the first session, patients are also taught about the medical consequences of smoking and the medical benefits of quitting. Patients learn about the normal stages of quitting so they will understand that quitting smoking is not an all-or-nothing phenomenon. Patients are shown how to use wrap sheets (structured tracking sheets that wrap around a pack of cigarettes) to record accurate baseline smoking data and to reinforce progressive reductions in smoking rate. Patients are paired with other patients in a get-acquainted exercise so that they have an opportunity to connect with at least one other person. A former smoker from a prior smoking cessation group shares his or her quitting experience in order to reduce anxiety and to provide a coping model. Humor and fun are encouraged during all sessions. One of the goals of the first session is to move patients into the preparation stage of quitting, which occurs when patients set their target quit date for exactly 4 weeks later, on the day of session 5.
Sessions 2, 3, and 4 deal with the action stage of quitting, in which patients actually work on altering their smoking behavior. These sessions also provide an opportunity for group cohesiveness to develop. Patients are taught the skills they will need to implement their goals of reducing and ultimately eliminating smoking, and they also learn relaxation and/or self-hypnosis to reduce anxiety and harness the power of self-suggestion. They are taught strategies for avoiding or altering smoking cues or substituting alternatives to smoking. Patients practice using a nonsmoking strategy in a specific targeted situation (e.g., putting sugarless candy in ashtrays and keeping cigarettes in the trunk of the car while driving) to get practice at being a nonsmoker in one situation before their quit day. Patients are taught about \textit{nicotine fading} by switching to a brand of cigarettes that has about half the nicotine of their normal brand, which helps reduce nicotine dependence before the quit date. Smokers’ partners are taught to eliminate nagging, shunning, and punishing behaviors while increasing supportive and reinforcing behaviors. Taste aversion, or \textit{smoke holding}, is provided to interested smokers to help associate a negative taste with cigarettes. In this procedure, smokers repeatedly hold cigarette smoke in the mouth for 30 seconds (each time they inhale) so that the smoke will taste bad.

The maintenance stage, during which patients work to maintain cigarette abstinence, begins on session 5, quit day. Patients are encouraged to set up stop-smoking contests at their work sites. To help reduce anxiety and withdrawal symptoms for heavy (more than pack-a-day) smokers who have never quit for more than 2 weeks, nicotine replacement is emphasized. Although nicotine replacement is described as more effective for heavy smokers, it is offered to all participants who want to try it. By design, patients’ patch doses are continuously decreased, at 1-week intervals, from 21 mg to 14 mg to 7 mg; then the patch is discontinued. Patients are asked to set a short-term goal (usually between 1 day and 2 weeks) for quitting and to create a written contract in which they agree to send money (usually from $1 to $100) to their least favorite politicians if they fail to achieve their short-term goal. In a strategy called relapse prevention, patients are asked to predict the situations in which they are most likely to relapse and to devise plans for coping with those situations and for addressing relapse thoughts. To assist in this process,
patients fill out the Smoking Self-Efficacy Questionnaire (Baer et al. 1986). Session 6 is designed to help patients maintain gains; further follow-up sessions are scheduled for those who need help in weaning themselves from the patch.

**Adding Nicotine Replacement to Behavior Therapy**

Nicotine gum and transdermal nicotine patches as forms of nicotine replacement have become standard components of many behavioral treatment programs. Nicotine replacement is featured prominently in the clinical practice guidelines for smoking cessation published by the U.S. Agency for Health Care Policy and Research (Fiore et al. 1996). The difficulties in interpreting the effectiveness of nicotine gum and transdermal nicotine independently of behavioral treatment are that these forms of nicotine are designed to be combined with behavior therapy and that the vast majority of published studies include some form of behavioral intervention when nicotine replacement is used (Klesges et al. 1996). Comparison studies involving nicotine replacement and behavior therapy rarely have single-intervention conditions. This fact makes it difficult to determine how behavior therapy alone (i.e., without the nicotine replacement or placebo) would fare in a direct comparison with nicotine replacement alone or the combination treatment.

Outcome with nicotine gum has been summarized (Lam et al. 1987) in a meta-analysis of 14 randomized, controlled trials of nicotine gum. In specialized smoking cessation clinics that included intense behavioral interventions, abstinence rates at 6 months with the combination of behavior therapy and nicotine gum versus the combination of behavior therapy and placebo were 27% and 18%, and the 12-month rates were 23% and 13%, respectively. In general medical practice with minimal interventions (i.e., little or no behavioral counseling), the results were less promising. The abstinence rate at 6 months in the nicotine gum group was 11.4% and in the placebo group was 11.7%. These trials demonstrate the benefit of combining nicotine gum with behavior therapy; use of nicotine gum as the sole intervention is unlikely to be of significant benefit (Lam et al. 1987).
In a meta-analysis (Fiore et al. 1994) of 17 double-blind, placebo-controlled Studies in which the nicotine patch was applied as an adjunct to behavioral management, abstinence rates were higher with the active patch (22% abstinence) than with the placebo patch (9% abstinence) at 6-month follow-up. These results with behavior therapy plus transdermal nicotine were generally in the range reported for other successful smoking cessation programs. The optimal duration of transdermal nicotine therapy remains an empirical question, although in one review it was concluded that the use of this therapy beyond 6 weeks (but no more than 8 weeks) may be indicated only for the most dependent smokers (Fiore et al. 1992). A recent study found that behavior therapy combined with 3 weeks of transdermal nicotine therapy resulted in an outcome (28% abstinence) similar to that for behavior therapy combined with 12 weeks of transdermal nicotine therapy (29% abstinence) at 1 month following termination of nicotine replacement (Bolin et al. 1999). In general, use of the active patch without behavior therapy has been disappointing compared with use of the placebo patch (e.g., Joseph et al. 1996). We were unable to find any published reports directly comparing the efficacy of the nicotine patch alone with that of the patch plus behavior therapy.

Adding the nicotine patch to behavioral treatments offers a number of clinical benefits. With the patch, more people are willing to try to quit smoking, and more people trying to quit means more people quitting. The Butt Out smoking cessation groups at the Reno Department of Veterans Affairs Medical Center have consistently had patient enrollment that is 2 to 3 times higher than the enrollment before the patch became available. There is evidence the patch helps reduce craving and other withdrawal symptoms. Also, patients appear to have less anxiety about quitting with nicotine replacement. In one of the few studies (Cinciripini et al. 1996) to use a condition of behavior therapy alone, behavior therapy plus patch resulted in significantly higher abstinence than behavior therapy alone at the end of treatment through the 3-month follow-up. These effects became weaker and did not attain statistical significance at the 6- and 12-month follow-ups. There was evidence that the group with behavior therapy plus patch experienced less general distress and more self-efficacy than the group with behavior therapy alone. Unfortunately, due to bad luck during random assignment, the
group with behavior therapy alone had significantly heavier smokers, casting some doubt on the advantage of the combined condition. Also, there was no condition including behavior therapy plus placebo to help control for the expectation of receiving nicotine replacement. We were unable to find any studies with what we consider the ideal design, which would include four conditions: behavior therapy alone, behavior therapy plus patch, behavior therapy plus placebo, and patch alone.

**Reasons for Caution in Nicotine Replacement Treatment**

As with any drug intervention, there are reasons for caution regarding nicotine replacement:

1. There is the philosophical problem of helping patients stop using the drug to which they are addicted by using the same drug in treatment.
2. Nicotine replacement is expensive, especially if used as directed for 6–12 weeks. Pharmacies currently offer the patch for about $150 for a 6-week supply.
3. Many patients are able to quit without nicotine replacement.
4. Some patients inappropriately “put all their eggs in one (nicotine-patch) basket” and do not try the behavioral strategies vigorously.
5. Some patients use the patch only to cut down, not to quit. In other nicotine replacement research (Johnson et al. 1992), it was found that in a general outpatient medical setting, only 1 in 20 nicotine gum users attended a structured behavioral treatment program. More than half the patients continued to smoke while using the gum. Similar smoking rates are found with the patch. In a sample of U.S. military veterans using behavior therapy combined with the patch, 68% smoked at least one cigarette while wearing the patch (Bolin et al. 1999). In one minimal intervention study (Sachs et al. 1993), 55% of patch users were still smoking after 12 weeks of using the patch. In a naturalistic follow-up of elderly patch users, 47% smoked while using the patch, including 20% who smoked every day (Orleans et al. 1994).
6. Concomitant smoking has been strongly associated with failure to achieve abstinence (Bolin et al. 1999; Kenford et al. 1994; Orleans et al. 1994). Because many patients do continue to smoke (usually less than 10 cigarettes per day) while using the patch, some may inappropriately be counted as nonsmokers through the measurement of standard carbon monoxide (CO) levels. Although there is currently no evidence of increased morbidity (Joseph et al. 1996), case reports suggest that there may be a small minority of patients who experience increased cardiovascular risk from smoking while using the patch. Although the possibility of harm reduction or decreased morbidity from long-term nicotine replacement exists, it has yet to be demonstrated empirically (Hughes 1998).

7. Longer use of the patch may prolong withdrawal too long for some patients. Withdrawal, which can be essentially accomplished in 1 week, may, with use of the patch, take 6 weeks or more. Unlike nicotine gum, the patch delivers nicotine constantly to patients, whether they want it or not. Some patients have a hard time weaning themselves from the patch. The patch causes skin irritation in some patients and may cause sleep disruption (Physicians' Desk Reference 1996).

8. Cigarette abstinence while using the patch is not equivalent to cigarette abstinence while using placebo or while not using the patch. Obviously, patients using the patch still need to withdraw from nicotine, a powerfully reinforcing and potentially harmful drug. Most studies inappropriately count patients as abstinent even if they are still using nicotine replacement. To consider nonsmoking patch users abstinent would be analogous to considering nondrinking alcoholics abstinent if they were receiving transdermal alcohol (Antonuccio 1994). The DSM-IV (American Psychiatric Association 1994) diagnosis of nicotine dependence is appropriate until the drug is eliminated. Most patch studies count follow-up as the number of weeks following the beginning of treatment or as the number of weeks following the target quit day. However, the follow-up clock actually should start ticking when patch subjects stop using the patch, not when they quit smoking. Since patch subjects quit nicotine considerably later (often 12 weeks or more) than pla-
cebo subjects, there will be an overestimate of the quit rates for patch subjects at each follow-up point. When the follow-up period is calculated from the first actual nicotine-free day, the outcome advantage of the patch over placebo may be less clear. Especially in minimal-intervention studies, the patch may only delay (not reduce) relapse to nicotine dependence by delaying the nicotine-free day (Antonuccio 1994). The double blind may be penetrated (Hughes and Krahn 1985) in many studies using a placebo patch, because both patient and therapist can tell who is getting the real drug by observing side effects and withdrawal symptoms. Therefore, the patch and placebo groups are probably extremely discrepant in terms of expectations for successful quitting. Expectations have not been adequately addressed in nicotine patch research. However, one nicotine gum study (Gottlieb et al. 1987) found that the beliefs about nicotine content, but not actual nicotine content, had an effect on withdrawal or relapse. Subjects who believed they were getting nicotine gum reported fewer physical symptoms of withdrawal, showed less arousal, and smoked fewer cigarettes during the first week of quitting compared with those who thought they were receiving placebo gum.

Mention should be made of the addition of bupropion to behavior therapy as an aid to smoking cessation. In studies funded by the manufacturer, 1-year abstinence rates (23%–30%) for bupropion combined with behavioral counseling (Hurt et al. 1997; Jorenby et al. 1999) were similar to those found for the patch combined with behavior therapy. Although this treatment appears promising, independent replication is required before the treatment can be considered to have an established efficacy.

**Suggestions for Practice**

As an adjunct to the recently published practice guidelines for smoking cessation (Fiore et al. 1996), from our review of the cessation literature (Antonuccio et al. 1992; Bolin et al. 1999) we offer the following suggestions regarding the addition of nicotine replacement to behavior therapy for smoking cessation:
1. Require compliance with some form of self-help, individual treatment, or group cognitive-behavioral treatment (e.g., one of the programs entitled Butt Out, Quit Smart, Freedom from Smoking, or Freshstart) in order to get access to the patch. These programs are generally relatively cheap, well packaged, and effective.

2. Build in maintenance sessions and withdrawal from nicotine replacement.

3. Strongly warn patients not to smoke while using the patch, if for no other reason than that it significantly decreases their chances of quitting.

4. Use CO monitoring to give feedback, reinforce success, and verify abstinence.

5. Terminate the patch if there is evidence that the patient is still smoking after 2 weeks. Have the patient set a new target quit date and try again later.

6. Provide the patch at 1-week intervals to ensure compliance with behavioral treatment.

7. Use a 3-week rapid-deployment nicotine replacement schedule for most patients, because it is cheaper than and as effective as a longer regimen.

8. Always terminate the patch after 6 weeks, because there is no evidence of improved outcome with a longer regimen.

9. To reduce the likelihood of smoking while using the patch, consider using aversive strategies, which have received considerable support in the literature (Antonuccio et al. 1992), to help make cigarettes taste bad prior to quit day.

Following such guidelines is highly likely to make the combination of nicotine replacement and behavior therapy safer, less costly, and more effective. Ultimately, these are issues that can be addressed by future studies.

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Beginning with the period when Europeans settled in the Western Hemisphere, nicotine has been one of the most widely used of psychoactive substances, exceeded only by ethanol and caffeine. In modern society, it has become arguably the most vilified of these substances because of the clear connection between tobacco consumption (smoking, chewing, etc) and disease. There can be no serious doubt that the presence of nicotine is required for the reinforcing effects of tobacco, yet it is intriguing that nicotine alone is not very reinforcing to humans and that nicotine abuse without tobacco is virtually nonexistent. Nicotine appears to have some similarities to other abused substances, but the differences appear to outnumber the similarities. Alone, it does not produce marked euphoria, relaxation, or sense of well-being. In fact, nonsmokers usually find the acute effects of nicotine unpleasant and dysphoric. Unlike other abused substances, nicotine appears to maintain or even improve cognitive performance while lowering anxiety, a relatively rare combination.

The past several decades have seen a decline in smoking in the United States to a median prevalence across states of 22.9%. \(^1\) How-

ever, this rate appears to have stabilized and among adolescents may even be increasing. The reasons for this stabilization may have to do with the population that continues to smoke. It appears that psychiatric disorders are overrepresented in current smokers compared to the general population, suggesting that individuals with such conditions may be more vulnerable to the reinforcing effects of tobacco and/or that nicotine has specific effects that either mitigate or worsen certain psychiatric symptoms. Given the potential morbidity and mortality of chronic tobacco use, treatment of comorbid tobacco dependence should become a mandatory part of the treatment of other primary psychiatric diagnoses. In part, resistance to including treatment for tobacco dependence in most health plans or as part of the treatment of psychiatric disorders may represent undue pessimism about the efficacy of the available treatments. However, we do not abandon treatment of other chronic medical conditions simply because we cannot “cure” them immediately. Nor do we regard as futile the treatment of other potentially lethal conditions simply because of relapses: the alcohol abuser is not simply left to his or her bottle the first time he or she falls off the wagon. This should be the case with tobacco: there should be easily available, repetitive treatment with an eclectic approach using biochemical, social, and psychological methodologies. Psychiatrists should become practiced with these treatment strategies. As Hughes states in the Foreword to this volume, tobacco use is one of the most preventable and treatable known causes of medical morbidity and mortality. The potential payoff in improved emotional and physical health from enthusiastically and vigorously treating this problem is enormous.

Advances in molecular and cellular neuroscience have produced a highly detailed picture of the workings of the nicotinic cholinergic receptor, probably the most complete such picture for any neurotransmitter receptor. We know that a variety of molecular subtypes of nicotinic receptors exist in the mammalian brain, and we know their approximate distribution. Further, at a cellular level, we understand many of the direct consequences of nicotinic receptor activation. However, the role(s) of nicotinic systems in the normal actions of the brain remain incompletely understood. It appears that nicotinic receptors do not mediate much direct information transfer via neurotransmission but have modulatory roles over diverse brain
transmitter systems. Loss of or alterations to such receptors may play a role in a variety of brain disorders such as Alzheimer’s disease or schizophrenia. Although we have clues about the expression of nicotinic receptor pathology in some neuropsychiatric diseases (e.g., attentional function in schizophrenia, information acquisition in Alzheimer’s disease, motor speed in Parkinson’s disease), continued research will be necessary to elucidate how important these receptors are in the functional disturbances found in these disorders. The development of gene knockout animals, especially those in whom the gene knockout is restricted to particular brain regions (e.g., hippocampus), has provided a valuable tool in the search to define the vital role of these receptor systems. The human analogy is either rare nicotinic gene mutations or perhaps more common polymorphisms or the use of pharmacological challenge models that use nicotinic antagonists. These produce a brief, reversible neurochemical lesion and have yielded important clues about the effects of the loss of nicotinic receptors.

Impressive advances in pharmaceutical chemistry, molecular biology, and behavioral pharmacology have resulted in a series of novel nicotinic agonists with potential therapeutic effects in a wide variety of central nervous system applications beyond smoking cessation. These include symptomatic improvement of degenerative conditions such as Alzheimer’s disease and Parkinson’s disease and of psychiatric disturbances such as attention-deficit/hyperactivity disorder and schizophrenia, as well as diverse other applications such as for analgesia and treatment of inflammatory bowel disease. Neuroprotection is another potential long-term application of nicotinic agonists. However, although the preclinical and early human data appear impressive, subtype-selective agonists will have to prove themselves in the clinic. Significant problems remain to be solved in order to produce useful pharmaceuticals from these agents. The problems of rapid desensitization of the nicotinic receptor, upregulation of receptor number, and narrow therapeutic index of most agents will have to be overcome. A further issue is that, although there is an array of molecular subtypes of nicotinic receptors in the mammalian brain (e.g., α4β2), it is not clear whether these are pharmacologically distinguishable in a clinically meaningful way. Allosteric modulation of nicotinic receptors at sites other than the
agonist binding site may also become a valuable strategy, analogous to benzodiazepine modulation of \( \gamma \)-aminobutyric acid (GABA) receptors. The potential exists for a new generation of selective nicotinic agonists to become adjunctive or even primary therapies for certain conditions.

The field of nicotine neurobiology is still young. However, the vigor of this field is shown by the exciting developments in molecular neuroscience, behavioral pharmacology, and pharmacotherapeutics; the numerous scientific meetings devoted to smoking and nicotine; and the emergence of scientific societies devoted to research in this area (e.g., the Society for Research on Nicotine and Tobacco). It is likely that an understanding of how nicotinic receptor systems interact with diverse brain systems will be as important for an understanding of psychiatric pathology and therapeutics for the next generation of progress as understanding the importance of catecholamines and indolamines has been for the last.
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