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Introduction

Nicotine addiction is the fundamental reason that individuals persist in using tobacco products, and this persistent tobacco use contributes to many diseases described in this report. The 1988 report, *The Health Consequences of Smoking: Nicotine Addiction: A Report of the Surgeon General* (U.S. Department of Health and Human Services [USDHHS] 1988, p. 9), describes the pharmacologic basis of tobacco addiction and arrives at three major conclusions:

1. Cigarettes and other forms of tobacco are addicting.

2. Nicotine is the drug in tobacco that causes addiction.

3. The pharmacologic and behavioral processes that determine tobacco addiction are similar to those that determine addiction to drugs such as heroin and cocaine.

Tobacco addiction remains a substantial problem in the United States and worldwide. Of those individuals who have ever tried smoking, about one-third become daily smokers (USDHHS 1994, p. 67). Of those smokers who try to quit, less than 5 percent are successful at any one time (Centers for Disease Control and Prevention [CDC] 2002, 2004). Although not all smokers become nicotine dependent, the prevalence of individuals diagnosed as nicotine dependent is higher than that for any other substance abuse disorder (Anthony et al. 1994; CDC 1995b; Kandel et al. 1997). Any efforts to reduce tobacco-related disease must take into account the addiction potential of a tobacco product.

Since the 1988 Surgeon General's report was published, significant advances have been made in understanding the physiological effects of nicotine and the basis for addiction:

1. identifying specific genotypes and receptor subtypes that may contribute to and play an important role in nicotine addiction,

2. observing sensitivities and responses to nicotine in adolescents that might make them more susceptible to nicotine addiction than adults are and recognizing the different trajectories for the development of nicotine dependence,

3. developing a greater awareness of the important role of associative learning in addiction,

4. recognizing the strong associations between smoking and comorbid psychiatric disorders, and

5. achieving a better understanding of the relapse and recovery processes.

The goals of this chapter are to describe these advances and their implications and to discuss future directions.

Definition of Nicotine Addiction

The crux of understanding the pathophysiology of tobacco addiction and its measurement relies on the identification of critical characteristics and the definition of addiction. This area continues to evolve, and significant gaps in research are evident. There is no established consensus on criteria for diagnosing nicotine addiction. However, researchers have identified several symptoms as indicators of addiction. The 1988 Surgeon General's report lists the following general "criteria for drug dependence," including nicotine dependence (USDHHS 1988, p. 7):

Primary Criteria
- Highly controlled or compulsive use
- Psychoactive effects
- Drug-reinforced behavior

Additional Criteria
- Addictive behavior, often involves:
  – stereotypic patterns of use
  – use despite harmful effects
  – relapse following abstinence
  – recurrent drug cravings

- Dependence-producing drugs often produce:
  – tolerance
  – physical dependence
  – pleasant (euphoriant) effects

These criteria are consistent with those for a diagnosis of dependence provided in the *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed. (*DSM-IV*) (American Psychiatric Association [APA] 2000) and the *International Classification of Diseases, Tenth Revision* (*ICD-10*) (Table 4.1) (World Health Organization [WHO] 1992). The diagnosis of dependence using these diagnostic systems depends on the person experiencing a specific number of these symptoms. The relevance of some of these symptoms to nicotine addiction may be questionable because the *DSM* criteria are used across different drugs of abuse. For example, one symptom of addiction is that a great deal of time is spent in activities necessary to obtain the substance or recover from its effect. This criterion may not be as relevant to the diagnosis of nicotine addiction compared with other abused substances. Another prominent instrument that researchers have used to determine the degree or severity of dependence in smokers is the Fagerström Tolerance Questionnaire (FTQ) (Fagerström 1978; Fagerström and Schneider 1989), and a later, modified version, the Fagerström Test for Nicotine Dependence (FTND) (Heatherton et al. 1991). The items on these scales, which describe the extent of nicotine exposure, the impaired control over use, and the urgency for use, are listed in Table 4.2. The first item, time to first cigarette after waking, is by itself a stronger predictor of relapse than is any other self-report measure of dependence (Baker et al. 2007). The 1988 Surgeon General's report describes the general characteristics and criteria for drug dependence, *DSM-IV* and *ICD-10* describe the criteria necessary for diagnosis of dependence, and the FTQ and FTND can be used to determine the degree of dependence. The core features across these diagnostic methods include (1) repeated and compulsive self-administration; (2) impaired control over use (e.g., repeated unsuccessful attempts to stop use or continued use despite known harmful consequences); (3) high motivation to seek the drug, because of cravings, regulation of affect (e.g., smoking to ease a depressed mood, for relaxation, or for stimulation), or other reasons associated with the psychoactive effects of the drug; (4) judgment of greater value from

Table 4.1 Criteria for substance (nicotine) dependence

DSM-IV	***ICD-10***
A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by 3 or more of the following criteria, occurring at any time in the same 12-month period	
• Tolerance—need increased amounts of substance to achieve desired effect, or diminished effect with continued use of same amount	• Increased tolerance
• Withdrawal symptoms	• Physical withdrawal at times
• Substance often taken in larger amounts or over longer period than intended	• Strong desire to take drug
• Persistent desire or unsuccessful efforts to cut down or control substance use	• Difficulty controlling use
• Great deal of time spent in activities necessary to obtain substance, use substance, or recover from its effects	
• Important social, occupational, or recreational activities given up or reduced because of substance use	• Higher priority given to drug use than to other activities and obligations
• Substance use continued despite knowledge of having persistent or recurrent physical or psychological problem likely to have been caused or exacerbated by substance	• Persistent use despite harmful consequences

Source: Adapted from Royal College of Physicians of London 2000 with permission from Royal College of Physicians, © 2000.
Note: ***DSM-IV*** *= Diagnostic and Statistical Manual of Mental Disorders,* 4th ed.; ***ICD-10*** *= International Classification of Diseases, Tenth Revision.*

Table 4.2 Questions, answers, and scoring for Fagerström Test for Nicotine Dependence and Fagerström Tolerance Questionnaire

Questions	Answers	Points
Fagerström Test for Nicotine Dependence[a]		
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
Do you find it difficult to refrain from smoking in places where it is forbidden (e.g., in church, at the library, in the cinema, etc.)?	Yes	1
	No	0
Which cigarette would you hate most to give up?	The first one in the morning	1
	All others	0
How many cigarettes/day do you smoke?	≤10	0
	11–20	1
	21–30	2
	≥31	3
Do you smoke more frequently during the first hours after waking up than during the rest of the day?	Yes	1
	No	0
Do you smoke if you are so ill that you are in bed most of the day?	Yes	1
	No	0
Fagerström Tolerance Questionnaire[b]		
How soon after you wake up do you smoke your first cigarette?	Within 30 minutes	1
	After 30 minutes	0
Do you find it difficult to refrain from smoking in places where it is forbidden (e.g., in church, at the library, in the cinema, etc.)?	Yes	1
	No	0
Which cigarette would you hate to give up?	The first one in the morning	1
	Any other	0
How many cigarettes/day do you smoke?	≤15	0
	16–25	1
	≥26	2
Do you smoke more during the morning than during the rest of the day?	Yes	1
	No	0
Do you smoke if you are so ill that you are in bed most of the day?	Yes	1
	No	0
What is the nicotine level of your usual brand of cigarette?	≤0.9 mg	0
	1.0–1.2 mg	1
	≥1.3 mg	2
Do you inhale?	Never	0
	Sometimes	1
	Always	2

Note: **mg** = milligrams.
[a]Data are from Heatherton et al. 1991.
[b]Data are from Fagerström and Schneider 1989.

use of the drug over other reinforcers or activities; and (5) manifestation of physical dependence, as evidenced by withdrawal or tolerance.

Despite acknowledgment of these core features, the current diagnostic criteria for nicotine addiction have certain limitations. Beginning in 2005, a group of scientists have worked to delineate the various issues surrounding the measurement of nicotine dependence. The results of this work were published in June 2009 (National Cancer Institute [NCI] 2009). These issues included the following:

1. whether nicotine addiction is categorical, dimensional, or emergent (changing over time) and, if emergent, whether different aspects of dependence are observed early or late in the process of dependence, for example, aspects more related to social, sensory, and associational learning versus a more physical dimension with a longer duration of drug use;

2. whether nicotine addiction is unidimensional or multidimensional and, if multidimensional, whether symptoms or dimensions warrant weighting or are additive;

3. whether a threshold of severity or a certain number or specific types of symptoms are needed for diagnosis of nicotine addiction;

4. whether motivations or cognitive processes for seeking a drug are important components of the addiction;

5. whether multiple profiles, patterns, and pathways of addiction exist; and

6. whether the quantity and frequency of use play a critical role in addiction.

Other current measures of nicotine addiction or tobacco dependence are shown in Table 4.3 that are beginning to consider and address some of the limitations of current definitions of addiction and that consider nicotine addiction to be comprised of more than one phenotype (expression of a trait on the basis of genetic and environmental influences). Developing valid measures of the various phenotypes of dependence is critical for research that (1) examines how these phenotypes are related to the trajectory and cessation of smoking behaviors and (2) determines whether these phenotypes are related to specific neurobiologic measures of addiction or to specific genes.

In this chapter, the terms "dependence" and "addiction" have been used interchangeably. For some disciplines, dependence has been primarily associated with physiological manifestations of repeated tobacco use, but compulsive drug seeking is typically at the core of both the technical term "dependence" and the more general term "addiction." Furthermore, the terms "nicotine dependence" and "tobacco dependence" are used interchangeably. Nicotine is the drug in tobacco that leads to compulsive drug seeking or addiction. However, several lines of epidemiologic and laboratory evidence presented in this chapter indicate that tobacco-delivered nicotine is substantially more addictive than are pure nicotine forms. Other tobacco constituents, delivery methods, and processes may play a critical supporting role.

Factors contributing to nicotine or tobacco addiction include the following:

1. the effects of the product itself, including the addictive constituents, their pharmacokinetics and pharmacodynamics, and the design of the product that delivers the addictive constituents (see Chapter 3, "Chemistry and Toxicology of Cigarette Smoke and Biomarkers of Exposure and Harm");

2. the response of the host, including genetic susceptibility and physiological response; and

3. the environmental setting that determines the availability of, accessibility to, and norms for use of the product.

Like the 1988 Surgeon General's report on nicotine addiction, this chapter focuses primarily on the effects of the product and the response of the host.

Table 4.3 Measures of nicotine addiction

Measures	Characteristics
Fagerström Tolerance Questionnaire (FTQ) (Fagerström 1978; Fagerström and Schneider 1989) Fagerström Test for Nicotine Dependence (FTND) (Heatherton et al. 1991)	Unidimensional and continuous scale that measures behavioral and physiological aspects of addiction (e.g., rate of smoking, morning smoking, and difficulty refraining from smoking) and was developed to measure physical dependence. Both FTQ and FTND show limited internal consistency (Pomerleau et al. 1990; Etter et al. 1999). FTND is a multidimensional scale (≤2 factors) summarized as single score (Haddock et al. 1999; Breteler et al. 2004). Adequate test-retest reliability, particularly with FTND (Pomerleau et al. 1994). Modestly correlates with levels of carbon monoxide, nicotine, and cotinine; weak predictor of withdrawal symptoms (Hughes and Hatsukami et al. 1986; Shiffman et al. 2004a; Etter et al. 2005); and modest or weak predictor of treatment outcome (Pinto et al. 1987; Silagy et al. 1994; Haddock et al. 1999; Etter et al. 2003a, 2005; Piper et al. 2006). Moderates efficacy of nicotine medications (Shiffman and Paton 1999). Does not have incremental value compared with measures of number of cigarettes/day (Razavi et al. 1999; Dale et al. 2001). A single item—time to first cigarette—is a good predictor of cessation success and reflects a pattern of heavy, uninterrupted, and automatic smoking (Transdisciplinary Tobacco Use Research Center et al. 2007). FTQ was modified for adolescents (Prokhorov et al. 1996, 2000). One item was eliminated—brand of cigarette or number of cigarettes per day—depending on study. Most items were changed to 4-point rating scales. One factor accounted for 41–53% of the variance. Interitem and item-to-total score correlations were weak to moderate. Internal consistency was adequate, with good test-retest reliability. Modest correlations were observed with amount smoked and between scales for individual items (except inhalation item) and cotinine levels. Stanford Dependence Index is also modified FTQ with only 5 items that are assessed on a 4- to 6-point scale. This measure was used in adults (Killen et al. 1990) and adolescents (Rojas et al. 1998). Adequate test-retest reliability was observed for both populations. In the adolescent population, total scores were significantly related to smoking rate, cotinine levels, and self-reported severity of withdrawal in past attempts to stop smoking.
Heaviness of Smoking Index (Heatherton et al. 1989)	Two items from FTQ: time to first cigarette of day and number of cigarettes/day.
Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (*DSM-IV*) (APA 1994)	Categorical (nicotine dependent and not nicotine dependent) diagnostic resource that measures cognitive, behavioral, and physiological aspects of addiction. Criteria are consensus driven rather than theory driven and involve pattern of repeated drug use that results in withdrawal, tolerance, and compulsive drug taking despite negative consequences. *DSM* diagnosis is assessed by structured and semistructured interviews, such as Diagnostic Interview Schedule (DIS) (Robins et al. 1990) or Composite International Diagnostic Interview Substance Abuse Module (Robins et al. 1990). DIS results in 2-factor structure (Radzius et al. 2004). Diagnosis of dependence is also made by surveys, such as National Comorbidity Survey and National Survey on Drug Use & Health [formerly the National Household Survey on Drug Abuse], or by self-reported measures such as Tobacco Dependence Screener (TDS) (Kawakami et al. 1999). TDS has a continuous score and acceptable internal consistency. *DSM-IV* diagnoses assessed in epidemiologic surveys are associated with heavier smoking and predict persistence in smoking (Breslau et al. 2001). *DSM-IV* diagnosis is a stronger predictor of cessation than FTND, but weaker than number of cigarettes/day (Breslau and Johnson 2000), and it is poorly correlated with FTND (Moolchan et al. 2002). TDS is associated with number of cigarettes/day, carbon monoxide levels, and duration of smoking (Kawakami et al. 1999; Piper et al. 2006). Limitation: dichotomous diagnostic classification does not capture dependence that varies in degree, assumes unidimensionality, and masks heterogeneity (e.g., diagnosis can be met by endorsement of any of several criteria).

Table 4.3 Continued

Measures	Characteristics
Hooked on Nicotine Checklist (DiFranza et al. 2002a)	Unidimensional, continuous, 10-item measure to stop smoking theoretically derived on the basis of theory of loss of autonomy. Items measure inability to stop smoking, difficulty refraining from smoking in prohibited places, craving and need for cigarette, and withdrawal and feeling addicted. One-factor solution explains 60% of variance. Strong internal reliability, moderate-to-strong test-retest reliability of individual items and total score (O'Loughlin et al. 2002), and strong positive relationship to maximum frequency of smoking and maximum amount smoked. Weak correlation with duration of smoking. Significantly associated (those who endorsed at least 1 item on the scale) with failed attempt at smoking cessation, continued smoking until end of follow-up, and progression to daily smoking. High rate of symptom endorsement even in persons who ever used tobacco.
Cigarette Dependence Scale (CDS) (Etter et al. 2003a, 2005)	Unidimensional, continuous measure and empirically derived scale (single-factor structure) that covers main criteria for *DSM-IV* and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*. Definitions for dependence include compulsion, withdrawal symptoms, loss of control, time allocation (the amount of time spent smoking), neglect of other activities, and persistence despite harm, but exclude tolerance. This scale has 2 forms, CDS-12 and CDS-5, with 12 and 5 items, respectively. Both scales have high test-retest reliability and moderate-to-strong internal consistency. CDS-12 scores were higher in daily smokers than in occasional smokers and were associated with strength of urge to smoke on last attempt to stop smoking and saliva cotinine levels. Both CDS-12 and CDS-5 scores decreased with reduction in cigarette smoking, but neither scale predicted smoking abstinence at follow-up. In a subsequent study, higher CDS-12 scores predicted smoking abstinence at 1 month after cessation. Higher baseline CDS-12 scores weakly predicted higher withdrawal ratings at follow-up, with the exception of appetite. Performs better than FTND on many of these measures.
Wisconsin Inventory of Smoking Dependence Motives (WISDM) (Piper et al. 2006)	Multidimensional, 68 items with 13 theory-based subscales: (1) affiliative attachment (to smoking); (2) automaticity (smoking without awareness or intention); (3) behavioral choice/amelioration (smoking despite constraints or alternative reinforcers); (4) cognitive enhancement; (5) craving; (6) cue exposure/associative process (reflects basic learning process); (7) loss of control; (8) negative reinforcement; (9) positive reinforcement; (10) social/environmental goads (potency of social stimuli that model or invite smoking); (11) taste/sensory properties; (12) tolerance; and (13) weight control. Identifies motivational dependence process that influences dependence criteria. Some subscales are highly correlated, indicating overlapping dimensions. All scales except social/environmental goads were weakly to strongly correlated with FTND and moderately to strongly correlated with the TDS. Total WISDM score was moderately predictive of number of cigarettes/day and carbon monoxide level, with variability of strength of prediction for subscales. Total WISDM score did not significantly predict relapse, whereas combination of subscales was predictive (e.g., automaticity, behavioral choice/amelioration, cognitive enhancement, and negative reinforcement).
Nicotine Dependence Syndrome Scale (NDSS) (Shiffman et al. 2004a; Shiffman and Sayette 2005)	Multidimensional, theoretically derived scale with 5 subscales: drive (craving and withdrawal, withdrawal avoidance, and subjective compulsion to smoke), tolerance (reduced sensitivity to effects of smoking), continuity (regularity of smoking rate), stereotypy (rigid patterns of tobacco use), and priority (preference for smoking over other reinforcers). Continuous factor scores and single total score can be obtained. Most of the reliability and validity testing were not conducted on the final 19 items that comprise this scale. Internal consistency of subscales is moderate to strong. Test-retest is modest to strong. In persons who did not stop smoking, NDSS scores modestly correlated with number of cigarettes smoked, difficulty in abstaining, and severity of past withdrawal symptoms. In treatment-seeking population, scales are modestly predictive of urges during smoking and during abstinence, acute withdrawal symptoms (except negative affect), and cessation outcome. Subscales show independent predictive usefulness (e.g., differential correlation with indices of dependence). NDSS strongly discriminates nonnicotine-dependent smokers who smoke a maximum of 5 cigarettes/day (chippers) from regular smokers. Scales also discriminated levels of intake and dependence among chippers. Relationship between NDSS remained even when controlled for FTQ score.

Note: Description and results on scales are illustrative and not comprehensive.

Tobacco Constituents and Pharmacokinetics

Nicotine and Other Tobacco Constituents

Tobacco products contain more than 4,000 chemicals, some of which could contribute to dependence. However, there is little debate that nicotine is a major tobacco component responsible for addiction (USDHHS 1988; Stolerman and Jarvis 1995; Royal College of Physicians of London 2000; Balfour 2004). Nicotine, 3-(1-methyl-2-pyrrolidinyl)pyridine, is a volatile alkaloid (pKa = 8.5) with a molecular weight of 162.23. The absorption and renal excretion of nicotine are highly dependent on pH. At a high (alkaline) pH, nicotine is in the nonionized state, which is associated with the ability to more easily pass through lipoprotein membranes (Stratton et al. 2001). Nicotine can be rapidly absorbed in the lungs through cigarette smoking because of the large surface area of the alveoli and small airways and the dissolution of nicotine in pulmonary fluid, which has a physiological pH that facilitates absorption. Similarly, nicotine from oral products that have an alkaline pH can be readily but more gradually absorbed through the oral mucosa. In addition, nicotine can be well absorbed in the small intestine, because of its more alkaline pH and large surface area. However, nicotine is poorly absorbed from the stomach, because of its acidic environment resulting in greater ionized nicotine. Unlike when it is swallowed, nicotine's bioavailability is greater through the lung or through the oral mucosa because nicotine reaches systemic circulation before passing through the liver (first-pass metabolism).

Earlier studies that examined a wide range of animal species have shown that nicotine alone can lead to self-administration in preference to an inert control substance (Henningfield and Goldberg 1983; USDHHS 1988; Swedberg et al. 1990; Rose and Corrigall 1997; Royal College of Physicians of London 2000). Humans have also demonstrated a preference for nicotine over a control substance in studies examining intravenous administration (Henningfield and Goldberg 1983; Harvey et al. 2004), nasal administration (Perkins et al. 1996a), and use of medicinal gum (Hughes et al. 1990a). Furthermore, if levels of nicotine in the body are altered, smokers tend to compensate or titrate their dose by (1) smoking more if the levels of nicotine are reduced or blocked by a nicotinic receptor antagonist or (2) smoking less if exogenous nicotine or higher levels of nicotine are administered (USDHHS 1988; NCI 1996, 2001). Titration of the level of nicotine in the body during smoking involves adjusting smoking behaviors by changing the (1) number of puffs on a cigarette, (2) duration of the puffs, (3) interpuff intervals, and/or (4) number of cigarettes smoked (Griffiths et al. 1982). For example, researchers observed this compensatory smoking behavior in smokers who had either switched from cigarettes with a high machine-determined yield of nicotine to cigarettes with a low yield (Scherer 1999; NCI 2001) or reduced the number of cigarettes smoked (Fagerström and Hughes 2002; Hecht et al. 2004). The resulting levels of cotinine and other biochemical indicators of exposure to tobacco were proportionately lower than expected, considering the reduction in the nicotine yield of the cigarette or the number of cigarettes smoked.

Researchers have observed that ingredients besides nicotine in tobacco or tobacco smoke (e.g., nornicotine and acetaldehyde) have either synergistic effects with nicotine or reinforcing effects of their own. Several pharmacologically active metabolites of nicotine were observed in the central nervous system (CNS) after acute administration of nicotine (Crooks and Dwoskin 1997). Nornicotine is both a metabolite of nicotine and a minor tobacco alkaloid. According to a review by Crooks and Dwoskin (1997), *S*(-)-nornicotine evokes concentration-dependent and calcium-ion (Ca^{2+})-dependent increases in endogenous release of dopamine from rat striatal slices and from mouse striatal synaptosomes. At low nornicotine concentrations, nicotinic receptor antagonists, such as mecamylamine and [^{3}H]-dihydro-β-erythroidine (DHβE), inhibit dopamine release evoked by *S*(-)-nornicotine. At high nornicotine doses, this inhibition is not observed, thereby indicating that at high doses, nonselective mechanisms may be associated with the release of dopamine. In addition, *S*(-)-nornicotine, *R*(+)-nornicotine, and nicotine appear to activate the neural mechanisms responsible for behavioral sensitization. For example, administration of *S*(-)-nornicotine desensitized nicotine receptors, but at a potency 12-fold lower than that of nicotine. *S*(-)-nornicotine also showed cross-desensitization with nicotine; that is, receptors desensitized by nicotine were also desensitized by *S*(-)-nornicotine. This result suggests the involvement of common subtypes of nicotinic receptors (Dwoskin et al. 2001).

Researchers have observed similar behavioral effects from nicotine and nornicotine. In one study examining acute or chronic (repeated) administration of *S*(-)-nicotine, *R*(+)-nornicotine, and *S*(-)-nornicotine on locomotor activity, the effects of both nornicotine enantiomers were qualitatively different from that of the *S*(-)-nicotine enantiomer after acute administration (Dwoskin et al. 1999a). Unlike *S*(-)-nicotine, neither nornicotine

enantiomer produced hyperactivity following acute injection with the doses used in the study. However, long-term administration of a nornicotine enantiomer, specifically *S*(-)-nornicotine, showed patterns of effects similar to those of nicotine. Furthermore, long-term pretreatment with either nornicotine enantiomer produced cross-sensitization to the locomotor stimulant effects after a nicotine challenge.

Studies in rats show that (-)-nornicotine substitutes for (-)-nicotine in a drug-discrimination paradigm (Goldberg et al. 1989) and partially substitutes for (+)-amphetamine as a discriminative stimulus, although it is less potent than (-)-nicotine (Bardo et al. 1997). In a study of self-administration by rats (Bardo et al. 1999), *S*(-)-nicotine and *RS*(±)-nornicotine produced a number of responses on a lever to obtain these drugs that was higher than the number on a lever to obtain an inactive or saline infusion used as a control. Furthermore, response decreased when saline was substituted for nornicotine, confirming that the animals were responding for nornicotine. Response increased when nornicotine was again available. In another study, pretreatment with (±)-nornicotine produced a dose-dependent decrease in nicotine self-administration (Green et al. 2000).

These results indicate that nornicotine functions as a positive reinforcer but has less potency than that of nicotine. Researchers have speculated that this reduced effect may be attributable to (1) the longer half-life of nornicotine; (2) the use of *RS*(±)-nornicotine rather than the pure *S*(-)-nornicotine, which is considered more potent in evoking dopamine release in the brain; or (3) the reduced potency of nornicotine in the release of dopamine (Bardo et al. 1999). Because nornicotine is present only as a minor metabolite, it is unclear whether it would have any significant pharmacologic effect in smokers.

Less data are available on cotinine, which is a major metabolite of nicotine (Benowitz and Jacob 1994). Studies suggest that cotinine is available in the CNS and stimulates nicotinic receptors to evoke the release of dopamine in a calcium-dependent manner from superfused rat striatal slices but that it is much less potent than nicotine or *S*(-)-nornicotine (Dwoskin et al. 1999b). (In superfusion, artificial central spinal fluid is poured over thin slices of brain tissue to maintain function and enable in vitro studies.) Other studies indicated that cotinine has a low affinity for nicotinic receptors (Abood et al. 1981, 1985) and may be associated with increased serotonin (5HT) levels (De Clercq and Truhaut 1963; Yamamoto and Domino 1965; Essman 1973; Rosencrans and Chance 1977; Fuxe et al. 1979; Risner et al. 1985; Goldberg et al. 1989; Takada et al. 1989; Erenmemisoglu and Tekol 1994). Studies in animals and humans have shown that cotinine is psychoactive and behaviorally active (Hatsukami et al. 1997, 1998a), but most studies showed this effect only with high cotinine doses. In human clinical studies, cotinine demonstrates effects opposite those of nicotine, indicating that cotinine may function as a nicotine antagonist (Keenan et al. 1994; Hatsukami et al. 1998a,b).

Acetaldehyde, a constituent in tobacco smoke that results from burning sugars and other materials in the tobacco leaf, may play a role in increasing the reinforcing effects of nicotine (DeNoble and Mele 1983). In a later study, acetaldehyde enhanced the acquisition of nicotine self-administration among adolescent rats but not among adult rats (Belluzzi et al. 2005). The authors point out that adolescence may be a time of particular sensitivity to the effects of nicotine. This observation is supported by the fact that even a limited exposure to nicotine during adolescence may lead to symptoms of dependence (Kandel and Chen 2000; DiFranza et al. 2002b). In animals, nicotine treatment during adolescence leads to neurochemical changes in the brain that differ from those observed in adults (Adriani et al. 2002; Slotkin 2002). Furthermore, studies show an increased sensitivity to the rewarding effects of nicotine in adolescent compared with adult rodents (Adriani et al. 2002; Levin et al. 2003; Belluzzi et al. 2004). Further research is needed to understand the mechanism(s) by which acetaldehyde enhances the reinforcing effects and other effects of nicotine.

Fowler and colleagues (2003) point out that compared with nonsmokers and former smokers, current smokers had lower levels of MAOA, which preferentially oxidizes norepinephrine and serotonin, and of MAOB, which preferentially oxidizes phenethylamine. Both forms of MAO also oxidize dopamine, tyramine, and octopamine. Because former smokers showed normal MAO levels, the low levels in smokers appear to result from the pharmacologic effects of tobacco use, rather than from an inherent characteristic of smokers. Low levels of MAO may contribute to the reinforcing effects of tobacco use, because of the resulting higher levels of catecholamines. Nicotine does not appear to be responsible for this effect. Rather, the responsible constituents appear to be extracts (2,3,6-dimethyl-benzoquinone and 2-naphthylamine) from flue-cured tobacco leaves (Khalil et al. 2000; Hauptmann and Shih 2001). Animal studies with rats and mice have also shown that cigarette smoke and solutions of cigarette smoke (Yu and Boulton 1987; Carr and Basham 1991), as well as cigarette tobacco extract (Yu and Boulton 1987), inhibit MAO activity in the brain. The MAO inhibition in smokers is partial, with reductions at about 30 and 40 percent for MAOA and MAOB, respectively (Fowler et al. 2003). The reduction in MAOB levels does not appear to be rapidly reversible, as demonstrated by a study that showed no difference in MAOB levels when smokers were scanned by positron emission tomography (PET) at 10 minutes or

11 hours after smoking a cigarette (Fowler et al. 2000). One study found that the intensity of the withdrawal symptoms was inversely related to platelet MAO activity (Rose et al. 2001a); that is, smokers with low platelet activity at baseline experienced the most severe withdrawal symptoms.

In summary, nicotine is the most potent constituent associated with the reinforcing effects of tobacco. However, researchers have identified other constituents in tobacco and tobacco smoke that may be reinforcing or facilitate reinforcing effects of tobacco. Nicotine metabolites have also been identified as potential reinforcers or enhancers of the reinforcing effects of nicotine. Researchers have observed that in addition to nicotine and other constituents of tobacco and tobacco smoke, sensory aspects of nicotine and environmental stimuli also have a significant role in maintaining smoking behavior (Rose et al. 1993; Shahan et al. 1999; Caggiula et al. 2001, 2002b; Perkins et al. 2001d) (for details, see "Learning and Conditioning" later in this chapter).

Pharmacokinetics

Nicotine addiction depends on the amount of nicotine delivered and the way in which it is delivered, which can either enhance or reduce its potential for abuse: the faster the delivery, rate of absorption, and attainment of high concentrations of nicotine, the greater is the potential for addiction (Henningfield and Keenan 1993; deWit and Zacny 1995; Stitzer and de Wit 1998).

Nicotine can be readily absorbed in the lung, oral mucosa, and nose, and through the skin. Table 4.4 shows (1) the bioavailability and amount of nicotine absorbed per unit dose of products containing nicotine and (2) the time to reach maximum blood concentrations of nicotine (T_{max}). Figure 4.1 shows the concentrations of nicotine in venous blood and the peak concentrations across the products containing nicotine. The mean peak concentrations of nicotine are higher with use of tobacco products than with use of nicotine replacement products, and cigarette smoking produced both the highest peak concentration and most rapid rate of nicotine absorption. Venous concentrations of nicotine from smoking are lower than arterial concentrations. Ratios of arterial concentrations to venous concentrations ranged from 2.3 to 10 across studies (Henningfield et al. 1993; Gourlay and Benowitz 1997; Rose et al. 1999). What accounts for the variability in arterial to venous nicotine concentration ratios observed across studies is unclear but may be a function of the study procedures and cigarette brands that were tested. In one study, lower-than-expected arterial nicotine concentrations were observed. The low concentration was attributed to the distribution of nicotine into the lungs and the slow release of nicotine into arterial circulation (Rose et al. 1999). The greater reinforcing efficacy of rapid delivery of nicotine was therefore thought to be due to both direct effects on the CNS and to stimulation of nicotinic receptors in the lung. These results would also suggest that neuronal nicotinic receptors associated with reinforcing effects of nicotine may be sensitive to low concentrations of nicotine. Clearly, more studies are needed to resolve the issues related to arterial concentrations of nicotine and consequent physiological effects.

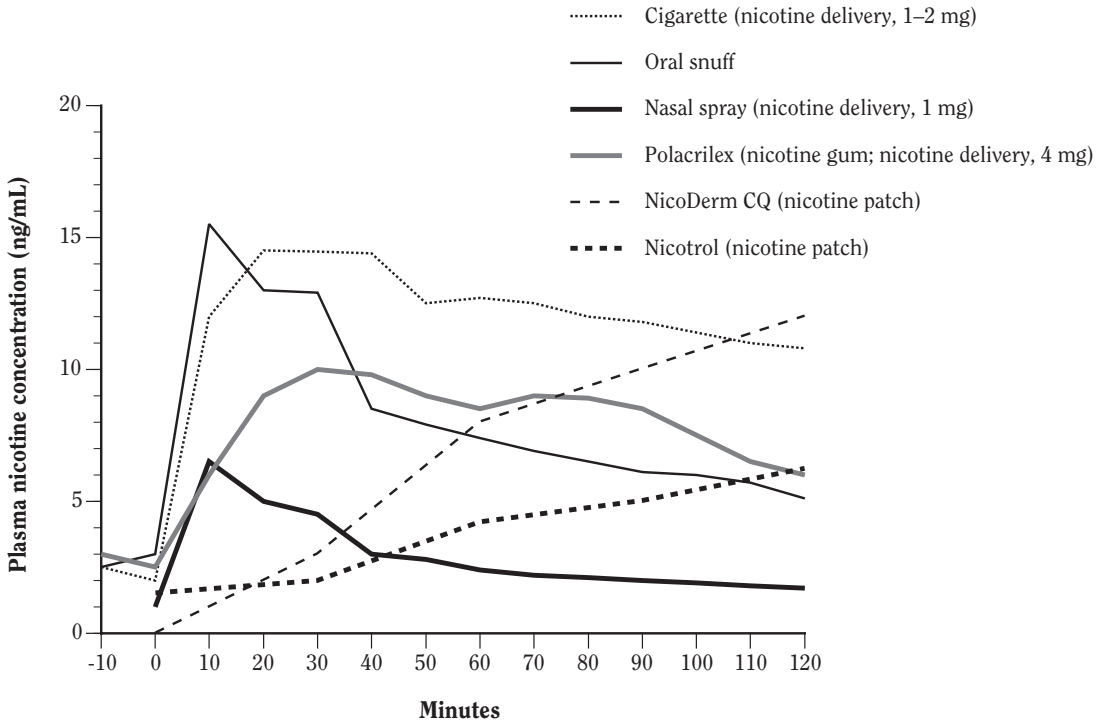
Oral use of smokeless tobacco products results in high venous concentrations of nicotine equal to those for use of cigarettes. Although the T_{max} for delivery of nicotine in nasal spray appears to be less (faster) than that for

Table 4.4 Bioavailability and amount of nicotine absorbed per unit dose and time to maximum venous blood concentration of nicotine by product

Product	Bioavailability per dose	Time to maximum concentration
Cigarette	1–2 mg	Within 5 minutes
Nicotine gum (2 mg, 4 mg)	1 mg, 2 mg	30 minutes
Nicotine inhaler	2 mg/cartridge	20–30 minutes
Nicotine nasal spray	0.5 mg	10 minutes
Nicotine patch	15–22 mg (during 16–24 hours)	4–9 hours
Smokeless tobacco	3.6–4.5 mg	20–30 minutes

Source: Data are from Benowitz 1988; Fant et al. 1999a; Fagerström 2000; Medical Economics Company 2000. Table is adapted from Stratton et al. 2001 with permission from the National Academies Press, © 2001, National Academy of Sciences.
Note: **mg** = milligrams.

Figure 4.1 Venous blood concentrations of nicotine over time for various nicotine delivery systems



Source: Adapted from Fant et al. 1999b with permission from Elsevier, © 1999.
Note: **mg** = milligrams; **ng/mL** = nanograms per milliliter.

smokeless tobacco products, the addiction potential may be higher for smokeless tobacco than for nicotine nasal spray, because the rate of nicotine absorption for smokeless tobacco is faster. Within 10 minutes after administration of a smokeless tobacco product, a nicotine boost of 10 nanograms per milliliter can be achieved (Holm et al. 1992) compared with two to three times longer after administration of nasal spray. However, the rise of arterial concentrations from nicotine nasal spray compared with smokeless tobacco is unknown. A further complication is that the rate and amount of nicotine absorption vary across smokeless tobacco products (Figure 4.2). This variability results from the processing and pH of the smokeless tobacco product. Cigarettes also vary in nicotine content. The tobacco plant, the curing process, and the additives can determine the pH of the tobacco and tobacco smoke (see Chapter 3, "Chemistry and Toxicology of Cigarette Smoke and Biomarkers of Exposure and Harm").

Nonetheless, although the pharmacokinetics of some smokeless tobacco products may overlap with those of medicinal nicotine products, medicinal products tend to have a slower rate and a lower amount of nicotine absorption than do the most popular brands of conventional smokeless tobacco products (Kotlyar et al. 2007). Among the medicinal nicotine products, nicotine nasal spray has the fastest rate of nicotine absorption, followed by nicotine gum, the nicotine lozenge, and the nicotine patch.

Together, these results demonstrate that the nicotine pharmacokinetics associated with cigarette smoking is likely to lead to high potential for addiction, whereas medicinal nicotine products have relatively minimal potential for addiction. For example, the extent of liking, and therefore the addiction potential for these products, are related to the speed of nicotine delivery (Henningfield and Keenan 1993). Nicotine delivered through cigarette smoking and intravenously shows the greatest dose-related liking for the drug, and nicotine delivered transdermally is associated with the least liking (Henningfield and Keenan 1993; Stratton et al. 2001).

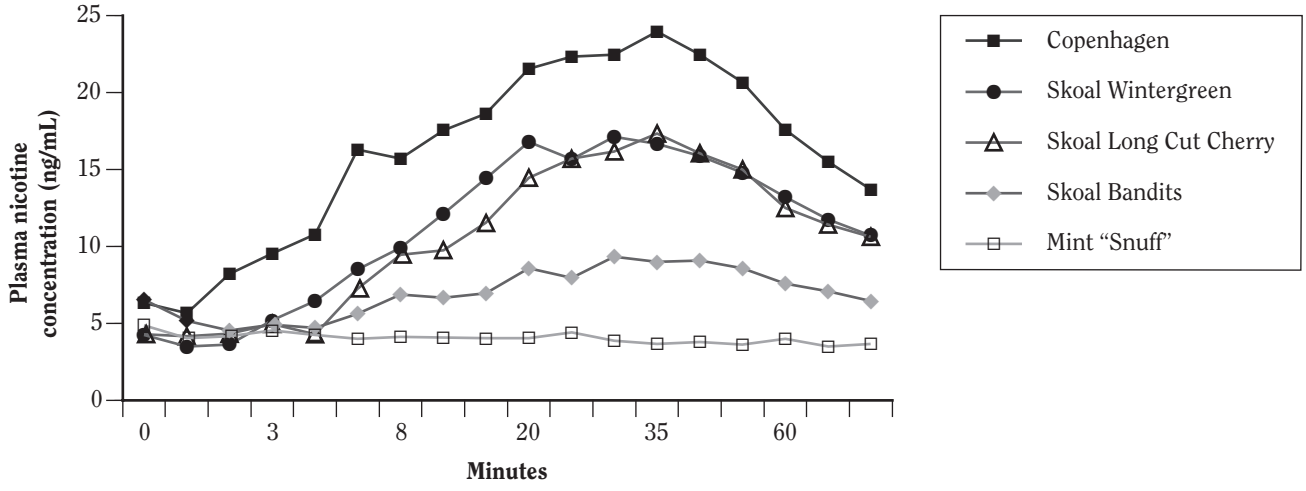
The pharmacokinetic profile of a drug can determine the user's pattern of drug delivery. Cigarette smoking results in rapidly rising arterial concentrations of nicotine that reach the brain in about 10 to 19 seconds (Benowitz

1990). The peak levels decline quickly as nicotine is taken up by peripheral tissues, followed by an elimination of nicotine from the body (Benowitz et al. 1988). This profile enables the smoker to finely control the nicotine dose to obtain the desired effect and enables frequent doses. These characteristics facilitate the addiction potential of cigarettes (Benowitz 1999). In contrast, oral nicotine products such as smokeless tobacco result in a more gradual rate of nicotine absorption and the nicotine levels are more sustained, resulting in a reduced ability of the smoker to manipulate the nicotine dose and less frequent dosing. The nicotine patch is the extreme example of slow absorption and once-a-day dosing, which results in a minimal potential for addiction.

Nicotine metabolism may also play a role in the reinforcing effects of nicotine. Researchers have hypothesized that the rate of nicotine metabolism should be related to smoking behaviors and that faster elimination of nicotine is associated with increased smoking and nicotine dependence (Benowitz 1999). Although surprisingly few published studies have tested this hypothesis, the research evidence has given some support to it (see "Genetics" later in this chapter). However, the evidence is modest. The rate of nicotine metabolism accounts for less than 16 percent of variation in the number of cigarettes smoked per day (Benowitz et al. 2003; Johnstone et al. 2006), and there is no significant variance in the FTND (Benowitz et al. 2003; Johnstone et al. 2006; Kandel et al. 2007) or in scoring on the Horn-Russell Scale (Johnstone et al. 2006). Kandel and colleagues (2007) found no significant association between the rate of metabolism and the number of cigarettes per day or nicotine dependence as measured by the FTND in a sample of young (18 through 26 years of age), less dependent, light smokers (average of 12 cigarettes per day). Possible reasons for the apparent disconnect between rate of metabolism and nicotine dependence include the following: (1) The questionnaire measures of adult nicotine dependence used may not be the most sensitive measures of the rate of metabolism (Benowitz et al. 2003; Johnstone et al. 2006). (2) The rate of metabolism may be related to nicotine dependence only during the transition from experimentation to "addicted" smoking (Benowitz et al. 2003). (3) The rate of metabolism is not an important determinant of smoking behavior in young smokers because of a low level of smoking (Kandel et al. 2007).

One of the reasons metabolism per se may not be directly related to measures of nicotine dependence is that the pharmacokinetics of nicotine metabolism are one step removed from the pharmacodynamics of nicotine, that is, from the impact (1) on neurotransmitters in the reward pathway, (2) on central effects, as measured by electroencephalography and cerebral blood flow, and (3) on peripheral effects such as cardiovascular responses. Both central and peripheral effects contribute to subjective reactions to nicotine and the subsequent likelihood

Figure 4.2 Mean plasma nicotine concentrations after administration of each of four smokeless tobacco products or mint snuff



Source: Adapted from Fant et al. 1999a with permission from BMJ Publishing Group Ltd., © 1999.
Note: **ng/mL** = nanograms per milliliter.

of continued smoking. (For discussion of the pharmacodynamics of nicotine in the brain, see "Pathophysiology of Nicotine Addiction" later in this chapter.)

The factors contributing to the high addiction potential of tobacco products are undoubtedly multiple and have complex interrelationships, making it a challenge to parse their relative contributions. In addition, smoking results in rapid delivery of nicotine by cigarette smoke and in exposure to chemicals other than nicotine that have central and sensory effects, including taste and draw resistance, as well as stimuli associated with smoking (Scherer 1999; Caggiula et al. 2002a; Rose 2006). Relatively few studies have been conducted outside the tobacco industry to determine how features of the cigarette are engineered to increase its addictive potential. However, tobacco industry documents suggest that more than nicotine dosing and pharmacokinetics are important in determining the overall addiction potential of modern cigarettes (Slade et al. 1995; Hurt and Robertson 1998; Wayne et al. 2004). (For description of design features that can enhance nicotine delivery and absorption rate, see Chapter 3, "Chemistry and Toxicology of Cigarette Smoke and Biomarkers of Exposure and Harm.")

Components of Nicotine Addiction

What are the effects of nicotine, and how does it cause addiction? The factors that may contribute to addictive behaviors include (1) neuroadaptations that occur with the persistent use of nicotine (e.g., tolerance), (2) withdrawal symptoms experienced when intake of the drug is stopped, and (3) the effects of nicotine that reinforce dependence. The primary reinforcing effects can entail the rewarding (psychoactive or psychostimulant) effects of nicotine (positive reinforcement) and/or the alleviation of aversive or negative states or stimuli—for example, relief from withdrawal symptoms (negative reinforcement). Nicotine may also enhance the reinforcing values of other reinforcers or stimuli, which may also contribute to its reinforcing effects.

Strong learning processes also contribute to addictive behaviors. These learning processes include conditioning in which stimuli associated with drug use evoke responses that are similar to the effects from the drug or similar to withdrawal symptoms or that may modulate drug effects. One hypothesis is that incentive sensitization can occur, in which some of the conditioned stimuli (CSs) are given priority in the allocation of attention and become a strong source of motivation to seek the drug (Robinson and Berridge 2001). Incentive sensitization consists of neuroadaptations from repeated use of a drug that render brain-reward systems hypersensitive (sensitized) to drug-associated stimuli. Also, nicotine's ability to be a secondary reinforcer of CSs to other reinforcers strengthens its addictive effects. Nicotine tolerance, withdrawal, and reinforcement in humans are examined in the next section, which is followed by a section on learning and conditioning in nicotine addiction.

Physiological Mechanisms and Indicators: Nicotine Tolerance, Withdrawal, and Reinforcement

Chronic Tolerance

Tolerance is a reduced responsiveness to a drug as a function of earlier exposure to that drug. This reduction in responsiveness is a consequence of drug use (Kalant et al. 1971). Therefore, tolerance should be distinguished from innate differences in drug responses that may relate to an initial risk of dependence, such as responses attributable to genetic or other constitutional factors (see "Genetics" later in this chapter). Sensitization, the opposite of tolerance, is an enhanced responsiveness to nicotine as a function of earlier exposure to the drug (Kalant et al. 1971). Sensitization is not addressed here, because it has not been clearly demonstrated in clinical studies. However, animal research suggests that sensitization occurs in response to locomotor activity and other physical and behavioral effects of exposure to nicotine (Le Foll et al. 2003; Samaha et al. 2005).

Tolerance and sensitization can be characterized on the basis of the time course of the adaptation involved. Acute tolerance develops within minutes after the initial exposure of the day (e.g., first few cigarettes) and is generally lost with overnight abstinence from smoking (Perkins et al. 1995). Acute tolerance may help to explain patterns of smoking during the course of a day (Balfour et al. 2000), but researchers think it is less important than chronic tolerance for an understanding of dependence (Di Chiara 2000). Chronic tolerance develops over weeks, months,

or years (Kalant et al. 1971). Tolerance can also be distinguished on the basis of mechanisms. Pharmacokinetic tolerance is a reduced response to a drug because of an increase in drug clearance or metabolism that results in a smaller concentration of the drug in the body for a given administered dose. This type of tolerance is not discussed here, because clinical studies showed no evidence of a pharmacokinetic tolerance to nicotine in humans (Benowitz and Jacob 1993). However, innate differences in nicotine metabolism are well known (see "Genetics" later in this chapter). Pharmacodynamic tolerance is a reduced response to a given concentration of a drug in the body that results from changes in tissue sensitivity. The following discussion focuses on the association between chronic pharmacodynamic tolerance to nicotine and dependence on nicotine.

Chronic Tolerance to Nicotine

Chronic tolerance to nicotine or to most drugs is difficult to examine in clinical studies for practical and ethical reasons. The time required for the onset of chronic tolerance generally precludes longitudinal studies of changes in tolerance. Thus, the study of chronic tolerance usually requires cross-sectional comparisons between groups that differ in past histories of smoking, which can require administering nicotine to nonsmokers. Such comparisons may also introduce potential bias due to self-selection of drug history and because smoking history may covary with many other important differences that affect responses to nicotine, such as history of other drug use and psychiatric history (Hughes et al. 2000; Richter et al. 2002).

Despite methodologic limitations, studies have clearly shown a chronic tolerance for many self-reported responses to nicotine, such as a subjective mood. For example, smokers show fewer responses than do nonsmokers to the same amount of nicotine, as evidenced by measures of subjective stimulation that may be viewed as pleasurable, such as arousal, vigor, and a subjective experience often referred to as "head rush" or "buzz," as well as some experiences that may be viewed as aversive, including tension and nausea (Perkins et al. 2001b). However, chronic tolerance is less apparent for many other effects of nicotine, including cardiovascular responses (Perkins et al. 2001b). Chronic tolerance is virtually absent for simple psychomotor effects such as finger-tapping speed and Stroop task performance (Perkins et al. 2001b). This research is reviewed in detail elsewhere (Perkins 2002).

Association of Nicotine Tolerance with Dependence in Adults

Chronic tolerance to some effects of nicotine develops after long-term smoking. However, tolerance appears to be a nonsensitive marker for dependence among those with any history of extensive smoking (Perkins 2002). Perkins hypothesized that if a close association exists between tolerance and the level of dependence, then (1) more dependent smokers would show tolerance greater than that of less dependent smokers, (2) tolerance to nicotine before smoking cessation would predict the success of a subsequent attempt to stop smoking, and (3) tolerance would decrease with a longer duration of abstinence after cessation, indicating loss of dependence. However, the limited evidence suggests no such links between tolerance and dependence (Perkins 2002).

First, some research (Shiffman et al. 1992; Perkins et al. 2001b) shows little or no difference in tolerance to most effects of nicotine between dependent smokers and a subset of smokers who do not meet dependence criteria—for example, smokers of up to five cigarettes per day who do not experience withdrawal symptoms and who often go for long periods without smoking (Shiffman et al. 1992). Second, the magnitude of tolerance to nicotine before smoking cessation does not predict the severity of withdrawal or the duration of abstinence after an attempt to stop smoking, although a measure of nicotine reinforcement predicts both (Perkins et al. 2002a). Third, longitudinal studies show no change in chronic tolerance within one week or one month of smoking cessation and no difference in tolerance between former smokers who stopped smoking for 1 to 4 years or 6 to 19 years (Perkins et al. 2001c).

The conclusion that tolerance among smokers is not a good index of dependence warrants additional research (Perkins 2002). Most of these studies compared responses at low doses of nicotine to avoid aversive effects in groups with histories of limited smoking. Even so, tolerance to higher doses of nicotine may be associated with indices of dependence. Moreover, the acute effects of nicotine that explain its reinforcing quality are still not understood fully, so chronic tolerance to responses that were not assessed in this earlier research may be tied closely to dependence. In addition, chronic tolerance may be more critical during the onset of dependence in the adolescent years than it is in adults (Kandel and Chen 2000), because tolerance to the aversive effects of nicotine must occur for adolescents to escalate from one to two cigarettes per day to one pack per day (see "Epidemiology of Tobacco Use and Nicotine Dependence in Adults" later in this chapter). However, chronic tolerance may no longer be important after the onset of dependence.

Withdrawal

In tobacco-dependent smokers, a reliable consequence of abstaining from smoking for more than a few

hours is the onset of distress indicated by self-reported behavioral, cognitive, and physiological symptoms and by clinical signs (APA 2000; Shiffman et al. 2004b; Hughes 2007). The subjective symptoms of withdrawal are manifested by affective disturbance, including irritability and anger, anxiety, and a depressed mood. The behavioral symptoms include restlessness, sleep disturbance, and an increased appetite, typically assessed by self-reports. Cognitive disturbances usually center on difficulty concentrating (Shiffman et al. 2004b; Hughes 2007). Researchers believe these symptoms—known collectively as withdrawal—are major factors that impair the ability to remain abstinent from smoking (Patten and Martin 1996; see "Trajectory of Recovery or Relapse" later in this chapter). The management of withdrawal and craving symptoms (e.g., the urge to smoke) is a primary treatment strategy to maintain smoking cessation. Withdrawal symptoms typically emerge within a few hours after the last cigarette is smoked, peak within a few days to one week, and return to precessation baseline levels after two to four weeks (Shiffman et al. 2004b). However, individual variability in the time course of withdrawal may be substantial and clinically significant (see "Trajectory of Recovery or Relapse" later in this chapter).

Individual withdrawal symptoms are often viewed as different manifestations of the same underlying process. One approach suggests that symptoms should be tightly linked in terms of pattern, intensity, time course, relationship to relapse, and neurobiologic factors. Another-approach suggests that symptoms should be assessed individually instead of by aggregating symptom scores into one total score (Shiffman et al. 2004b) (see "Pathophysiology of Nicotine Addiction" and "Trajectory of Recovery or Relapse" later in this chapter).

Unlike nicotine tolerance, the severity of withdrawal is more strongly related to some of the indices of nicotine dependence (such as cessation). For example, although nicotine-dependent and nonnicotine-dependent smokers generally do not differ in tolerance to nicotine, nicotine-dependent smokers are more likely to experience more severe withdrawal during initial abstinence (Shiffman 1989b). The observation that withdrawal but not tolerance is associated with dependence has also been noted for other drugs of abuse, especially alcohol (Schuckit et al. 1999; Hasin et al. 2000; O'Neill and Sher 2000).

Individual Differences in Withdrawal

Individual differences in the severity and pattern of withdrawal are topics of major clinical interest (see "Trajectory of Recovery or Relapse" later in this chapter). A history of major depression may exacerbate withdrawal after smoking cessation (Pomerleau et al. 2004) and may increase the risk of relapse in women but perhaps not in men (Hall et al. 1998). The role of a major depressive disorder in relapse has been inconsistent and may be related to how depression is defined (see "Trajectory of Recovery or Relapse" later in this chapter), and few other characteristics have been associated with differences in withdrawal for men and women. For example, even though women generally have more difficulty than do men in maintaining abstinence from smoking, the severity of withdrawal in men and women does not appear to differ (Benowitz and Hatsukami 1998). However, withdrawal severity may be moderated by the phase of the menstrual cycle in women, with more severe withdrawal and depressed mood among women who stop smoking during the luteal phase than among those who stop during the follicular phase (Allen et al. 1996; Perkins et al. 2000). Other than studies of the effects of medication to relieve withdrawal symptoms, few researchers have examined other factors that acutely modify withdrawal.

Reinforcement

In behavioral psychology, a stimulus is considered reinforcing if it increases a response or behavior resulting in obtaining that stimulus. Thus, a drug is reinforcing if it is self-administered more than an inert substance used for comparison (e.g., placebo). "Reward," on the other hand, is a less specific term defined as an index of subjective hedonic effects of substance use (Everitt and Robbins 2005), and it is typically assessed after drug intake by ratings such as "liking" and "good effects." Ratings of drug reward may help to explain reinforcement, but they should be kept distinct from measures of reinforcement, which are inherently behavioral.

After a drug is established to be reinforcing, research can then focus on the neurobiologic or behavioral underpinnings of the reinforcing effects. (For discussion of research on the neurobiology of nicotine reinforcement, see "Pathophysiology of Nicotine Addiction" later in this chapter.) Behavioral or subjective effects of nicotine that may be reinforcing have not been definitively identified. Methodologic issues complicate the study of what makes nicotine either positively or negatively reinforcing. Pleasurable effects indicate positive reinforcement, whereas reductions in negative effects, such as relief from withdrawal, indicate negative reinforcement. These distinctions are important because exploration of positively reinforcing effects may be critical to understanding why adolescents begin to smoke cigarettes (i.e., onset of addiction) and why persons relapse after an attempt to stop smoking. Negatively reinforcing effects may be specific to relief from acute withdrawal and thus relevant only to relapse and not to the initiation of smoking or the

onset of addiction. Some research in nonsmokers links acute self-administration of nicotine with pleasurable subjective responses of increased vigor and arousal, suggesting that positive reinforcement occurs with initial experience with nicotine (Perkins et al. 2001a). Similar research should focus on whether initial nicotine reinforcement is linked to relief from preexisting aversive symptoms, such as depressive symptoms.

Other effects of nicotine may also reinforce its use, but their links with self-administration have not been clearly established. These effects include modulating negative affect (e.g., reducing fatigue, anxiety, or sadness) (Kassel et al. 2003), enhancing attention and concentration during cognitively demanding tasks (Heishman et al. 1994), and perhaps preventing hunger and maintaining a lower body weight (Perkins 1993). Evidence suggests that these effects are observed largely in abstinent smokers experiencing withdrawal and are thus examples of negative rather than positive reinforcement.

Finally, animal research indicates that nicotine may have a secondary reinforcing function, aside from the direct (primary) reinforcing effects noted here. These studies, conducted mostly by Caggiula, Donny, and colleagues (e.g., Chaudhri et al. 2006), show that nicotine can enhance the reinforcing value of other reinforcers not associated with nicotine intake. Primary reinforcing effects require rapid administration of nicotine and are contingent on a response, whereas other reinforcement-enhancing effects can occur regardless of the speed of nicotine delivery or the contingency of response. Although recent work suggests the occurrence of reinforcement-enhancing effects of nicotine (Barr et al. 2008), the clinical research is insufficient to warrant extensive discussion of how this influence promotes nicotine dependence. However, this influence may help to explain why smoking appears to acutely increase consumption of other reinforcers, such as alcohol (Mitchell et al. 1995), and it may facilitate understanding of the difficulties involved in smoking cessation. If nicotine has reinforcement-enhancing effects, then smoking cessation removes these effects, leading to a lessening of reinforcement from many other reinforcers and not just the loss of reinforcement from smoking.

Smoking Frequency and Tobacco Addiction

The most common index of reinforcement in research on tobacco or nicotine addiction is the number of cigarettes smoked per day (smoking frequency). That is, drugs that are highly reinforcing will tend to be self-administered to a greater extent. Typically, the number of cigarettes smoked per day is assessed by self-report. Biochemical measures of the amount of smoking exposure include blood, salivary, and urinary levels of cotinine, the main metabolite of nicotine. Smoking frequency is related to a variety of dependence measures including scores on scales of nicotine dependence such as the widely used FTND (Hughes et al. 2004a). Higher frequency of smoking was found to predict a more severe withdrawal and a faster relapse after an attempt to stop smoking (Ockene et al. 2000), which are both important clinical indices of addiction. Higher frequency of smoking is also associated with early lapses after smoking cessation, such as smoking on the first day of cessation or within the first two weeks, which are each strongly associated with an increased risk of relapse (Kenford et al. 1994). Other indices of smoking reinforcement or persistence are related to a high level of addiction. These indices include a longer duration of smoking, young age at smoking initiation, no previous attempt to stop smoking, and a shorter duration of abstinence during previous attempts to stop smoking (Ockene et al. 2000) (see "Trajectory of Recovery or Relapse" later in this chapter).

Acute Measures of Reinforcement

Reinforcement is often assessed in basic research studies by analyzing regular, or extent of, smoking behavior over a period of time. This is usually determined by the number of cigarettes smoked per day but occasionally by microtopographic measures of puffing behaviors, blood nicotine levels, or the percentage of carbon monoxide in expired air (Lee et al. 2003), a biochemical index of acute smoking exposure. Smoking behavior in such short-term studies has been sensitive to a variety of manipulations of nicotine exposure, demonstrating the reinforcing effects of nicotine. For example, the intensity of acute smoking behavior increases when the nicotine yield of the cigarette is lowered, which is a compensation to maintain nicotine intake (Zacny and Stitzer 1988). The increase in plasma concentrations of nicotine from smoking is greater after pretreatment with mecamylamine, a nicotine receptor antagonist. The increase is probably a result of more intense puffing in an attempt to overcome the blockade of nicotine receptors (Rose et al. 2001b). Factors have been observed to moderate the reinforcing effects of tobacco. Some studies have shown increased smoking reinforcement after pretreatment with alcohol (Nil et al. 1984; Mitchell et al. 1995) or with stimulant drugs such as *d*-amphetamine (Tidey et al. 2000), methylphenidate (Rush et al. 2005), or cocaine (Roll et al. 1997), but not with other stimulants such as caffeine (Nil et al. 1984; Lane and Rose 1995). The increase in smoking reinforcement from acute pretreatment with drugs may help to explain the association between a history of drug use and nicotine dependence (Richter et al. 2002).

Several other procedures provide sensitive and acute measures of smoking or nicotine reinforcement. These procedures include performance on a task (operant responding) on various schedules of reinforcement for puffs on a cigarette and the choice of nicotine or nonnicotine cigarettes. Instances of working for puffs on a cigarette and choosing nicotine over nonnicotine cigarettes increase with smoking abstinence (Perkins et al. 1994, 1996b). The operant response to obtain puffs on a cigarette increases when the required number of responses per reinforcer is changed and access to alternative reinforcers is reduced, showing regulation of smoking intake (Johnson and Bickel 2003). A slightly different procedure—responding for puffs on a progressive-ratio schedule by gradually increasing the response requirements after each earned puff—may also provide a sensitive measure of the reinforcing value of smoking (Perkins et al. 2002b). However, few findings have related this measure to nicotine dependence.

Separation of Nicotine Reinforcement from Smoking Reinforcement

Nicotine dependence generally involves the intake of nicotine by tobacco use, especially cigarette smoking. Therefore, the contribution of the many nonnicotine aspects of tobacco associated with smoking cigarettes should be distinguished from the influence of nicotine per se. The self-administration of cigarette smoke is not the same as the self-administration of nicotine. Among many differences between nicotine delivery through smoking and delivery in other forms, the smoke stimuli that typically accompany nicotine from cigarette smoking may acquire conditioned reinforcing effects that maintain smoking behavior (Caggiula et al. 2001) (see "Learning and Conditioning" in the next section).

Nevertheless, some of the manipulations that alter smoking behavior also alter the self-administration of novel nicotine formulations. Nicotine alone, isolated from tobacco smoke, is reinforcing in humans (Perkins et al. 1996a; Harvey et al. 2004). The choice of nicotine nasal spray instead of a placebo nasal spray increases with smoking abstinence (Perkins et al. 1996b) and subsequently predicts a more severe withdrawal and a faster relapse during an attempt to stop smoking without medication (Perkins et al. 2002a). Blocking the effects of nicotine with mecamylamine pretreatment increases the intravenous self-administration of nicotine (Rose et al. 2003a). Also, under the same conditions of assessment, the amount of nicotine spray used voluntarily is correlated with the amount of voluntary smoking (Perkins et al. 1997). This finding indicates a generalizability between nicotine reinforcement through smoking and reinforcement through at least one novel form of nicotine delivery.

Individual Differences in Nicotine Reinforcement

Individual differences in nicotine reinforcement may provide direction for the study of individual differences in nicotine addiction and in approaches to treating addiction. In some studies, the reinforcing effects of nicotine tend to be less in women than in men, but the reinforcing effects of nonnicotine stimuli related to tobacco smoke (e.g., "cues") tend to be greater in women than in men (Perkins et al. 2001d, 2002b). In light of the generally greater difficulty most women have with smoking cessation, this observation suggests that the influence of nonnicotine stimuli can be important to the persistence of smoking behavior (i.e., dependence) (Caggiula et al. 2001; Rose 2006). Other characteristics that may be associated with greater reinforcement from smoking or from nicotine include comorbid psychiatric disorders (Lasser et al. 2000), a history of alcohol dependence (Keenan et al. 1990; Hughes et al. 2000), and perhaps other drug dependence (Richter et al. 2002), as well as other subgroups associated with a high prevalence of smoking and low rates of cessation. Similarly, smokers who are not obese may find the nicotine in cigarettes more reinforcing than do obese smokers (Blendy et al. 2005).

Learning and Conditioning

Nicotine and Secondary Reinforcement

Perhaps as powerful as the direct effects of smoking and nicotine on neural functioning are the associative processes that develop with repeated tobacco use (Caggiula et al. 2002a; Hyman 2005). The classic conditioning paradigm provides an important conceptual and theoretical framework for consideration of the powerful associative learning processes that, according to Bevins and Palmatier (2004), develop in a specific manner. Smoking serves as the unconditioned stimulus (US), and the subjective and physiological effects of smoking and exposure to nicotine serve as unconditioned responses. Exteroceptive (environmental) and interoceptive (internal) stimuli that occur repeatedly in temporal proximity to smoking become CSs. CSs include smoking paraphernalia (e.g., an ashtray), sensory aspects of smoking (e.g., cigarette smell or taste), and/or situational cues (e.g., smoking in the car while driving to work). The acquired response evoked by CSs becomes a conditioned response. With longer-term smoking, conditioned responses include urges to smoke. Repeated pairings of these CSs with cigarette smoking result in the CSs alone (before smoking) triggering urges to smoke (to want and to seek a cigarette) (Niaura 2000; Berridge and Robinson 2003).

Nicotine as a Conditioned Stimulus

Bevins and Palmatier (2004) have extended the associative learning model of nicotine dependence by hypothesizing that nicotine also has important actions as a CS of smoking behavior (the conditioned response) (Figure 4.3). The traditional role of nicotine has been limited to serving as a US. As a CS, nicotine acquires new or additional affective properties through being paired repeatedly with other stimuli such as coffee. In other words, nicotine enhances the salience of these and numerous other stimuli, which strengthens the associative bond and increases smoking behavior.

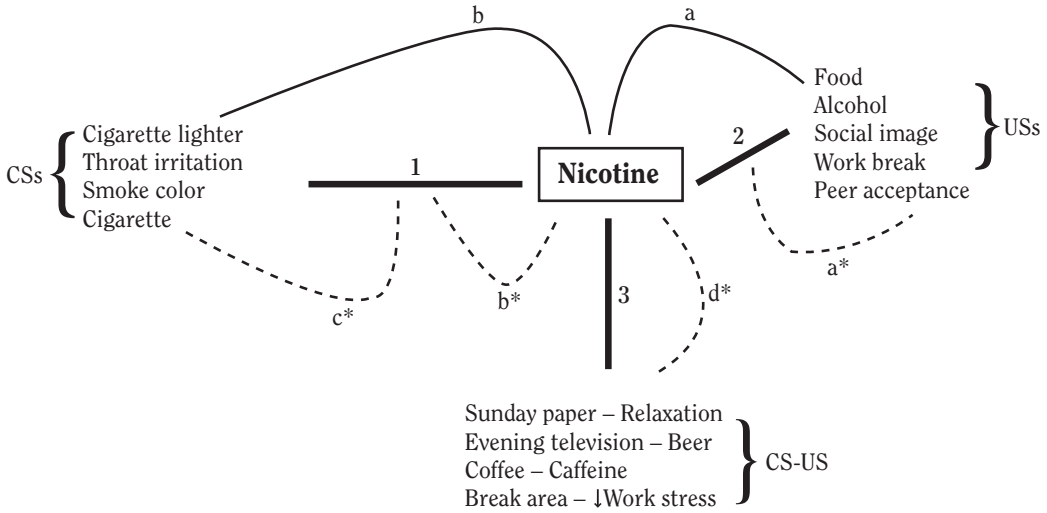
Nicotine as a Modifier of Associative Processes

In addition to serving as a CS, nicotine modifies associative processes in conditioned and unconditioned manners (Bevins and Palmatier 2004). As a conditioned modulator (Figure 4.3), the interoceptive cuing of nicotine serves as a contextual stimulus that "sets the occasion" for an association between a discrete CS in the environment and smoking (Bevins and Palmatier 2004). The CS-US association is conditioned on the drug state (context). Examples include smoking while drinking alcohol to relax and smoking during a break at work to cope with distress. As an unconditioned modulator, nicotine may enhance the salience of other stimuli that have incentive values to the person (Bevins and Palmatier 2004). For example, as depicted in connector "a" (solid line) of Figure 4.3, nicotine enhances the incentive or reward value of alcohol, which has its own significant reward value. This "incentive amplification" is unconditioned because the effects of nicotine do not depend on a contingent association between smoking and the motivational stimulus. "Incentive amplification" by nicotine is not limited to other drug reinforcers. Nicotine also enhances the reinforcing effects of nondrug reinforcers, such as light stimulus (Palmatier et al. 2007).

Positive Reinforcement and Learning

The positive reinforcing action of nicotine is attributable in large part to its influence on the brain regions associated with reward processes (e.g., the mesolimbic dopaminergic system) (Balfour 2004). In a review of positive-reinforcement theory as applied to nicotine addiction, Glautier (2004) suggests several mechanisms underlying positive-reinforcement processes. Besides exerting a direct reinforcing action through its effects on core brain-reward centers, nicotine may enhance the reinforcing efficacy of smoking-related cues as a result of priming the smoker to selectively attend to those stimuli. In addition, nicotine acquires indirect reinforcing actions through its

Figure 4.3 Associative learning processes in nicotine addiction



Source: Adapted from Bevins and Palmatier 2004 with permission from Sage Publications Inc. Journals, © 2004.
Note: Connections 1, 2, and 3 reflect the role of the unconditioned stimuli (USs), conditioned stimuli (CSs), and occasion setter, respectively. Solid lines "a" and "b" refer to nicotine's ability to amplify incentive salience. Dashed lines ("a*" through "d*") denote potentially interesting feedback functions in which conditioned associations may be strengthened.

effect on other behaviors. According to Hogarth and Duka (2006), considerable evidence suggests that nicotine-conditioned effects are mediated by a smoker's expectations of the effects of nicotine coupled with an appetitive emotional response that reflects the positive value of nicotine to the smoker (e.g., pleasure or relaxation).

Although clearly influential, positive reinforcement is not a likely primary motivational influence on persistence in smoking (Baker et al. 2004), except possibly in the case of occasional smoking (Shiffman and Paty 2006). Unlike expectations of negative reinforcement, such as smoking to relieve stress, expectations of positive reinforcement do not predict the likelihood of a relapse after smoking cessation. This finding indicates that positive-reinforcement processes may have less motivational significance for relapse than do negative-reinforcement processes (Wetter et al. 1994). Relapse is less likely to occur during positive-affect states than during negative-affect states (Shiffman et al. 1996c) (see "Trajectory of Recovery or Relapse" later in this chapter).

Negative Reinforcement and Learning

Negative reinforcement refers to processes by which smoking or nicotine reduces aversive states, such as pain, craving, difficulty concentrating, and the negative-affect states generally associated with nicotine withdrawal. Nicotine addiction is maintained in part because persons learn during the early stages of smoking that tobacco use allows them to escape aversive states associated with smoking abstinence or because they learn later that it helps them to avoid these aversive states (Eissenberg 2004). These states include irritability and an anxious or depressed mood. With continued use of cigarettes by smokers over time, the associative link between tobacco use and the relief of withdrawal-associated aversive states is strengthened. Tiffany and colleagues (2004) hypothesize that a crucial phase in the development of nicotine addiction may be the transition from experimental smoking to smoking to reduce the experience of negative states.

Baker and colleagues (2004) extend the conceptualization of this negative-reinforcement model of tobacco dependence by focusing on the role of negative affect. Within this reformulation of negative reinforcement, negative affect is the core symptom of the nicotine withdrawal syndrome that drives a person to smoke to relieve aversive states. Traditional negative-reinforcement models have emphasized the role of environmental cues, such as interpersonal conflict, but not internal cues, such as physiological symptoms that signal impending withdrawal-related states of negative affect. With repeated pairings of nicotine withdrawal and smoking to relieve withdrawal, persons addicted to nicotine may learn over time to detect internal cues at a level that is not in the immediate awareness of the smoker, especially cues associated with negative-affect states, regardless of whether they are related to withdrawal (Baker et al. 2004). Nicotine operates on both aversive withdrawal states and distress associated with external stressors, according to Baker and colleagues (2004). However, nicotine may be less effective in reducing negative affect associated with distress from external stressors. Consistent with this view, cigarette smoking has not been found to attenuate experimentally induced negative affect in the laboratory setting (Conklin and Perkins 2005). Studies of smoking in real-world settings have found little or no association between subjective negative affect and smoking behavior (Piasecki 2006). Baker and colleagues (2004) further hypothesize that smokers acquire a "motivational-processing sequence in which interoceptive signals of negative affect engage drug self-administration response sequences and may induce awareness of the desire or urge to use a drug without awareness of the affective origins or setting events for the desire" (p. 47).

The finding that negative-reinforcement processes may not be consciously accessible (Baker et al. 2004) could contribute to the difficulty smokers experience in trying to stop smoking. When negative affect or external stressors become sufficiently strong, the person becomes aware of them, and the negative affect leads to biases in information processing. One example is attentional bias for negative affect cues that trigger smoking (Baker et al. 2004). Although it is provocative, Baker and colleagues' model of negative reinforcement should be viewed as provisional and requiring validation. Related individual differences, such as the inability to tolerate distress, may influence learning and conditioning processes (Brown et al. 2005). Using momentary ecological assessment, Shiffman and Waters (2004) found that rapid increases in negative affect exert especially strong influence in precipitating lapses to smoking (see "Trajectory of Recovery or Relapse" later in this chapter for a more detailed discussion of smoking relapse).

Environmental Context

Animal studies confirm the powerful role that environmental stimuli play in nicotine self-administration. When environmental stimuli are paired with nicotine self-administration, the extinguished drug-seeking behavior is reinstated (Le Foll and Goldberg 2005). The important role of environmental context in nicotine addiction is observed in its effect on relapse. (For more description, see "Trajectory of Recovery or Relapse" later in this chapter.) Studies of smokers consistently report an association among exposure to smoking cues, craving, and positive

and negative affective states, which could be construed as emotional cues followed by return to smoking after an attempt to stop (Shiffman 1982; Marlatt and Gordon 1985). These studies, however, rely on subjectively recalled events that may be prone to several types of memory bias. Using methods of ecological momentary assessment in an electronic diary, Shiffman and colleagues (1996c) confirmed that lapses in smoking abstinence were strongly associated with being in situations in which smoking was permitted, cigarettes were available, and other persons were smoking.

Clinical studies have used a cue-exposure paradigm to explore the association of smoking cues with craving and physiological and behavioral responses. These studies are premised on the assumption that they yield insights into how environmental and internal stimuli play a role in provoking smoking and relapse (Niaura et al. 1988; Caggiula et al. 2001; Chiamulera 2005). Stimuli are presented in a variety of modes, including photographic and video, auditory, in vivo (presence of cigarette paraphernalia or smoking by another person), and the use of imagery (e.g., request to imagine specific situations). In a meta-analytic review, Carter and Tiffany (1999) found that exposure to smoking cues increased craving most reliably, followed in order by sweat gland activity and heart rate changes. Sweating and changes in heart rate probably reflect an increased arousal of the sympathetic nervous system. Other researchers have noted cue effects on an increase in reaction time (Sayette and Hufford 1994), cognitive interference on the Stroop test (Munafò et al. 2003), and similar paradigms used to assess attentional interference (Mogg and Bradley 2002). Imaging studies of cue responses also suggest that neural activity is greatest in brain areas involved in emotion and reward, including the prefrontal cortex, limbic lobe (anterior cingulate, posterior hippocampus, and right posterior amygdala), medial thalamus, and midbrain structures (ventral tegmentum) (Due et al. 2002; McClernon and Gilbert 2004; David et al. 2005).

Exposure to smoking cues among smokers also decreases the prepulse inhibition of the acoustic startle reflex, an effect associated with an increase in dopaminergic activity in the ventral tegmental brain region (Hutchison et al. 1999b). The effects of smoking cues on neural responses and craving are also moderated by factors such as the perceived availability of cigarettes. After cue exposure, craving increased more when there is an expectation of the opportunity to smoke (perceived availability) than when there is perceived unavailability (Carter and Tiffany 1999). Exposure to a cigarette cue under the condition of perceived availability is associated with an increase in activation of the ventromedial prefrontal cortex and a decrease in activation of the dorsolateral prefrontal cortex compared with exposure to a neutral cue (Wilson et al. 2004). This pattern of neural activation with corresponding increases in craving can be seen as setting the stage for behaviors that culminate in smoking.

Responses to cues in laboratory experiments are associated with responses to smoking cessation treatments. For example, acute increases in heart rate assessed among smokers in response to a cue exposure at the end of a treatment protocol were related to a later relapse to smoking (Niaura et al. 1989). An acute deceleration in heart rate assessed when smokers observed a cigarette being lit during the cue-exposure procedure also predicted relapse. Heart rate deceleration in this context may reflect a greater attention paid to the stimulus (e.g., a lit cigarette). Subsequently, Waters and colleagues (2004) found that a cue-provoked craving before treatment predicted relapse, but only among those who were treated with an active nicotine patch instead of a placebo patch, suggesting inconsistent results or uncertainty in the link between cue-provoked craving in the laboratory and relapse.

If cue-provoked responses assessed in the laboratory are associated with smoking relapse, then treatments that decrease or blunt these responses may increase the likelihood of successful smoking cessation. A review by Conklin and Tiffany (2002) suggests that conventional extinction-type treatments, such as exposure to smoking-related cues unaccompanied by the reinforcing effects of nicotine or exposure with response-prevention treatments, are ineffective in helping persons to stop smoking. This finding may relate to the possibility that stimulus-response pairing, if sufficiently strong, cannot be forgotten or unlearned (LaBar and LeDoux 2001; Conklin and Tiffany 2002; Niaura 2002). In addition, the large number of potential cues likely serves to maintain smoking behavior or the state-dependent learning processes. However, methods such as use of denicotinized cigarettes or antagonists (e.g., mecamylamine) show significant effects on reducing the rewarding value of smoking cues and have the potential to enhance smoking cessation (Rose and Behm 2004; Rose 2006). Other cognitive or behavioral methods based in modern learning theory may also show more promise in suppressing the stimulus-response bond. Pharmacologic treatments show some promise in decreasing cue reactivity. Compared with a placebo gum, nicotine polacrilex gum diminished the craving response to smoking cues more rapidly (Shiffman et al. 2003). In a study using the same cue-exposure paradigm, a more recent formulation of a rapid-release nicotine gum reduced craving more than did conventional nicotine polacrilex gum (Niaura et al. 2005). Nicotine polacrilex gum is an effective smoking cessation aid (Silagy et al. 2004). Its efficacy may be associated with its ability to diminish a cue-provoked craving.

Other rapid-release formulations of nicotine replacement therapy (NRT), including gum and nasal spray, may similarly help persons to stop smoking, in part because these formulations decrease the craving response to cues. In contrast, although slower-releasing NRT formulations (e.g., a nicotine patch) appear to lower absolute levels of craving, these formulations do not blunt cue-provoked craving (Tiffany et al. 2000; Waters et al. 2004). One study has suggested that treatment with bupropion blunts cue-provoked craving, but the study did not control for abstinence status (Brody et al. 2004a). Other non-nicotine compounds (e.g., naltrexone and olanzapine) also may blunt cue-provoked craving (Hutchison et al. 1999a, 2004). This finding suggests that the cue-exposure paradigm may be a useful screening tool for testing pharmacologic aids to smoking cessation; however, further studies need to be conducted to better understand why some medications affect cue-induced cravings and others do not.

Summary and Future Directions

Long-term exposure to nicotine produces biologic adaptations leading to reduced sensitivity to some of the effects of nicotine (tolerance) and symptoms of distress soon after cessation of drug use (withdrawal). Tolerance of nicotine in adolescent smokers may be related to onset of drug dependence, even though tolerance in adult smokers does not appear to be related to different indices of nicotine addiction. Withdrawal symptoms, especially self-reported cravings and negative affect, are related to some indices of addiction. A narrower focus on the individual withdrawal symptoms most strongly related to relapse, such as negative affect (e.g., depressed mood), may increase understanding of the underlying mechanisms associated with the maintenance of nicotine addiction and requires further study.

Positive reinforcement from nicotine may play a more significant role in the initiation of smoking, and negative reinforcement, particularly relief from withdrawal, is an important contributor to the persistence of smoking and relapse. Measures of nicotine's reinforcing effects, especially the most common measure—self-reported number of cigarettes smoked per day—are consistently related to other indices of addiction, including the risk of relapse. However, other objective measures of nicotine's reinforcing effects, especially those reflecting persistence in smoking behavior, may provide even stronger markers of addiction for predicting clinical outcomes and for testing the efficacy of new treatments or tobacco products. Such measures may also be useful as endophenotypes of dependence for future research into the etiology of addiction, including the influence of a person's genetic composition. Therefore, the development of these validated markers and measures for nicotine and smoking reinforcement is critical for future research examining the etiology and treatments for nicotine addiction and for tobacco product testing.

Nicotine addiction results not only from the pharmacodynamic effects of nicotine but also from associative learning and conditioning. Nicotine serves not only as a US, but can also serve as a CS and a modifier of associative processes. Motivational influences on persistent smoking are more likely tied to negative reinforcement than to positive reinforcement.

Interoceptive (internal) cues of negative affect have been linked to craving and relapse, whereas positive affective states are less likely to lead to relapse. Exteroceptive (environmental) cues also play an important role in eliciting craving and relapse. Reactivity to both internal and environmental cues may provide another measure of nicotine addiction. Factors such as age, gender, and psychiatric comorbid history are important to consider in future research, because they have or may have an important role in moderating responses to nicotine (see "Epidemiology of Tobacco Use and Nicotine Dependence in Adults" later in this chapter). Because of the importance of learning in the development and maintenance of nicotine addiction, this is an area that requires more extensive research.

Pathophysiology of Nicotine Addiction

Because nicotine is one of the primary constituents responsible for tobacco addiction, research to promote an understanding of the neurobiology of tobacco addiction focuses on the mechanisms mediating nicotine addiction. As noted previously, dependence on nicotine is characterized by both the persistence of a drug-taking behavior and the emergence of withdrawal symptoms on abrupt cessation of nicotine administration (Wikler 1973; Levine 1974; Stewart et al. 1984; Ludwig 1986; O'Brien et al. 1990; Hughes and Hatsukami 1992; Koob et al. 1993; Markou et al. 1993, 1998; APA 1994; Kenny and Markou 2001). Therefore, both the neurosubstrates (brain structures, pathways, and systems) mediating the reinforcing effects of acute administration of nicotine and those

mediating the nicotine withdrawal syndrome are relevant to drug dependence. The physiological systems that develop adaptations to repeated nicotine administration and lead to the emergence of withdrawal signs on cessation of nicotine administration are likely to intersect with systems that mediate the acute effects of nicotine (Markou et al. 1998; Kenny and Markou 2001). That is, drug dependence develops as a neurobiologic adaptation to chronic drug exposure.

Accordingly, this section first reviews the systems and pathways mediating the reinforcing effects of nicotine and then discusses the neuroadaptations that occur because of chronic nicotine exposure. These neurobiologic adaptations mediate the tolerance to and effects of withdrawal from nicotine that are interlinked in most theoretical conceptualizations. Researchers have hypothesized that the sensitization to the locomotor-activating effects of drugs, including effects observed after repeated nicotine administrations, reflect a progressive augmentation in the motivation to self-administer the drug (Robinson and Berridge 1993). (The locomotor-activating effects consist of progressively increased locomotor responses to repeated drug-challenge injections.) However, no direct evidence suggests that sensitization to the locomotor-activating effects of nicotine reflects any aspect of dependence on nicotine. Therefore, sensitization is not covered in this section. If sensitization to the reinforcing effects of nicotine develops, it will most likely be relevant to early phases of tobacco use involving the acquisition of tobacco smoking as a continuing behavior.

The final discussion focuses on the comorbidity of nicotine dependence and psychiatric disorders in the context of shared substrates that mediate nicotine dependence and depression-like aspects of psychiatric disorders (Markou et al. 1998; Markou and Kenny 2002; Paterson and Markou 2007).

Nicotinic Acetylcholine Receptors

Nicotine, an alkaloid in concentrations of approximately 1 to 3 percent in tobacco (Browne 1990), is an agonist at the nicotinic acetylcholine receptors (nAChRs) expressed both in the peripheral nervous system and the CNS (Henningfield et al. 1996; Vidal 1996; Holladay et al. 1997; Paterson and Norberg 2000). Similar to other ligand-gated ion channels, neuronal nAChRs are composed of five membrane-spanning subunits that combine to form a functional receptor (Lindstrom et al. 1996; Role and Berg 1996; Albuquerque et al. 1997; Lèna and Changeux 1998, 1999; Dani 2000; Gotti et al. 2006). Neuronal nAChR subunits are arranged in different combinations to form nAChRs with distinct pharmacologic and kinetic properties. The neuronal α subunit exists in nine isoforms (α2 through α10), whereas the neuronal β subunit exists in three isoforms (β2, β3, and β4) (Arneric et al. 1995; Wonnacott 1997; Elgoyhen et al. 2001). Study of oocyte expression systems injected with pairwise combinations of different neuronal α and β subunits indicate that these subunits combine with a stoichiometry of 2α:3β to produce a functional neuronal nicotinic hetero-oligomeric receptor (Deneris et al. 1991; Conroy and Berg 1995; Colquhoun and Patrick 1997). In contrast, α7, α8, and α9 subunits form homo-oligomeric complexes composed of five α subunits and no β subunits (Chen et al. 1998). Only the α7 pentamer is expressed in the CNS.

Neuronal nAChRs in rats are divided broadly into three classes: (1) those with a high-affinity binding site for racemic nicotine—the nAChRs containing α4, of which the α4β2 combination is the most abundant (Flores et al. 1992; Picciotto et al. 1995); (2) those with a high affinity for the radioiodine [^{125}I]α-bungarotoxin that correspond to the homomeric α7 nAChRs (Clarke 1992); and (3) those with a high affinity for neuronal bungarotoxin—the α3-containing nAChRs (Schulz et al. 1991). The precise combinations of nAChR subunits that constitute active brain nAChRs in vivo have been primarily inferred from their pharmacologic profile (Sershen et al. 1997; Kaiser et al. 1998; Luo et al. 1998; Sharples et al. 2000). However, advances have identified nAChR subunits expressed by individual neurons in specific brain regions (Lèna et al. 1999; Sheffield et al. 2000).

The predominant role of nAChRs in the brain is the modulation of neurotransmitter release, because nAChRs are situated primarily on presynaptic terminals (Wonnacott 1997). Nevertheless, nAChRs are also found at somatodendritic, axonal, and postsynaptic sites (Sargent 1993). As a result of actions at the nAChR sites, nicotine stimulates the release of most neurotransmitters throughout the brain (Araujo et al. 1988; Toide and Arima 1989; McGehee and Role 1995; Gray et al. 1996; Role and Berg 1996; Wilkie et al. 1996; Albuquerque et al. 1997; Alkondon et al. 1997; Kenny et al. 2000; Grady et al. 2001). Therefore, as discussed in the next section, various transmitter systems are likely to be involved in the rewarding effects of nicotine and in the adaptations that occur in response to chronic exposure to nicotine, which give rise to dependence and withdrawal responses.

Neurosubstrates of Nicotine Reinforcement

The mesocorticolimbic brain system in the midbrain of mammals is composed of interconnected brain

structures. This system has been shown to be critically involved in the effects of drugs of abuse (Koob 2008). Among the main components of this system are the dopaminergic neurons originating in the ventral tegmental area (VTA) and projecting to the nucleus accumbens and the frontal cortex. The activity of these VTA dopamine neurons is regulated by the release of the excitatory neurotransmitter glutamate from neuronal projections originating from several sites, including the nucleus accumbens and the frontal cortex. Other inputs that also regulate activity of the mesolimbic system are (1) γ-aminobutyric acid (GABA) inhibitory interneurons located within the VTA and the nucleus accumbens and (2) cholinergic projections from brainstem nuclei to the VTA. These cholinergic projections release the endogenous neurotransmitter acetylcholine, which acts on excitatory nAChRs located on glutamate and GABA neuronal terminals in the VTA (Figure 4.4). Extensive investigations over decades have conclusively demonstrated a critical role of the mesocorticolimbic system and its connections in several behavioral and affective responses to drugs of abuse.

Dopamine and Nicotinic Acetylcholine Receptors

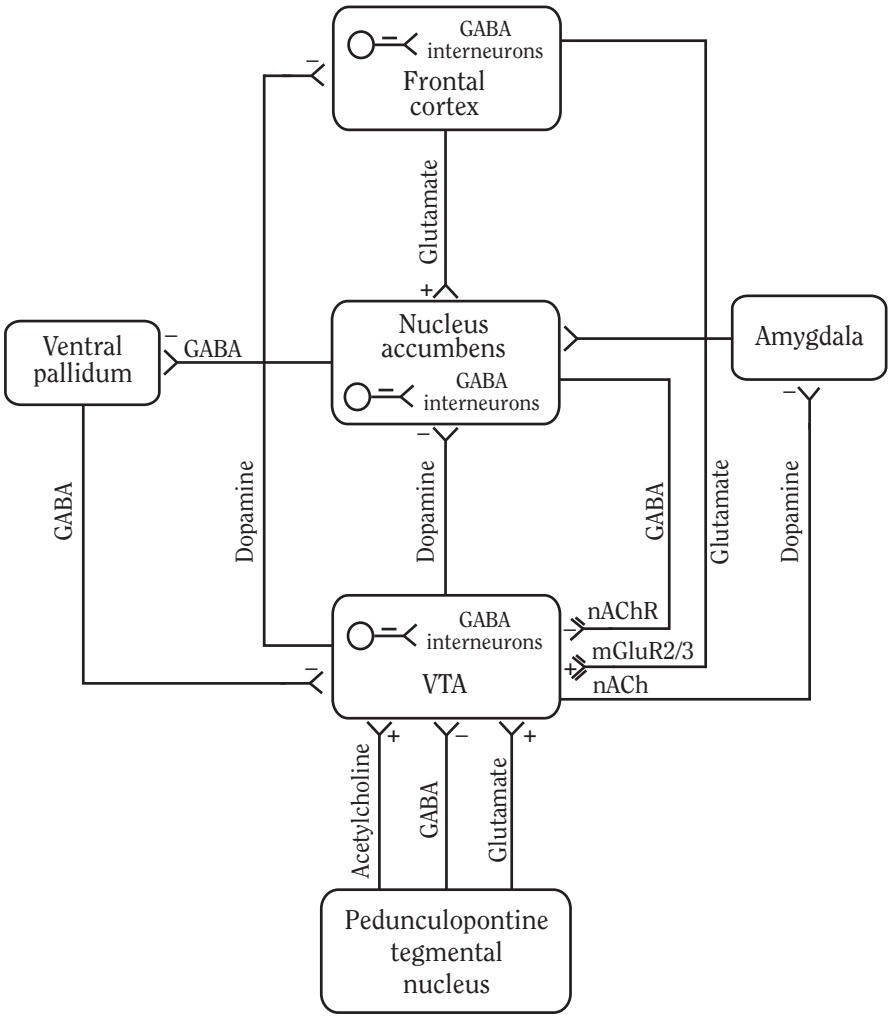
As with other drugs of abuse, it has been demonstrated that the mesolimbic dopaminergic system and nAChRs within that system are critically involved in the reinforcing properties of nicotine (Watkins et al. 2000; Picciotto and Corrigall 2002; Balfour 2004). Acute administration of nicotine increased the firing rate of dopaminergic neurons in the VTA (Grenhoff et al. 1986; Pidoplichko et al. 1997) and elevated dialysate levels of dopamine in the shell of the nucleus accumbens (Imperato et al. 1986; Damsma et al. 1989; Mifsud et al. 1989; Benwell and Balfour 1992; Pontieri et al. 1996; Nisell et al. 1997; Carboni et al. 2000). These effects of nicotine may occur through excitatory actions at nAChRs on the mesolimbic dopaminergic neurons in both the VTA and the nucleus accumbens and at nAChRs located on local neuronal circuitry within these brain regions (McGehee and Role 1996; Nisell et al. 1997; Teng et al. 1997). The nAChRs in the VTA play a more important role than those in the nucleus accumbens in the effects of nicotine on the release of dopamine from the nucleus accumbens (Nisell et al. 1994a,b, 1997).

Several findings support the conclusion that nAChRs located within the VTA are involved in nicotine reinforcement. Intravenous nicotine self-administration is a procedure that allows the assessment of the reinforcing effects of nicotine by measuring the number of infusions a rat chooses to receive intravenously through an indwelling permanent catheter by pressing a lever during one-hour daily sessions in a testing chamber. Each of four factors decreased intravenous nicotine self-administration in rats (Picciotto and Corrigall 2002). The factors were (1) injections of the competitive nAChR antagonist DHβE into the VTA (Williams and Robinson 1984) but not the nucleus accumbens (Corrigall et al. 1994), (2) development of lesions of the mesolimbic dopaminergic projections from the VTA to the nucleus accumbens (Corrigall et al. 1992), (3) development of cholinergic lesions of the brainstem pedunculopontine tegmental nucleus that project to the VTA (Lança et al. 2000), and (4) systemic administration of dopamine receptor antagonists (Corrigall and Coen 1991b). Studies suggest an involvement of the nAChR subtypes containing α4β2 in both the nicotine-induced release of dopamine and nicotine reinforcement (Picciotto et al. 1998; Schilström et al. 1998b; Watkins et al. 1999; Grillner and Svensson 2000; Sharples et al. 2000). In addition, mutant mice with hypersensitive α4 nAChRs show a 50-fold increase in sensitivity to the reinforcing effects of nicotine measured by a place-preference procedure (Tapper et al. 2004). A place-preference procedure assesses the rewarding effects of a drug by measuring the preference a rat exhibits for a compartment previously associated with the effects of a drug instead of a compartment associated with an injection of saline. The place-preference finding by Tapper and colleagues (2004) further indicates a critical role of α4 nAChRs in nicotine reinforcement. The α7 homomeric receptors may be involved in the reinforcing effects of nicotine. Methyllycaconitine, an antagonist with limited selectivity for the α7 nAChR, decreased the intravenous nicotine self-administration procedure in rats (Markou and Paterson 2001), although another study with rats showed no effects of this antagonist on nicotine-induced hyperactivity or nicotine self-administration (Grottick et al. 2000). Finally, both the α4β2 and α7 subtypes are implicated in the effects of nicotine on memory (Levin et al. 1999; Bancroft and Levin 2000) and the anxiolytic effects of nicotine (Gordon 1999; Cheeta et al. 2001), which also contribute to persistent tobacco use (USDHHS 1988).

Glutamate

Other mechanisms by which nicotine may elevate striatal dopamine levels include increases in excitatory glutamatergic inputs from the frontal cortex to the nucleus accumbens and/or excitatory glutamatergic inputs to VTA dopaminergic neurons projecting to the striatum. Nicotine increases the release of glutamate by agonist actions at excitatory presynaptic nAChRs on glutamatergic terminals in various brain sites, including the VTA (Fu et al. 2000; Grillner and Svensson 2000; Mansvelder and McGehee 2000), nucleus accumbens (Reid et al. 2000), prefrontal cortex (Gioanni et al. 1999), and hippocampus (Gray et al. 1996). In the VTA, nicotine acts

Figure 4.4 Neural pathways for γ-aminobutyric acid, glutamate, dopamine, and excitatory neurotransmitters



Source: Markou 2006. Reprinted with permission from Wiley-Blackwell, © 2006.
Note: The circular symbol with the reverse arrow attached to it depicts a neuron. The circle is the cell body, and the reverse arrow is the terminal that releases neurotransmitter(s) out of its open site into the synapse at the indicated projection brain site. The minus sign (-) indicates inhibitory input of the neurotransmitter, and the plus sign (+) indicates excitatory input of the neurotransmitter. Some neurons are interneurons projecting within a particular brain site, and other neurons project from one brain site to another distant brain site. **GABA** = γ-aminobutyric acid; **nAChR** = nicotinic acetylcholine receptor; **mGluR2/3** = metabotropic glutamate 2/3 receptor; **VTA** = ventral tegmental area.

at presynaptic α7 nAChRs located on glutamate neurons (neurons that release glutamate as the primary neurotransmitter). Activation of these α7 nAChRs on glutamate neurons (Mansvelder and McGehee 2000) increases the release of glutamate in the VTA. This activity, in turn, stimulates the release of dopamine in the nucleus accumbens (Nisell et al. 1994a,b; Schilström et al. 1998a,b; Fu et al. 2000; Mansvelder and McGehee 2000). That is, this increased release of glutamate acts at metabotropic and ionotropic glutamate receptors located on postsynaptic dopamine neurons (neurons that have dopamine as the primary neurotransmitter). Activation of these glutamate receptors leads to excitation of the dopamine neurons that results in increased release of dopamine in terminal brain sites where these neurons project, such as the nucleus accumbens, the amygdala, and the frontal cortex.

Ionotropic antagonists of *N*-methyl-D-aspartate receptors blocked (prevented) tolerance to the locomotor depressant effects of acute nicotine administration (Shoaib and Stolerman 1992; Shoaib et al. 1994) and blocked sensitization to the locomotor stimulant effects of chronic nicotine administration (Shoaib and Stolerman 1992). Most relevant to addiction is the finding that blockade of the postsynaptic metabotropic glutamate receptor subtype 5 (mGluR5) with 2-methyl-6-(phenylethynyl)pyridine (MPEP) decreased intravenous nicotine self-administration in rats and mice (Paterson et al. 2003) and decreased the motivation to self-administer nicotine (Paterson and Markou 2005). These effects are likely mediated by decreasing the nicotine-stimulated release of dopamine in the mesolimbic system. At doses that blocked nicotine self-administration, MPEP had no effect on response for food (Paterson et al. 2003). The progressive-ratio schedule of reinforcement, which gradually increases the response requirements after each earned reward, allows the assessment of the motivation for reinforcers, such as nicotine or food, by evaluating the maximal number of responses emitted by the rat (i.e., breaking point) to receive a single intravenous infusion of nicotine or a single food reward. In this schedule, MPEP had a greater effect on motivation for nicotine than on motivation for food, even when the magnitudes of reinforcer value were equated to support equal breaking points for nicotine and food under baseline conditions (Paterson and Markou 2005). This selectivity of the MPEP effects for nicotine reinforcement versus food reinforcement suggests that MPEP selectively blocks the reinforcing effects of nicotine without affecting motor performance or food reinforcement. Furthermore, evidence suggests a potential role of ionotropic glutamate receptors in the effects of nicotine. Animals that self-administered nicotine chronically exhibited an increase in ionotropic glutamate receptor subunits in brain regions, such as the VTA and the frontal cortex, that are implicated in the reinforcing effects of nicotine (Wang et al. 2007).

γ-Aminobutyric Acid

GABA is the major inhibitory transmitter in the brain and is another transmitter system critically involved in the reinforcing effects of acute nicotine administration. Several factors inhibit the release of mesolimbic dopamine, including inhibitory GABA transmission on ascending afferents to dopaminergic VTA neurons from the pedunculopontine tegmental nucleus (Walaas and Fonnum 1980; Yim and Mogenson 1980), descending GABA-ergic inputs from the ventral pallidum and the nucleus accumbens, GABA interneurons within the VTA, and medium spiny GABA neurons in the nucleus accumbens (Walaas and Fonnum 1979; Heimer and Alheid 1991; Churchill et al. 1992; Dewey et al. 1992; Kalivas et al 1992; Klitenick et al. 1992; Sugita et al. 1992; Engberg et al. 1993). As suggested by this neuroanatomy and extensive electrophysiological studies, interactions between the GABA, dopaminergic, and glutamatergic systems in the VTA are complex (Mansvelder and McGehee 2000; Mansvelder et al. 2002). Glutamate afferents to the VTA excite dopamine neurons, and GABA-ergic afferents to the VTA inhibit dopamine neurons. Excitatory nAChRs are located on both glutamate and GABA-ergic neurons. The nAChRs on GABA neurons desensitize quickly to chronic administration of nicotine, but the nAChRs on glutamate neurons require higher doses of nicotine for desensitization. This delicate balance leads to a nicotine-induced increase in the release of dopamine in the nucleus accumbens, the terminal area of VTA neurons (Schilström et al. 1998b; Mansvelder and McGehee 2000). Similar transmitter interactions may also occur in other brain sites.

Increased GABA-ergic transmission abolishes both the nicotine-induced increases in dopamine in the nucleus accumbens and the reinforcing effects of nicotine (Dewey et al. 1999; Brebner et al. 2002). Systemic injections of γ-vinyl GABA (vigabatrin) increased GABA levels and decreased nicotine self-administration in rats (Paterson and Markou 2002). Vigabatrin is an irreversible inhibitor of GABA transaminase, the primary enzyme involved in GABA metabolism (Jung et al. 1977; Lippert et al. 1977). Systemic injections of vigabatrin also abolished the expression and acquisition of nicotine-induced conditioned place preference (Dewey et al. 1998). The administration of vigabatrin also lowered nicotine-induced increases in dopamine in the nucleus accumbens in both untreated rats and those receiving long-term treatment with nicotine in a dose- and time-dependent manner measured by in vivo microdialysis. In addition, vigabatrin abolished nicotine-induced increases in striatal dopamine in primates, as determined by PET scan (Brebner et al. 2002).

The use of receptor-selective agonists in animals suggests the involvement of $GABA_B$ receptors in the reinforcing effects of nicotine. Systemic injections or microinjections of baclofen or CGP44532 [(3-amino-2[*S*]-hydroxypropyl)-methylphosphinic acid]—two $GABA_B$ receptor agonists—into the nucleus accumbens shell, the VTA, or the pedunculopontine tegmental nucleus that sends cholinergic, GABA-ergic, and glutamatergic projections to the VTA decreased the reinforcing effects of nicotine (Shoaib et al. 1998; Corrigall et al. 2000, 2001; Fattore et al. 2002; Paterson et al. 2004). However, injections into the caudate-putamen did not have these effects. The decreases in nicotine self-administration persisted even after administration of CGP44532 for 14 days, indicating

little tolerance to this effect of the $GABA_B$ receptor agonist with this duration of treatment (Paterson et al. 2005b); that is, the reduction in nicotine self-administration persisted over time. The issue of tolerance is important because long-term administration of drug therapies is necessary to achieve smoking cessation. However, in studies of rats, vigabatrin and $GABA_B$ receptor agonists also decreased response for food, although at doses higher than the threshold doses for inducing decreases in nicotine self-administration (Paterson and Markou 2002; Paterson et al. 2004, 2005b). These effects on response for food may reflect nonspecific effects on performance by GABA-ergic compounds or specific effects on food intake. The possibility of effects on food intake is intriguing, because weight gain associated with abstinence from smoking is often a concern for smokers, especially women, who want to stop smoking cigarettes.

Thus, increased GABA transmission through the activation of $GABA_B$ receptors blocks the reinforcing effects of nicotine. However, a clinical study shows that one dose of baclofen had no effect on either the number of cigarettes smoked or the craving for nicotine (Cousins et al. 2001). Nevertheless, other clinical studies show that long-term administration of baclofen reduced abuse of cocaine and alcohol, as well as cue-induced brain activation (Ling et al. 1998; Addolorato et al. 2000, 2002a,b). Therefore, long-term treatment with these GABA-ergic drugs may first be required to reduce tobacco smoking.

Opioid, Endocannabinoid, and Serotonin Systems

The data on the possible role of opioid systems in the rewarding effects of nicotine remain inconclusive. Nicotine did not induce a conditioned place preference in μ-opioid receptor **NULL*-mutant mice, but it did so in wild-type animals (Berrendero et al. 2002). Similarly, nicotine induced a conditioned place preference in wild-type but not in preproenkephalin **NULL*-mutant mice. A nicotine-induced elevation in dopamine overflow in the nucleus accumbens was absent in **NULL* mutants (Berrendero et al. 2005). However, systemic or intra-VTA administration of the opiate receptor antagonist naltrexone or the opiate receptor agonist D-Ala^2,*N*-Me-Phe^4-Gly-ol-enkephalin, respectively, had limited or no effects on nicotine self-administration in rats (Corrigall and Coen 1991a; Corrigall et al. 2000).

In humans, acute and short-term nicotine administration leads to the release of β-endorphins, endogenous opioid peptides that have reinforcing effects (Davenport et al. 1990; Boyadjieva and Sarkar 1997). Furthermore, in humans, the acute administration of naltrexone decreased the reinforcing value of nicotine in a procedure involving choice between puffs on nicotinized versus denicotinized cigarettes (i.e., compared with placebo, naltrexone significantly reduced the number of nicotine cigarette choices) (Rukstalis et al. 2005). This result is consistent with a previous finding that acute administration of naltrexone significantly decreased the total number of choice cigarettes smoked (e.g., subjects were given a choice to smoke four cigarettes in a two-hour period of time) (Epstein and King 2004). However, a randomized, double-blind trial of naltrexone for smoking cessation found only a nonsignificant trend toward increased cessation rates, and the effect disappeared at 12 months after cessation (Covey et al. 1999). Other clinical trials examining the effects of naltrexone versus placebo in smokers who were assigned nicotine patches to aid cessation have also observed no significant effects of naltrexone on improving treatment outcomes (King et al. 2006; O'Malley et al. 2006). Thus, the possible involvement of the opiate system in the reinforcing effects of nicotine remains at best unclear, and the use of opiate antagonists as treatments for dependence on tobacco smoking appears unwarranted. A Cochrane review in 2001 concluded that opioid antagonists failed to significantly increase long-term abstinence from smoking on the basis that the limited evidence was insufficient to support a conclusive finding on whether naltrexone is an aid to smoking cessation (David et al. 2006). Although one study suggested an effect of gender, women benefited more than men from treatment with naltrexone (King et al. 2006).

The evidence is much stronger for the role of serotonin in the reinforcing effects of nicotine. Acute administration of nicotine elevated extracellular serotonin in the nucleus accumbens (Schiffer et al. 2001) and the VTA (Singer et al. 2004). Serotonin was also implicated in a neurochemical sensitization to nicotine, which some researchers hypothesize to be relevant to aspects of nicotine dependence. The administration of the serotonin ($5HT_2$) receptor agonist (±)-2,5-dimethoxy-4-iodoamphetamine (Olausson et al. 2001) or the $5HT_{2C}$ receptor agonist (*S*)-2-(chloro-5-fluoro-indol-1-yl)-1-methylethylamine fumarate (Di Matteo et al. 2004) blocked the increased overflow of serotonin observed after a nicotine challenge in nicotine-treated rats. In addition, nicotine increased serotonin overflow in cortical areas (Toth et al. 1992; Ribeiro et al. 1993; Summers and Giacobini 1995; Singer et al. 2004) and in the dorsal hippocampus (Singer et al. 2004). In contrast, Balfour and Ridley (2000) found a decrease in the serotonin overflow after acute administration of nicotine. However, Singer and colleagues (2004) used anesthetized rats, and Balfour and Ridley (2000) used in vivo microdialysis in conscious rats. In addition, administration of nicotine for at least 20 days was associated with decreased serotonin levels in the dorsal hippocampus (Benwell and Balfour 1979; Balfour and Ridley

2000). However, nicotine administration for 14 days was associated with increased serotonin levels (Takada et al. 1995). Nicotine infusion into the ventromedial nuclei or the lateral hypothalamic area increased the release of serotonin in this area (Yang et al. 1999; Ramos et al. 2004). Together, the findings suggest that acute administration of nicotine increases serotonin levels but that long-term administration leads to decreases in serotonin levels that may mediate the affective aspects of nicotine dependence and withdrawal (Harrison et al. 2001).

Studies provide conflicting evidence on the role of cannabinoid subtype 1 (CB_1) receptors in modulating the reinforcing effects of nicotine. CB_1 knockout mice (i.e., mice genetically engineered to lack CB_1 receptors) self-administered nicotine (Cossu et al. 2001) but did not exhibit conditioned place preference to nicotine (Castañe et al. 2002). Furthermore, the CB_1 receptor antagonist rimonabant (SR141716) decreased nicotine seeking and self-administration of nicotine induced by the presentation of conditioned cues and also attenuated a nicotine-induced release of dopamine in the nucleus accumbens shell (Cohen et al. 2002, 2005; De Vries et al. 2005). Thus, the data from experimental studies of rodents on the role of the cannabinoid system are inconclusive and so are the clinical data (Le Foll and Goldberg 2005). However, an analysis of data pooled from three clinical trials of rimonabant compared with a placebo showed modest success at the end of treatment (Cinciripini et al. 2006).

Norepinephrine

Data also suggest a role of norepinephrine in the effects of nicotine. Acute nicotine administration increases extracellular norepinephrine in the nucleus accumbens, the hippocampus, and the cortex in rats (Brazell et al. 1991; Mitchell et al. 1993; Summers and Giacobini 1995; Benwell and Balfour 1997; Schiffer et al. 2001). Nicotine-evoked hippocampal release of norepinephrine in vivo was attenuated by α-bungarotoxin but was unaffected by either of the nAChR antagonists mecamylamine or DHβE, implicating α7 nAChRs, rather than α4β2 nAChRs associated with the release of norepinephrine in this region of the brain (Fu et al. 1999). However, norepinephrine release from hippocampal synaptosomes in rats was sensitive to mecamylamine, DHβE, and methyllycaconitine suggesting that the release of norepinephrine may not be specific to α7 nAChRs (Clarke and Reuben 1996). Additional studies suggest the role of norepinephrine in nicotine's effects. Intravenous self-administration of nicotine increased norepinephrine concentrations in the amygdala and the hypothalamic paraventricular nucleus (Fu et al. 2001, 2003). In vitro studies indicated that nicotine increased release of norepinephrine in (1) prefrontal cortex slices of rats (Rao et al. 2003) and (2) locus coeruleus neurons of fetal rats grown in cultures (Gallardo and Leslie 1998).

Consistent with these neurochemical findings, short-term or long-term administration of reboxetine, the selective noradrenaline reuptake inhibitor, decreased nicotine self-administration in rats (Rauhut et al. 2002). However, reboxetine also decreased sucrose-maintained response, although to a lesser degree than nicotine-maintained response. Reboxetine acts as a noncompetitive nAChR antagonist, in addition to blocking noradrenaline reuptake (Miller et al. 2002). Thus, it is not conclusive that the effects of reboxetine on nicotine self-administration are attributable to its effects on noradrenaline reuptake rather than to its actions as an nAChR antagonist.

Bupropion, a smoking cessation aid, also inhibits reuptake of norepinephrine, as well as dopamine (Ferris et al. 1983). Administration of bupropion increased extracellular concentrations of dopamine and epinephrine in the nucleus accumbens, hypothalamus, and prefrontal cortex (Nomikos et al. 1989, 1992; Li et al. 2002). Furthermore, electrophysiological studies indicated that bupropion decreased the firing rates of dopamine neurons in the nucleus accumbens and noradrenergic neurons in the locus coeruleus but had no effect on firing of serotonin dorsal raphe neurons (neurons located in the dorsal raphe firing) (Cooper et al. 1994).

Despite the demonstrated effects of bupropion on neurotransmitter and receptor systems that appear to mediate the effects of nicotine, bupropion had inconsistent effects on nicotine self-administration in rats. Some studies showed a decrease in nicotine self-administration in fixed-ratio schedules of reinforcement but had no effects in a progressive-ratio schedule (Glick et al. 2002; Bruijnzeel and Markou 2003). In contrast, another study (Shoaib et al. 2003) indicated that repeated daily administration of bupropion increased nicotine self-administration in a fixed-ratio schedule, but the results were not significant (Shoaib et al. 2003). Finally, Rauhut and coworkers (2003) showed that low doses of bupropion increased and high doses of bupropion decreased nicotine self-administration and response for sucrose.

In summary, these findings suggest a strong effect of nicotine on transmission of norepinephrine, but bupropion, which inhibits the reuptake of both dopamine and norepinephrine, has inconsistent effects on nicotine self-administration in rodents. Thus, other properties of bupropion, such as relief from withdrawal symptoms, may contribute to its efficacy as an aid to smoking cessation.

Neurosubstrates of Nicotine Dependence and Withdrawal

Nicotine Withdrawal Syndrome in Rodents

Smoking cessation leads to an aversive withdrawal syndrome lasting one to four weeks after cessation (Shiffman et al. 2004b). As noted previously, this withdrawal syndrome has affective, behavioral, somatic, and cognitive components (see "Physiological Mechanisms and Indicators: Nicotine Tolerance, Withdrawal, and Reinforcement" earlier in this chapter). The nicotine withdrawal syndrome is considered an important motivational factor that contributes to the perpetuation of nicotine dependence and continuing behaviors related to tobacco smoking (Markou et al. 1998; Kenny and Markou 2001). Withdrawal signs are often opposite to the acute effects of the drug (e.g., improved concentration versus poor concentration), probably reflecting the finding that the development of nicotine dependence leads to changes in brain function to counteract the acute effects of nicotine (e.g., increase in receptor number).

One of the first and most widely used measures developed to investigate the neurobiology of the nicotine withdrawal syndrome and nicotine dependence is the frequency of somatic signs reliably observed in rats, but less reliably observed in mice (Malin et al. 1992; Epping-Jordan et al. 1998; Hildebrand et al. 1999; Isola et al. 1999; Carboni et al. 2000; Malin 2001; Semenova and Markou 2003; Salas et al. 2004). The most prominent somatic signs in rats are abdominal constrictions (writhes), gasps, ptosis, facial fasciculation, and eyeblinks. These somatic signs are both centrally and peripherally mediated (Hildebrand et al. 1999; Carboni et al. 2000; Watkins et al. 2000; Malin 2001; Cryan et al. 2003).

The somatic components of nicotine withdrawal are unpleasant. However, avoidance of the negative affect and depression-like components of withdrawal may play a more important role in the maintenance of nicotine dependence than do the somatic aspects of withdrawal (Hughes 1992; Kenny and Markou 2001). In rodents, a valid and reliable measure of the affective and motivational aspects of drug withdrawal is the elevation of brain-reward thresholds observed after cessation of long-term administration of nicotine (Epping-Jordan et al. 1998; Harrison et al. 2001; Cryan et al. 2003; Semenova and Markou 2003). Elevations of reward thresholds are an operational measure of "diminished interest or pleasure" in rewarding stimuli (i.e., anhedonia), which is a symptom of nicotine withdrawal and a core symptom of depression (APA 1994). Similar threshold elevations are observed during withdrawal from all major drugs of abuse in rodents (Kokkinidis et al. 1980; Markou and Koob 1991; Schulteis et al. 1994, 1995; Paterson et al. 2000; Spielewoy and Markou 2003). Several dissociations have been identified between the threshold elevations and the somatic signs of nicotine withdrawal, and these observations are similar to those in clinical studies (see "Physiological Mechanisms and Indicators: Nicotine Tolerance, Withdrawal, and Reinforcement" earlier in this chapter). These findings suggest that the various aspects of withdrawal are mediated by different substrates (Epping-Jordan et al. 1998; Watkins et al. 2000; Harrison et al. 2001; Semenova and Markou 2003). Other rodent models that may be relevant to the disruption of behavioral performance in humans involve (1) disruptions induced by termination of administration of nicotine on behavioral responses maintained by food (Carroll et al. 1989); (2) increases in the acoustic startle response in rats (Helton et al. 1993); and (3) decreases in prepulse inhibition (i.e., decrease in the adaptation response to a stronger stimuli after presentation of a prior weaker stimuli) in mice (Semenova et al. 2003).

Important study data indicate that rats with threshold elevations reflecting a reward deficit associated with nicotine withdrawal can become conditioned to previously neutral environmental stimuli (Kenny and Markou 2005) (see "Learning and Conditioning" earlier in this chapter). Nicotine-dependent rats were presented with a light and tone CS and received injections of the nicotinic receptor antagonist DHβE for four consecutive days before an assessment of brain-reward thresholds. This procedure led to elevations of brain-reward thresholds in the nicotine-dependent rats. When the rats were presented with just the light and tone CS on the test day, thresholds were again elevated, reflecting a conditioned state of negative affect. This type of conditioned affective response may lead to a relapse to tobacco smoking to alleviate this conditioned state of negative affect. This finding may partly explain the relapse observed months or even years after a person last smoked a cigarette.

Subsequent data suggest that the experience of nicotine withdrawal in male adolescent rats may differ from that in adult rats. At the time of this review, no females have been tested. The evidence for this hypothesis is threefold. First, male adolescent rats displayed fewer somatic signs of nicotine withdrawal than did adult males. Second, although male adolescent rats displayed a conditioned place aversion produced by nicotine withdrawal, it was less robust than that seen in adult males. Third, adolescent male rats did not display the decreases in brain-reward function seen in adult rats experiencing withdrawal (O'Dell et al. 2006, 2007).

Neurochemical Correlates of Nicotine Withdrawal

Several experimental approaches are used to investigate the neuronal substrates of nicotine dependence and withdrawal. In vivo microdialysis studies provide information about the neurochemical changes occurring in specific brain sites with nicotine dependence. The precipitation of nicotine withdrawal in nicotine-treated rats, but not in controls, with administration of drugs that probe various transmitter systems and receptors suggests that chronic exposure to nicotine induces adaptations in specific transmitter systems and receptors. The combination of the in vivo microdialysis technique with the precipitated nicotine withdrawal technique indicates that the circuits mediating the acute effects of nicotine develop adaptations with nicotine dependence that lead to the withdrawal syndrome (Figure 4.4 depicts the brain structures and their interconnections forming circuits discussed in this chapter).

During nicotine withdrawal precipitated by systemic or intra-VTA administration of the nAChR antagonist mecamylamine in nicotine-treated rats, dialysate levels of dopamine were decreased in the nucleus accumbens (Fung et al. 1996; Hildebrand et al. 1998; Carboni et al. 2000) and in the central nucleus of the amygdala (Panagis et al. 2000). These mecamylamine injections into the VTA also produced, in a dose-dependent manner, most of the somatic signs of nicotine withdrawal (Hildebrand et al. 1999). This finding suggests the involvement of nAChRs in the VTA in the expression of the somatic signs of nicotine withdrawal. Most important, similar decreases in levels of dopamine in the nucleus accumbens were observed in rats allowed to self-administer nicotine for 25 days, beginning 24 to 48 hours after the last session for self-administration of nicotine (Rahman et al. 2004). Decreases in dopamine levels in the nucleus accumbens are also associated with withdrawal from other drugs of abuse, such as ethanol, morphine, cocaine, and amphetamine (Rossetti et al. 1992). In contrast, the increases in dialysate dopamine levels observed in the frontal cortex (Hildebrand et al. 1998; Carboni et al. 2000) were similar to those observed during withdrawal from other drugs of abuse (Imperato et al. 1986). Thus, it appears that common substrates are involved in the mediation of the withdrawal signs associated with different drugs of abuse that involve alterations in dopamine transmission in the nucleus accumbens and the frontal cortex.

The smoking cessation aid bupropion, an atypical antidepressant, acts at least partly by inhibiting the neuronal uptake of dopamine, which thereby increases dopamine transmission (Nomikos et al. 1992). Bupropion reverses both the threshold elevations and the somatic signs associated with nicotine withdrawal (Cryan et al. 2003) in rats, although its effects on nicotine self-administration are inconsistent (Glick et al. 2002; Bruijnzeel and Markou 2003; Shoaib et al. 2003). Taken together, the above data strongly suggest that a decrease in mesolimbic dopaminergic transmission mediates aspects of nicotine withdrawal.

Another transmitter system that may be involved in nicotine dependence and withdrawal is the norepinephrine system. However, to date, the role of this system in nicotine dependence has not been investigated as extensively as that of the dopamine system. Acute administration of nicotine elevates extracellular noradrenaline levels in the nucleus accumbens (Schiffer et al. 2001), hippocampus (Brazell et al. 1991; Mitchell et al. 1993; Benwell and Balfour 1997), cortex (Summers and Giacobini 1995), amygdala, and hypothalamic paraventricular nucleus (Fu et al. 2001). These findings indicate that nicotine withdrawal may be characterized by a decrease in noradrenergic transmission. This hypothesis is supported by evidence for the beneficial effects on smoking cessation of nortriptyline, a norepinephrine reuptake inhibitor (Hughes et al. 2004b) and the ameliorative effects of the α2-adrenoceptor agonist clonidine on nicotine withdrawal in double-blind, placebo-controlled studies (Covey and Glassman 1991).

Other neurotransmitter systems such as serotonin, endocannabinoid, or opioid may also be involved in withdrawal, but research on these systems is limited. A few studies suggest the involvement of the opioid system. For example, naloxone precipitates somatic signs of withdrawal in nicotine-dependent rats (Malin et al. 1993; Watkins et al. 1999). Some studies also demonstrate the involvement of the serotonin system (see "Antidepressant and Antipsychotic Drugs and Nicotine Withdrawal" later in this chapter).

Receptors and Behavioral Signs of Nicotine Withdrawal

Studies document that administration of a variety of nAChR antagonists induces behavioral signs of withdrawal in addition to the neurochemical effects of withdrawal in nicotine-treated rats. Systemic or intra-VTA administration of mecamylamine or systemic or intraventricular administration of chlorisondamine induced somatic signs and/or elevation of reward threshold in nicotine-dependent rats only (Hildebrand et al. 1999; Watkins et al. 2000). Administration of the nAChR antagonist DHβE, which is selective for high-affinity nAChRs containing α4 (Harvey and Luetje 1996), induced threshold elevations (Epping-Jordan et al. 1998; Bruijnzeel and Markou 2004) but did not induce increases in somatic signs in nicotine-dependent rats (Epping-Jordan et al. 1998). This finding demonstrates that the threshold elevations are not

due to nonspecific performance effects of the antagonists. Together, these results illustrate the involvement of nAChRs in the VTA in both the somatic and affective aspects of withdrawal.

In addition, work in knockout mice demonstrates a critical role of β4 but not β2 nAChRs in the somatic signs of withdrawal (Salas et al. 2004; Jackson et al. 2008). β2 nAChRs are critical for the reinforcing effects of nicotine (Picciotto and Corrigall 2002) and for the affective signs of nicotine withdrawal, as reflected in anxiety-like behavior and conditioned place aversion (Jackson et al. 2008). The α7 homomeric nAChRs may be involved in the reinforcing effects of nicotine (Markou and Paterson 2001) and perhaps only in some somatic aspects but not in the affective aspects of nicotine withdrawal (Markou and Paterson 2001; Jackson et al. 2008). Specifically, administration of the α7 nAChR antagonist methyllycaconitine did not precipitate either the typical somatic signs of nicotine withdrawal or the reward deficits reflected in threshold elevations in nicotine-dependent rats (Markou and Paterson 2001). However, in α7 knockout mice, no hyperalgesia was present during nicotine withdrawal, an effect seen in wild-type mice during nicotine withdrawal (Jackson et al. 2008). However, these α7 knockout mice showed normal levels of somatic and affective signs of nicotine withdrawal. Thus, the role of α7 nAChRs may be limited to some somatic signs, including hyperalgesia, of nicotine withdrawal. Finally, α4 nAChRs have been shown to be involved in the reinforcing effects of nicotine (Tapper et al. 2004). Their role in nicotine withdrawal has not been clearly delineated, but it may influence both affective and somatic withdrawal effects (Salas et al. 2004; Gonzales et al. 2006; Jorenby et al. 2006; Jackson et al. 2008). Overall, the observation that nAChR antagonists precipitate the behavioral and neurochemical signs of withdrawal in nicotine-dependent rats, but not in controls, suggests that chronic exposure to nicotine induces a compensatory reduction in endogenous cholinergic tone that leads to the nicotine withdrawal syndrome.

Because glutamate stimulates dopamine release (Schilström et al. 1998a; Mansvelder and McGehee 2000), decreased glutamate transmission may mediate nicotine withdrawal. Systemic or intra-VTA administration of the mGluR subtype 2/3 (mGluR2/3) agonist LY314582 led to withdrawal-like threshold elevations in nicotine-dependent rats but not in control rats (Kenny et al. 2003). These mGluR2/3 receptors are found primarily presynaptically (i.e., on the transmitting neuron at the synaptic terminal that extends to the synapse, and the released transmitters target the postsynaptic neuron), where they inhibit glutamate transmission (Cartmell and Schoepp 2000; Kenny and Markou 2004). The increased sensitivity of nicotine-dependent rats to an agonist at the presynaptic inhibitory mGluR2/3 suggests that nicotine dependence is characterized by increased inhibition of glutamate transmission through these receptors, resulting in decreases in the release of glutamate when nicotine is no longer present to stimulate glutamate release. Consistent with this hypothesis, the mGluR2/3 antagonist LY341495 reversed the threshold elevations observed in rats that had spontaneous nicotine withdrawal (Kenny et al. 2003). Similarly, activity decreased in postsynaptic α-amino-3-hydroxy-5-methyl-4-isoxazole proprionic/kainate receptors, although no adaptations in mGluR5 receptors were observed in nicotine-dependent rats (Kenny et al. 2003). This result was somewhat surprising considering the important role found for this receptor in the reinforcing effects of nicotine (Paterson et al. 2003; Paterson and Markou 2005). Taken together, all of the above findings indicate that decreased glutamate transmission resulting from adaptations in presynaptic and postsynaptic receptors may contribute to the affective aspects of nicotine withdrawal.

These data on the lack of adaptations in mGluR5 activity highlight the finding that not all systems involved in the reinforcing effects of nicotine develop changes with long-term exposure to nicotine. This notion is also supported by data demonstrating that there are no changes in GABA transmission, $GABA_B$ receptor activity, or α7 nAChR activity in nicotine-dependent rats, despite the important role of the $GABA_B$ receptor and possibly the α7 nAChR in the reinforcing effects of nicotine (Markou and Paterson 2001; Paterson and Markou 2002; Paterson et al. 2004, 2005a,b).

Molecular Mechanisms

Activated nAChRs are permeable to both sodium ions and Ca^{2+}, which lead to activation of the neurons and thus the release of many transmitters (Wonnacott et al. 2005). The widespread brain activation induced by acute or long-term administration of nicotine is shown by the expression of *C-FOS* in areas such as the amygdala, bed nucleus of the stria terminalis, lateral septum, hypothalamic nuclei, striatum, parts of the cortex, superior colliculus, optic tract, interpeduncular nucleus, supramammillary nucleus, periaqueductal gray matter, nucleus of the solitary tract, and locus coeruleus (Merlo Pich et al. 1999). *C-FOS*–related antigens are C-FOS proteins that heterodimerize with C-JUN proteins to produce complexes of activator protein-1 and transcriptionally regulate large numbers of genes related to plasticity (Dobranzki et al. 1991; Merlo Pich et al. 1997).

Another protein researchers have studied extensively is the cyclic adenosine monophosphate–response element binding protein (CREB), because it is part of the signaling cascade for several receptors, including nAChRs (Nestler 2001). Acute treatment with nicotine had no effect on levels of total CREB or phosphorylated CREB (p-CREB). However, 18 hours after withdrawal from long-term administration of nicotine, total concentrations of CREB and p-CREB decreased in the shell but not in the core of the nucleus accumbens (Pluzarev and Pandey 2004) and in the medial and basolateral amygdala but not in the central amygdala (Pandey et al. 2001). The high Ca^{2+} permeability of nAChRs also leads to the stimulation of additional intracellular messenger systems such as calmodulin-dependent protein kinases, including Ca^{2+} calmodulin-dependent protein kinase II (CaMKII), which is the most abundant kinase in the brain (Schulman and Hanson 1993). Acute administration of nicotine in mice induced increases in CaMKII expression in the spinal cord that was involved in the antinociceptive effects of nicotine (Damaj 2000).

These are a few examples of the molecular changes observed after acute or long-term administration of nicotine and on withdrawal from long-term administration. These molecular changes demonstrate that nicotine induces changes in molecular mechanisms involved in long-term plasticity. Such molecular effects are likely to mediate several aspects of dependence on nicotine.

Clinical Imaging Studies

Clinical imaging studies have confirmed findings from basic research in rodents and have provided additional critical information about brain sites and processes involved in tobacco addiction in humans that cannot readily be investigated in animals (e.g., hedonic responses and craving). Some of the effects of nicotine in various regions of the brain have also been described elsewhere (see "Learning and Conditioning" earlier in this chapter). Similar to other drugs of abuse, nicotine decreases global glucose metabolism in the brain, as determined by PET with [^{18}F]fluorodeoxyglucose (Stapleton et al. 2003). Long-term exposure to tobacco smoke also inhibits MAOA and MAOB activity (Volkow et al. 1999). Congruent with the suggested role of mesolimbic dopamine in the rewarding effects of nicotine in rodents, PET studies with [^{11}C]raclopride indicate that cigarette smoking increased dopamine levels in the striatum of smokers (Brody et al. 2004b) and that the hedonic response of the smoker to cigarette smoking was proportional to the dopamine released in the striatum (Barrett et al. 2004). Other areas activated by nicotine or smoking are the prefrontal cortex, ventral putamen, anterior cingulated cortex, superior parietal cortex, and thalamus (Kumari et al. 2003; Rose et al. 2003b; Brody et al. 2004b; Fallon et al. 2004; Jacobsen et al. 2004; Brody 2006). Smoking-associated images during inductions of craving that often lead to smoking increased the functional magnetic resonance imaging signal in reward circuits such as the right posterior amygdala, posterior hippocampus, VTA, and medial thalamus (Due et al. 2002). As mentioned previously, long-term administration of bupropion attenuated cue-induced craving and led to blunted activation of the perigenual and ventral anterior cingulate cortex (Brody et al. 2004a).

Functional magnetic resonance imaging was used in an interesting comparison of the effects of nicotine on the brains of patients with schizophrenia and the brains of control participants. Nicotine-induced activation of the anterior cingulate cortex and bilateral thalamus was greater in patients with schizophrenia than in control participants during performance of a cognitive task (Jacobsen et al. 2004). This finding suggests that nicotine may improve cognitive performance in patients with schizophrenia by enhancing the thalamocortical functional connectivity (Jacobsen et al. 2004) (see "Schizophrenia and Nicotine Dependence" later in this chapter). Relevant to the high prevalence of smoking among patients with depression, smokers showed cortical responses suggesting vulnerability to depression in a study that used tryptophan depletion to increase the depressed mood in smokers (Pergadia et al. 2004).

Psychiatric Comorbidity

Antidepressant and Antipsychotic Drugs and Nicotine Withdrawal

Another experimental approach used to identify systems that mediate nicotine withdrawal and dependence is a study of pharmacologic manipulations that reverse spontaneous nicotine withdrawal. Inferences can be made regarding the underlying abnormality associated with withdrawal through the mechanisms associated with the pharmacotherapy. On the basis of the phenomenological similarities among depression, the depression-like aspects of nicotine withdrawal, and the negative symptoms of schizophrenia, researchers hypothesize that overlapping neurobiologic substrates may mediate these depressive symptoms and that antidepressant and atypical antipsychotic treatments would alleviate the depression-like aspects of nicotine withdrawal (Markou et al. 1998; Markou and Kenny 2002).

Such common substrates mediating nicotine dependence and psychiatric disorders may explain the high

prevalence of tobacco smoking among psychiatric populations. Compared with the percentage of smokers in the general population (20 to 30 percent), a higher percentage of mentally ill patients were smokers (26 to 88 percent, depending on the mental illness) (Lasser et al. 2000), particularly those with schizophrenia, depression, or addiction to alcohol or other drugs (Hughes et al. 1986; Glassman et al. 1990; Breslau 1995). For illustrative purposes, substrates that mediate depression, schizophrenia, and nicotine dependence are described in the following sections.

Depression and Nicotine Dependence

Although the estimates vary across age, population, and criteria for tobacco dependence, most estimates suggest that the incidence of major depressive disorder among smokers is approximately two to three times that among nonsmokers (Hughes et al. 1986; Glassman et al. 1988, 1990; Kandel et al. 2001; Fergusson et al. 2003). A history of major depression increased the risk for progression to daily smoking and nicotine dependence, and a history of daily smoking and nicotine dependence increased the risk for major depression (Breslau et al. 1993b, 1998). A depressed mood is one of the symptoms of tobacco withdrawal syndrome experienced by a significant proportion of persons who attempt to stop smoking (West et al. 1984; Hughes and Hatsukami 1992; APA 1994). Therefore, tobacco smoking may be self-medication for either the depression that preceded the drug use or the smoking-induced depression (Pomerleau et al. 1978; Waal-Manning and de Hamel 1978; Hughes et al. 1986; Glassman 1993; Markou et al. 1998).

In particular, 5HT and the 5HT1A receptors appear to be critically involved in the mode of action of several antidepressant drugs used clinically (Markou et al. 1998) and may play a role in nicotine withdrawal (Kenny and Markou 2001). Systemic administration of 5HT1A receptor agonists, such as 8-hydroxy-2-dipropylaminotetralin (8-OH-DPAT), exacerbated the increased startle response observed during nicotine withdrawal, whereas 5HT1A receptor antagonists (e.g., WAY-100635) alleviated this increased response (Rasmussen et al. 1997, 2000). In addition, the responsiveness of dorsal raphe nucleus neurons to 8-OH-DPAT increased during nicotine withdrawal (Rasmussen and Czachura 1997). Thus, nicotine withdrawal may increase the inhibitory influence of somatodendritic 5HT1A autoreceptors in the raphe nuclei, and thereby decrease the release of serotonin in the forebrain and limbic brain sites (Benwell and Balfour 1979, 1982; Ridley and Balfour 1997). This conclusion is supported by the observation that a serotonergic antidepressant treatment involving the coadministration of the selective serotonin reuptake inhibitor fluoxetine and the 5HT1A receptor antagonist p-MPPI [4-(2′-methoxy-phenyl)-1-[2′-(n-2″-pyridinyl)-p-iodobenzamido]ethyl-piperazine] rapidly reversed the elevation in thresholds of brain-stimulation reward observed in rats with nicotine withdrawal, but the treatment did not block the somatic signs of withdrawal (Harrison et al. 2001). Consistent with this finding, the 5HT1A receptor partial agonist buspirone has shown limited efficacy in smoking cessation trials and may reduce the severity of withdrawal in persons attempting to stop smoking (West et al. 1991; Hilleman et al. 1992, 1994; Schneider et al. 1996). In conclusion, like depressions not induced by drugs, the depression-like aspects of nicotine withdrawal may be at least partly mediated by a decrease in monoaminergic transmission.

Consistent with the hypothesis that shared substrates mediate nicotine dependence and depression, clinical trials indicate that two of the antidepressant drug treatments are efficacious aids for smoking cessation. The atypical antidepressant bupropion, which primarily inhibits the reuptake of dopamine, was more effective than a placebo in clinical trials to achieve smoking cessation (Fiore et al. 2008), and bupropion has been approved for this use by the U.S. Food and Drug Administration (FDA). Preclinical research suggests that bupropion reverses both the depression-like and somatic aspects of nicotine withdrawal (Cryan et al. 2003), although its effects on the rewarding effects of nicotine are inconsistent (Bruijnzeel and Markou 2003). In addition, the tricyclic antidepressant nortriptyline, which primarily inhibits the reuptake of norepinephrine, is recommended by WHO and the U.S. Public Health Service (Fiore et al. 2008) as a smoking cessation aid. In conclusion, similar monoaminergic mechanisms appear to be involved in both depression and nicotine dependence.

Schizophrenia and Nicotine Dependence

More than 80 to 90 percent of patients with schizophrenia smoke compared with 20 to 30 percent of the general population (Masterson and O'Shea 1984; Goff et al. 1992; de Leon et al. 1995; Hughes 1996; Diwan et al. 1998). Persons with schizophrenia are commonly heavy smokers (>1.5 packs of cigarettes per day); smoke high-tar cigarettes, which are also high in nicotine content; and extract more nicotine from cigarettes than do smokers without schizophrenia (Masterson and O'Shea 1984; Hughes et al. 1986; Olincy et al. 1997).

The mesolimbic dopamine system and its efferent and afferent connections to other brain sites and systems, particularly dopamine-glutamate interactions, are strongly implicated in both the reinforcing effects of nicotine and schizophrenia (Snyder 1976; Carlsson 1977).

Abnormalities in these systems may render patients with schizophrenia more susceptible to the rewarding effects of nicotine (Chambers et al. 2001). Such patients may use nicotine to counteract the cognitive and/or depression-like aspects of schizophrenia that are not effectively treated with most antipsychotic drugs (Markou and Kenny 2002). Nicotine administration through tobacco smoking ameliorated visuospatial cognitive deficits of patients with schizophrenia (George et al. 2002) that involve the prefrontal cortex (Funahashi and Kubota 1994; Goldman-Rakic 1995; Callicott et al. 1998; Kikuchi-Yorioka and Sawaguchi 2000; Manoach et al. 2000).

Two forms of sensory-gating deficits (the inability to ignore or filter out irrelevant sensory information) that patients with schizophrenia exhibit may be influenced by actions on α7 or other nAChRs (Freedman et al. 1997; Adler et al. 1998). The two deficits are (1) auditory P50 gating, a form of sensory blocking, and (2) prepulse inhibition of the startle response. Thus, smoking may be a form of self-medication to compensate for these gating deficits. In support of this hypothesis, one study found that acute nicotine treatment reversed disruptions in prepulse inhibition induced in mice by the administration of the *N*-methyl-D-aspartate receptor antagonist phencyclidine, which mimics human psychosis (Spielewoy and Markou 2003).

Nicotine administration may be a form of self-medication for the depression-like negative symptoms of schizophrenia. The atypical antipsychotic drug clozapine treats the negative symptoms of schizophrenia most effectively and has decreased tobacco smoking in some persons without any encouragement to reduce smoking (George et al. 1995). In addition, long-term pretreatment with clozapine attenuated the severity of the nicotine withdrawal syndrome in rats (Semenova and Markou 2003).

Summary and Future Directions

The VTA region of the brain and the dopamine neurotransmitter are primarily responsible for the positive reinforcing aspects of nicotine addiction. An increase in dopamine levels is mediated by nicotine directly stimulating nAChRs, primarily α4β2 and α7 homomeric nAChRs in the VTA. Nicotine stimulates nAChRs on glutamatergic terminals that release glutamate, an excitatory neurotransmitter, which results in increased dopamine release in the nucleus accumbens and the frontal cortex. Nicotine also excites nAChRs on GABA-releasing terminals. Thus, levels of GABA, an inhibitory neurotransmitter, are also increased by nicotine. However, the interplay between the quick desensitization of nAChRs on the GABA neuron and the higher doses of nicotine required to desensitize nAChRs on the glutamate neuron results in a greater increase in dopamine levels. A critical role may also be played by nicotine-induced increases in norepinephrine transmission, although the role of this transmitter system in nicotine dependence has not been investigated as extensively as that of the dopamine, glutamate, and GABA systems. The role of endocannabinoids, serotonin, and endogenous opiates in nicotine addiction is less certain.

The neurophysiology associated with withdrawal symptoms may be based on the type of symptoms experienced (e.g., somatic versus affective). The nAChRs appear to be involved in both the somatic and affective components of nicotine withdrawal. Animal studies suggest that β4 plays an important role in the somatic symptoms of withdrawal, whereas β2 seems to play a role in the affective symptoms of withdrawal. The neuronal subunit α7 may be involved only in some of the somatic (e.g., hyperalgesia) aspects of withdrawal. The role of α4 is unclear, but it may influence both affective and somatic withdrawal effects. Decreased mesolimbic dopaminergic transmission seems to mediate various aspects of the withdrawal syndrome. Noradrenergic and serotonergic systems may also play a role in withdrawal. Decreased glutamate transmission appears to mediate the affective aspects of withdrawal, but GABA transmission does not appear to change with withdrawal. Although not discussed in this section, some studies also suggest that a dysregulation in the hypothalamic-pituitary axis occurs subsequent to withdrawal (al'Absi et al. 2004), and this dysregulation has been associated with relapse to smoking (al'Absi et al. 2005). In future research, the involvement of specific neuroreceptors and neurotransmitters relevant to the various aspects of addiction needs to be differentiated (see "Physiological Mechanisms and Indicators: Nicotine Tolerance, Withdrawal, and Reinforcement" earlier in this chapter).

Finally, understanding the pathophysiology of depression and schizophrenia, other psychiatric illnesses, and substance abuse disorders, as well as the effects of medications used to treat these disorders in smokers, may enhance understanding of the pathophysiology of nicotine addiction. Because of the high amount of overlap between prevalence of nicotine dependence and comorbid psychiatric disorders, the similar monoamines affected by these disorders, and the use of similar treatment medications, it is possible that common substrates mediate nicotine dependence and depression or schizophrenia, as well as other psychiatric disorders and can provide insight into effective treatments.

Genetics

There is strong evidence for a genetic influence on smoking behavior. Since the last Surgeon General's report on nicotine addiction (USDHHS 1988), knowledge has significantly increased in this area. For example, estimates of heritability have been determined for various phenotypes of smoking behavior. Studies of molecular genetic association and linkage studies were conducted to identify loci that influence these phenotypes. Furthermore, pharmacogenetic studies of smoking cessation were undertaken to increase understanding of interactions between genes and treatments. This research offers the possibility of interventions for smoking cessation that are tailored to individual genotypes.

Heritability of Smoking Behavior

Smoking behavior and nicotine addiction have generated far less research in behavioral genetics than have other addictive behaviors such as alcoholism. This is despite evidence from animal studies suggesting that key factors—such as the number and distribution of nicotinic receptors and the development of nicotine tolerance—are under a strong genetic influence (Stitzel et al. 2000). The evidence that does exist from studies of twins, adoption, and separated twins, however, has consistently suggested a strong genetic component in smoking behavior (Gilbert and Gilbert 1995). Behavioral genetics studies enable the contribution of genetic influences, environmental influence shared by persons such as twins or biologic relatives (shared environmental influences), and environmental influences unique to an individual (unique environmental influences) to be distinguished. The heritability coefficient itself reflects the genetic contribution. According to this evidence, inherited factors account for 28 to 85 percent of the observed variation in current smoking behavior in the population from which the data were drawn (Gilbert and Gilbert 1995). Researchers have suggested that the evidence for a genetic influence on smoking behavior is stronger than that for a genetic influence on alcoholism (Heath et al. 1995). Moreover, these studies have also indicated that these genetic factors relate to two aspects of smoking behavior: initiation and persistence.

Smoking Initiation

By comparing concordance rates for being a current or former smoker versus a lifetime nonsmoker, researchers can estimate the genetic contribution to smoking initiation. Such comparisons suggest that genetic contributions to smoking initiation are substantial. For example, one study (Heath et al. 1995) reports heritability coefficients for smoking initiation of 0.44 in women and 0.51 in men in a sample of Swedish adults born between 1926 and 1958. This study also reports a strong influence of shared environmental factors on both smoking initiation and persistence, with little evidence of a role for unique environmental influences. Many additional studies have confirmed the heritability of smoking initiation, as well as smoking persistence and nicotine dependence (True et al. 1997; Kendler et al. 1999). Although the overall conclusion is robust, the specific heritability coefficients reported by individual studies are highly variable, ranging from less than 0.30 to more than 0.80 (Sullivan and Kendler 1999). This finding may be attributable to differences in the definitions of smoking initiation across studies. For example, current and former smokers are combined into a single "ever smoking" category in some studies, but not in others, and some studies require a threshold of exposure (e.g., 100 cigarettes smoked) and others do not have this requirement. Lack of critical attention to definition of phenotype may lead to inconsistencies across studies and to misleading conclusions.

The role of shared environmental influences on initiation of smoking and persistence in smoking is also inconsistent across populations, and some studies report minimal shared environmental influences (Heath et al. 1993). Differences in heritability coefficients by gender are generally not reported or are minimal, although one study (Hamilton et al. 2006) that tested differences by gender in the magnitude of genetic and environmental effects in a large cohort of twins indicated significantly higher heritability for smoking initiation in males than in females but no significant differences for smoking persistence. In that study, heritability for smoking initiation was defined as having smoked 100 or more cigarettes over their lifetime. In contrast, however, one meta-analysis (Li et al. 2003) reported higher heritability for smoking initiation in females than in males and higher heritability for smoking persistence in males than in females. Together, the evidence supports the importance of both genetic and shared environmental factors on smoking initiation. However, the relative importance of these factors is highly variable across populations. For example, one study reports different heritability coefficients for smoking behaviors in African Americans compared with White Americans (True et al. 1997). Nevertheless, evidence from non-Western cultures (Niu et al. 2000) suggests that the genetic influence on smoking behavior remains an important risk

factor even in populations with much higher prevalence of smoking (e.g., in China). Reported heritability coefficients may vary with environmental factors such as the prevalence of smoking. For example, some of the highest heritability coefficients for smoking initiation are reported in studies on the population of twins during the Vietnam era, in which the participants were members of the U.S. Army at a time when smoking prevalence in the military was very high (True et al. 1997). This natural experiment, in which environmental variation in smoking initiation was minimized, may account for the high heritability coefficients in this study.

Smoking Persistence and Nicotine Dependence

Understanding smoking initiation is important to elucidate the etiology of nicotine addiction. However, smoking persistence is responsible for the adverse health consequences of smoking. The evidence for a genetic influence on smoking persistence (i.e., studies comparing current smokers with former smokers) is also strong. Several studies reported heritability coefficients of more than 0.50 for smoking persistence (Heath and Martin 1993) and nicotine dependence (Broms et al. 2007) in both men and women, and some studies (Sullivan and Kendler 1999; Vink et al. 2004) reported heritabilities of more than 0.70 for nicotine dependence. Studies of multiple indices of nicotine dependence (Lessov et al. 2004) indicate that salient behavioral indices are similar for women and men, with measures such as time to the first cigarette in the morning and the number of cigarettes smoked per day that may represent the most highly heritable symptoms of nicotine dependence for both women and men. Interpreting these results is complicated because genetic factors that influence smoking initiation may also influence smoking persistence and subsequent dependence. Some data (True et al. 1999) also suggest a common genetic vulnerability to nicotine and alcohol dependence in men. The balance of evidence suggests that the risk of smoking initiation is influenced by both genetic and environmental factors (True et al. 1997). However, the risk of smoking persistence is more strongly a function of genetic factors and some of the genetic influences on smoking behavior contribute to a risk for both smoking initiation and persistence (Kendler et al. 1999). Few studies have directly assessed the heritability of smoking cessation. However, one research study (Xian et al. 2003, 2005) indicated a heritability of 0.54 for failed smoking cessation, and another (Broms et al. 2006) suggests that genetic factors are related to the number of cigarettes smoked per day and to smoking cessation but are largely independent of smoking initiation. Another study (Pergadia et al. 2006) has reported genetic influences specific to nicotine withdrawal, which may contribute both to smoking persistence and smoking cessation. However, because evidence from studies of twins and of adoption strongly indicates a genetic component in other aspects of smoking behavior, smoking cessation may also be strongly influenced by genetic factors.

Molecular Genetic Research on Smoking Behavior

Consistent evidence for the heritability of smoking behaviors led to molecular genetic studies designed to elucidate the specific genetic factors and biologic mechanisms involved in nicotine addiction. Two general scientific approaches to address this question include genetic linkage analysis and candidate gene studies. In linkage analysis, genetic variants or markers throughout the genome are tested within families (e.g., sibling pairs) and examined to identify markers that cosegregate with the trait of interest (e.g., nicotine dependence). This is a hypothesis-generating approach and does not require a priori knowledge about the biologic pathways involved. In contrast, studies of candidate genes, which are based on associations, use case-control methods to compare the prevalence of variants of candidate genes in two unrelated groups—for example, persons who are dependent on nicotine and those who are not dependent on nicotine. Although case-control studies have greater statistical power and are less costly than linkage analysis, such studies are not designed to identify novel genetic loci.

Cigarette smoking and nicotine dependence are complex traits arising from the interplay of multiple genetic and environmental influences. As mentioned previously (see "Definition of Nicotine Addiction" earlier in this chapter), definition of phenotype is a critical factor in genetic studies. Many genes are likely involved in smoking—for example, genes that influence the positive rewarding effects of nicotine, those that contribute to withdrawal symptoms and the negative reinforcing effects of nicotine (Pomerleau 1995), and those that determine general susceptibility to addiction (Nestler 2000). Interacting effects such as personality and environment are likely to also play an important role (Heath et al. 1995). Issues such as population heterogeneity (e.g., age, gender, and ethnicity) and bias (false positives results) introduced by ethnic admixture in study populations may also have a substantial impact on the outcome of association-based studies and may contribute to problems in replicating results (Munafò and Flint 2004).

Table 4.5 Genetic linkage studies of smoking behavior phenotypes

Study (country)	Population	Number of families	Number of markers	Primary phenotype	Markers of significant linkage	Chromosome number
Bergen et al. 1999 (United States)	Collaborative Study on the Genetics of Alcoholism	105 extended	296	Ever smoked vs. lifetime nonsmoking	D1S548 D2S379 D6S474 D9S64 D14S302 D17S968 D18S391 D21S120	1 2 6 9 14 17 18 21
Duggirala et al. 1999 (United States)	Collaborative Study on the Genetics of Alcoholism	105 extended	296	Pack-years[a] of smoking	D4S244 D5S1354 GATA193	4 5 17
Straub et al. 1999 (New Zealand and United States)	Convenience sample (Christchurch, New Zealand, and Richmond, Virginia)	130 and 91 nuclear, respectively	451	Nicotine dependence	D2S1326 D10S2469	2 10
Goode et al. 2003 (New Zealand and United States)	Framingham Heart Study	313 extended	401	Cigarettes/day (maximum)	ATA4F03 GATA151F03 GATA25A04 GATA47F05 321xd1	2 15 17 20 20
Li et al. 2003 (United States)	Framingham Heart Study	313 extended	401	Cigarettes/day	D9S257 D9S910 D11S1985 D11S2371 ATA78D02 D17S2196	9 9 11 11 17 17
Saccone et al. 2003 (United States)	Framingham Heart Study	313 extended	401	Cigarettes/day (maximum)	1648xb8 ATA59H06 GATA6B07 Mfd190 217xf4	5 9 13 14 22
Bierut et al. 2004 (United States)	Collaborative Study on the Genetics of Alcoholism	97 nuclear	366	Habitual vs. nonhabitual smoking	D5S815 D9S1120 D9A261 D9S904 D11S1354 D21S210	5 9 9 9 11 21
Sullivan et al. 2004 (New Zealand and United States)	Convenience sample (Christchurch, New Zealand)	130 nuclear	458	Nicotine dependence	D2S1326 D10S2469 CYP17	2 10 10

Table 4.5 Continued

Study (country)	Population	Number of families	Number of markers	Primary phenotype	Markers of significant linkage	Chromosome number
Vink et al. 2004 (The Netherlands)	Netherlands Twin Register	192 nuclear	379	Ever smoked vs. lifetime nonsmoking	D6S2410 D6S1053 Unk283 D14S617	6 6 14 14
				Cigarettes/day	D3S3050 D3S4545	3 3
				Both	D10S1412 D10S1430	10 10
Wang et al. 2005 (United States)	Framingham Heart Study	430 nuclear	401	Cigarettes/day	ATA4E02 GATA6G12 GATA5B02 GATA24D12 GATA6B02 GATA12C06 GATA48E02 290vc9 GATA185H04 ATA4E02	1 3 4 7 8 9 11 16 17 20
Gelernter et al. 2006 (United States)	Probands identified for panic disorder (Yale University, Connecticut)	12 extended	416	Habitual vs. nonhabitual smoking	D9S283 D9S1677 D11S4046	9 9 11

Note: Dominant ancestry for all studies was European.
[a]Pack-years = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

Linkage Studies

Representative genetic linkage studies of smoking behavior phenotypes up to mid-2005 are shown in Table 4.5, although several of these report data from the same study samples (e.g., Collaborative Studies on the Genetics of Alcoholism and the Framingham Heart Study). Despite the success of linkage approaches in unraveling the genetic antecedents of disease (Menzel 2002), these initial findings about smoking behavior have not been consistent. Potential explanations include lack of refinement in phenotype definition and the relatively small sample sizes in some studies of smoking behavior. Subsequent studies have taken into account the complexity and heterogeneity of the nicotine dependence phenotype by using alternate measures, such as heavy smoking, severity of withdrawal, and history of smoking cessation (Li et al. 2006; Swan et al. 2006). These data suggest that different genetic loci are linked to different measures and support a multidimensional concept of the nicotine dependence phenotype (Swan et al. 2006).

In addition to linkage studies, investigations using an approach of genomewide association can also reveal promising novel candidate genes for nicotine dependence (Bierut et al. 2007). With advancements in genotyping technology, phenotype definition, and analytic approaches, both case-control studies and linkage analysis will likely identify an increasing number of associations with novel variants important in nicotine dependence (Li 2006). Examples include *NTRK2* (Beuten et al. 2007), *GABARAP* (Lou et al. 2007), *CHRNA5* (Saccone et al. 2007), and *ANKK1* (Gelernter et al. 2006).

Candidate Gene Studies

A variety of plausible candidate genes have been examined for associations with smoking behavior. Most of these studies have focused on genetic variations in relevant neurotransmitter pathways, nicotine-metabolizing enzymes, or nAChRs. Genetic variants of relevant neurotransmitter pathways may have more generalized influences on addictive behaviors. Genes for nicotine-metabolizing enzymes and nAChRs may be specific for effects on nicotine dependence.

Nicotine Metabolism

To date, more than 20 published studies of candidate genes have investigated genes involved in the nicotine metabolism pathway (Table 4.6). Most of these studies investigated *CYP2A6*, for which researchers have identified functional genetic variants (Xu et al. 2002). Variants associated with **NULL* activity (e.g., **2/*4*) or reduced activity (**9/*12*) are associated with reduced levels of the CYP2A6 enzyme and slower rates of nicotine metabolism, resulting in higher plasma nicotine levels from a given dose of nicotine (Malaiyandi et al. 2006). Thus, persons who carry these low activity alleles tend to have a lower risk of becoming smokers and, if they smoke, have slower rates of nicotine metabolism and tend toward reduced cigarette consumption compared with persons with a wild-type genotype (e.g., **1/*1*). Furthermore, evidence from a meta-analysis that compared current versus former smokers suggests that the *CYP2A6* alleles for reduced activity may increase the likelihood of smoking cessation (Munafò et al. 2004). However, the results are not consistent within or across all studies (Table 4.6). These inconsistencies may be attributable to relatively small sample sizes in some studies and differences in definition of phenotype and ethnic ancestry and genetic background.

Some studies investigated other cytochrome genes (*CYP2D6* and *CYP2E1*), but evidence for a significant and reproducible role of these variants has not emerged, perhaps because the role of these enzymes in nicotine metabolism is limited.

Neuronal Nicotinic Receptors

Researchers have examined several genes for nAChR subunits to discover associations with smoking status (Table 4.7). The genes *CHRNA4*, *CHRNA7*, and *CHRNB2* code for the α4, α7, and β2 subunits, respectively. However, because the functional relevance of variation in these genes is not known, these studies have explored associations of single nucleotide polymorphisms (SNPs) of unknown functional significance. To date, there is no evidence for associations of SNPs in the *CHRNB2* gene with smoking behavior. However, two studies provide evidence for the role of *CHRNA4* in nicotine dependence (Feng et al. 2004; Li et al. 2005). A small study of smokers with schizophrenia indicated that the *CHRNA7* gene may be associated with smoking status. The relevance of this finding in the general population of smokers is unknown. However, studies have reported that these nAChR subtypes play a role in reinforcing the effects of nicotine and possibly withdrawal (see "Pathophysiology of Nicotine Addiction" earlier in this chapter). Moreover, because of the history of failure to replicate initial significant findings, these single studies require replication before the evidence can be considered to be confirmed.

Recently, genomewide scans have revealed an association of novel genes, such as *NRXN1* and *NRXN3*, with nicotine dependence (Bierut et al. 2007). In addition, genomewide association and candidate gene studies have identified associations of smoking behavior and nicotine dependence with SNPs in the *CHRNA5/CHRNA3/CHRNB4* gene cluster and in *CHRNB3*, which code for the nicotinic receptor subunits α5, α3, β4 and β3, respectively (Saccone et al. 2007; Berrettini et al. 2008; Bierut et al. 2008; Grucza et al. 2008; Sherva et al. 2008; Stevens et al. 2008; Thorgeirsson et al. 2008; Weiss et al. 2008; Caporaso et al. 2009; Chen et al. 2009).

Dopaminergic and Serotonergic Neurotransmitter and Receptor Systems

A large number of candidate gene studies have investigated genes involved in the dopamine pathway, and most have investigated the gene for the dopamine receptor D2 (*DRD2*) (Table 4.8). Most studies of the *DRD2 *TAQ1A* polymorphism have reported an association with smoking behavior, typically smoking status, but a substantial number have shown no association. Moreover, the functional significance of the **TAQ1A* polymorphism remains unclear, although there is some reported evidence for an association with the density of D2 receptors in the brain. One study investigated the functional *DRD2-141C *INS/*DEL* polymorphism and reported a significant association with smoking status (Yoshida et al. 2001). A modest number of studies have investigated other genes for dopamine receptors (*DRD1*, *DRD4*, and *DRD5*), *DAT*, and genes involved in dopamine synthesis and metabolism, including tyrosine hydroxylase (an enzyme that converts amino acid L-tyrosine to dihydroxyphenylalanine, a precursor of dopamine), DβH (an enzyme that converts dopamine to norepinephrine), and COMT (an enzyme that degrades dopamine).

Table 4.6 Studies of candidate genes for nicotine metabolism and smoking behavior

Study (country)	Population		Dominant ancestry	Gene
	Study group	Controls		
Cholerton et al. 1996 (United Kingdom)	100 current smokers	104 lifetime nonsmokers	NR	*CYP2D6*
Boustead et al. 1997 (United Kingdom)	100 current smokers	None	NR	*CYP2D6*
Pianezza et al. 1998 (Canada)	164 nicotine-dependent smokers 80 alcohol- and tobacco-dependent smokers	184 nonnicotine-dependent and former smokers	European	*CYP2A6*
London et al. 1999 (United States)	299 current or former smokers	161 lifetime nonsmokers	NR	*CYP2A6*
Gu et al. 2000 (United Kingdom)	142 current smokers	501 former smokers 389 lifetime nonsmokers	European	*CYP2A6*
Rao et al. 2000 (Canada)	292 current smokers	NA	European	*CYP2A6*
Saarikoski et al. 2000 (Finland)	85 current smokers	236 variable smokers 264 lifetime nonsmokers	European	*CYP2A6*
Tiihonen et al. 2000 (Finland)	285 current smokers	680 former smokers or lifetime nonsmokers	European	*CYP2A6*
Loriot et al. 2001 (United States)	65 current smokers	142 former smokers	European	*CYP2A6*
Schulz et al. 2001 (Germany)	130 current smokers	108 former smokers 109 lifetime nonsmokers	European	*CYP2A6*
Tan et al. 2001 (China)	380 persons who ever smoked	246 lifetime nonsmokers	East Asian	*CYP2A6*
Zhang et al. 2001 (Japan)	96 current smokers	141 nonsmokers	East Asian	*CYP2A6*
Ando et al. 2003 (Japan)	57 current smokers	44 former smokers 139 lifetime nonsmokers	East Asian	*CYP2A6*
Howard et al. 2003 (Canada)	1,512 smokers and nonsmokers	NA	Multiple (stratified)	*CYP2E1*
Minematsu et al. 2003 (Japan)	92 current smokers 111 former smokers	123 nonsmokers	East Asian	*CYP2A6*
Fujieda et al. 2004 (Japan)	1,705 smokers	NA	East Asian	*CYP2A6*
Iwahashi et al. 2004 (Japan)	103 smokers 101 nonsmokers	NA	East Asian	*CYP2A6*
O'Loughlin et al. 2004 (Canada)	228 adolescents who inhaled	NA	European	*CYP2A6*

Polymorphism	Primary phenotype	Main findings
**3, *4A, *5*	Smoking status	No association with smoking status
**3, *4A, *5*	Cigarettes/day Nicotine dependence	Association with nicotine dependence
**1, *2, *3*	Nicotine dependence	Association with nicotine dependence (dependent vs. nondependent smokers) and amount smoked
**1, *2, *3*	Smoking status Cigarettes/day	Marginal association with smoking status (lifetime nonsmokers vs. current and former smokers)
**1, *2, *NULL* (allele not stated)	Smoking status Cigarettes/day	Association with smoking status (former vs. current smokers and lifetime nonsmokers)
**1, *2, *4,* duplication	Cigarettes/day	Association with cigarettes/day
**1, *2, *3, *4B, *4C, *5, *10, *16*	Smoking status	Association with smoking status (heavy vs. variable smokers and lifetime nonsmokers)
**NULL* (allele not stated)	Smoking status Cigarettes/day	No association with smoking status or cigarettes/day
**1, *2, *4*	Cigarettes/day	No association with cigarettes/day
**1, *2, *3*	Smoking status Cigarettes/day	No association with smoking status or cigarettes/day
**1, *4*	Smoking status Pack-years[a]	No association with smoking status or pack-years
**1, *DEL*	Smoking status Cigarettes/day	No association with smoking status or cigarettes/day
**1A, *1B, *4C*	Smoking status Cigarettes/day	No association with smoking status or cigarettes/day
**1C, *1D*	Nicotine dependence Cotinine levels/cigarette Cigarettes/day	Association with nicotine dependence in those of East Asian ancestry and cotinine concentrations/cigarette in those of African ancestry
**1, *3, *DEL*	Smoking status Pack-years	Association with pack-years among current and former smokers
**1A, *1B, *4, *7, *9, *10, *11*	Cigarettes/day	Association with cigarettes/day
**1A, *1B, *4C*	Smoking status	Association with smoking status
**1, *2, *4, *9, *12*	Nicotine dependence Cigarettes/day	Association with increased risk of acquisition of nicotine dependence, but reduced cigarettes/day among those who become dependent

Table 4.6 Continued

Study (country)	Population		Dominant ancestry	Gene
	Study group	Controls		
Schoedel et al. 2004 (Canada)	375 current smokers	224 nonsmokers	European	*CYP2A6*
Vasconcelos et al. 2005 (Brazil)	144 current smokers 61 former smokers	207 nonsmokers	Mixed	*CYP2A6*

Note: **NA** = not applicable; **NR** = data not reported.
[a]Pack-years = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

Table 4.7 Studies of candidate genes for neuronal nicotine receptors and smoking behavior

Study (country)	Population		Dominant ancestry	Gene
	Study group	Controls		
Silverman et al. 2000 (United States)	317 high- and 238 low-nicotine dependent smokers	317 nonsmokers	European	*CHRNB2*
Lueders et al. 2002 (United States)	184 current smokers	132 former smokers 427 lifetime nonsmokers	European	*CHRNB2*
De Luca et al. 2004 (Canada)	108 current smokers with schizophrenia	69 current nonsmokers with schizophrenia	European	*CHRNA7*
Feng et al. 2004 (China)	577 male smokers from 206 families	Family-based design	East Asian	*CHRNA4*
Li et al. 2005 (United States)	1,568 smokers from 602 families	Family-based design	European and African	*CHRNA4* *CHRNB2*

Of the published studies of candidate genes involved in the serotonin pathway, eight investigated *5HTT*, and three investigated *TPH*, which is involved in serotonin synthesis (Table 4.9). All but one study of the functional *5HTTLPR* polymorphism found an association with smoking behavior. Three additional studies investigated the *MAOA* gene, which is involved in metabolism of both dopamine and serotonin and in norepinephrine pathways. Two of the three studies reported an association with smoking behavior that included both smoking status and cigarette consumption. Other studies of candidate genes are summarized in Table 4.10. Research is notably lacking on genes involved in glutamatergic and GABA-ergic mechanisms, despite basic research indicating the neurobiologic effects of nicotine on these systems. One study (Beuten et al. 2005) reports a significant association between a haplotype of SNPs in the $GABA_{B2}$ gene and nicotine dependence.

In summary, a few candidate genes appear to be associated with smoking behavior. Meta-analysis is a potentially powerful tool for assessing population-wide effects of candidate genes on complex behavioral phenotypes, such as smoking, although such meta-analysis requires that the phenotypes examined across studies are similar. It may also provide evidence for unrevealed diversity, such as heterogeneity in apparently similar populations (Munafò and Flint 2004). Despite the large number of studies reporting on the association between specific candidate genes and smoking behavior, one meta-analysis (Munafò et al. 2004) highlights the lack of depth of the research compared with the breadth that exists. The conclusion is that the "…evidence for a contribution of specific genes to smoking behavior remains modest" (p. 583). In this analysis, *5HTT* and *CYP2A6* were the only candidate genes for which there was evidence of an association with smoking behavior. Studies published

Polymorphism	Primary phenotype	Main findings
**1A, *1B, *2, *4, *5, *6, *7, *8, *9, *10, *12*	Smoking status Cigarettes/day	Association with smoking status and cigarettes/day
**1A, *1B, *2, *4, *9*	Smoking status	Association with smoking status (current and former smokers vs. nonsmokers) among those of European and mixed ancestry

Polymorphism	Primary phenotype	Main findings
Multiple	Smoking status Nicotine dependence	No association with smoking status or nicotine dependence
Haplotype	Smoking status Nicotine dependence	No association with smoking status or nicotine dependence
D15S1360	Smoking status	Association with smoking status (current smokers vs. nonsmokers)
Haplotype	Nicotine dependence	Association with nicotine dependence
Haplotype Haplotype	Nicotine dependence	Association of *CHRNA4* gene with nicotine dependence No association with *CHRNB2* gene

more recently strongly indicate that SNPs in the *CHRNA5/A3/B4* gene cluster are associated with smoking behavior and nicotine dependence (Berrettini et al. 2008; Bierut et al. 2008; Grucza et al. 2008; Sherva et al. 2008; Stevens et al. 2008; Thorgeirsson et al. 2008; Weiss et al. 2008; Caporaso et al. 2009; Chen et al. 2009; Saccone et al. 2009). Nonetheless, the relatively small effects and evidence for substantial heterogeneity between studies suggest that extreme care is necessary in the design of case-control studies of genetic association.

Pharmacogenetic Approaches

The basic premise of the pharmacogenetic approach is that inherited differences in drug metabolism and drug targets have important influence on the toxic effects and the efficacy of treatment (Evans and Relling 1999; Poolsup et al. 2000). Advantages of a pharmacogenetic approach to the study of smoking cessation treatments include (1) use of more refined phenotypes for genetic analyses, which is facilitated by prospective assessment of withdrawal symptoms, side effects of treatment, and measures of the level of reward from nicotine; (2) use of various treatment conditions to aid smoking cessation; and (3) use of experimental designs that control the dosing and timing of the therapy (Lerman and Niaura 2002; Munafò et al. 2005b; Caporaso et al. 2009).

Nicotine Replacement Therapy

To date, two pharmacogenetic trials of NRT have been conducted. One placebo-controlled trial using the nicotine patch by a large group of general practice physicians in the United Kingdom (Johnstone et al. 2004b; Yudkin et al. 2004) focused on variations in the dopamine pathway, including the *DβH* and *DRD2* genes. The

Table 4.8 Studies of candidate genes for dopamine and smoking behavior

Study (country)	Population		Dominant ancestry	Gene
	Study group	Controls		
Noble et al. 1994 (United States)	57 current smokers	115 former smokers 182 lifetime nonsmokers	European	*DRD2*
Comings et al. 1996 (United States)	312 current smokers	714 lifetime nonsmokers	European	*DRD2*
Comings et al. 1997 (United States)	371 current smokers	126 lifetime nonsmokers	European	*DRD1* *DRD2*
Lerman et al. 1997 (United States)	315 current smokers	232 lifetime nonsmokers	European	*TH*
Shields et al. 1998 (United States)	283 current smokers	192 lifetime nonsmokers	European and African	*DRD4*
Singleton et al. 1998 (United Kingdom)	104 current smokers	117 lifetime nonsmokers	NR	*DRD2*
Spitz et al. 1998 (United States)	46 current smokers	67 former smokers 13 lifetime nonsmokers	European	*DRD2*
Lerman et al. 1999 (United States)	289 current smokers	233 lifetime nonsmokers	European and African	*DRD2* *DAT*
Sabol et al. 1999 (United States)	283 current smokers	231 former smokers 593 lifetime nonsmokers	European	*DAT*
Batra et al. 2000 (Germany)	110 nicotine-dependent smokers	60 nonnicotine-dependent or light smokers	NR	*DRD2*
Bierut et al. 2000 (United States)	388 habitual smokers 566 nonhabitual smokers	Family-based study	European	*DRD2*
Costa-Mallen et al. 2000 (United States)	152 newly diagnosed Parkinson's disease patients	231 with no history of Parkinson's or other neurodegenerative disease	European	*DRD2*
Jorm et al. 2000 (Australia)	198 current smokers	211 former smokers 452 lifetime nonsmokers	European	*DAT*
McKinney et al. 2000 (United Kingdom)	225 current smokers	No controls	European	*DβH* *MAOA* *COMT*
Wu et al. 2000 (United States)	73 current smokers	61 former smokers 88 lifetime nonsmokers	European and African	*DRD2*
Sullivan et al. 2001 (United States)	595 current smokers	338 lifetime nonsmokers	European	*DRD5*
Yoshida et al. 2001 (Japan)	77 current smokers	57 former smokers 198 lifetime nonsmokers	East Asian	*DRD2*
David et al. 2002 (United Kingdom)	266 current smokers	270 former smokers 265 lifetime nonsmokers	NR	*COMT*
Hamajima et al. 2002 (Japan)	226 current smokers	133 former smokers 434 lifetime nonsmokers	East Asian	*DRD2*

Polymorphism	Primary phenotype	Main findings
**TAQ1A*	Smoking status	Association with smoking status (current and former smokers vs. lifetime nonsmokers)
**TAQ1A*	Smoking status	Association with smoking status
DDE1 **TAQ1A*	Smoking status Packs/day	Association of *DRD1* and *DRD2* genes with smoking status and packs/day
VNTR	Smoking status	No association with smoking status
VNTR	Smoking status Cigarettes/day	Association with smoking status in participants of African ancestry
**TAQ1A*	Smoking status Nicotine dependence	No association with smoking status or nicotine dependence
**TAQ1A* **TAQ1B*	Smoking status Age at smoking initiation	No association with smoking status Association of both polymorphisms with age at smoking initiation
**TAQ1A* *VNTR*	Smoking status	Association of *DAT* and *DRD2* genes with smoking status in participants of European ancestry
VNTR	Smoking status	Association with smoking status (current vs. former smokers)
FOK1 **TAQ1A*	Smoking status	Association of *FOK1* polymorphism with smoking status (nicotine-dependent vs. nonnicotine-dependent or light smokers)
**TAQ1A* **INTRON 2*	Smoking status	No association with smoking status
**TAQ1A* **TAQ1B*	Smoking status	No association with smoking status
VNTR	Smoking status	No association with smoking status
G1368A *C1460T* *A1947G* (**VAL/*MET*)	Cigarettes/day	Association of *DβH* and *MAOA* genes with cigarettes/day
**TAQ1A* **TAQ1B*	Smoking status Cigarettes/day	Association of both polymorphisms with smoking status (current vs. former smokers and lifetime nonsmokers) and cigarettes/day
Haplotype	Smoking status Nicotine dependence	No association with smoking status Association with nicotine dependence, although marginal
**TAQ1A* *-141C *INS/*DEL*	Smoking status	Association of *TAQ1A* polymorphism only with smoking status (current vs. former smokers and lifetime nonsmokers)
A1947G (**VAL/*MET*)	Smoking status	No association with smoking status
MBO1 **TAQ1A*	Smoking status	Association of *TAQ1A* polymorphism only with smoking status in men (current vs. former smokers and lifetime nonsmokers)

Table 4.8 Continued

Study (country)	Population		Dominant ancestry	Gene
	Study group	Controls		
Johnstone et al. 2002 (United Kingdom)	1,524 current smokers	NA	European	*DβH* *MAOA*
Qi et al. 2002 (China)	174 current smokers	152 former smokers and lifetime nonsmokers	East Asian	*DRD2*
Vandenbergh et al. 2002 (United States)	98 current smokers	153 former smokers 114 nonsmokers 214 lifetime nonsmokers	European	*DAT*
Ito et al. 2003 (Japan)	147 current smokers	99 former smokers 258 lifetime nonsmokers	East Asian	*MAOA* *MAOB*
Lee et al. 2003 (South Korea)	94 current smokers	93 lifetime nonsmokers	East Asian	*DRD2*
Anney et al. 2004 (Australia)	51 nicotine-dependent smokers	186 nonnicotine-dependent smokers	European	*TH*
Audrain-McGovern et al. 2004a (United States)	292 adolescents who ever smoked	NA	European	*DRD2* *DAT*
Johnstone et al. 2004b (United Kingdom)	732 current smokers	243 lifetime nonsmokers	European	*DRD2*
Ling et al. 2004 (China)	668 current smokers	Family-based study	East Asian	*DAT*
Luciano et al. 2004 (Australia)	769 current smokers and nonsmokers	Family-based study	European	*DRD4*
Olsson et al. 2004 (Australia)	77 nicotine-dependent smokers	39 nonnicotine-dependent smokers	European	*TH*
Colilla et al. 2005 (United States)	277 female current smokers	505 female former smokers	European and African	*COMT*
Costa-Mallen et al. 2005 (United States)	232 persons who ever smoked	158 lifetime nonsmokers	European	*DRD2* *MAOB*
Elovainio et al. 2005 (Finland)	37 current smokers	113 nonsmokers	European	*DRD4*
Freire et al. 2006 (Brazil)	220 alcoholic and nonalcoholic smokers	112 nonsmokers	European	*DRD2* *DβH*
Laucht et al. 2005 (Germany)	184 adolescents who ever smoked	119 adolescent lifetime nonsmokers	European	*DRD4*
Zetteler et al. 2005 (United Kingdom)	141 current smokers	NA	European	*DβH*

Note: **NA** = not applicable; **NR** = data not reported.

Polymorphism	Primary phenotype	Main findings
G1368A *C1460T*	Cigarettes/day	No association with cigarettes/day
**TAQ1A* **TAQ1B*	Smoking status Cigarettes/day	Association of **TAQ1A* polymorphism only with cigarette use No association with smoking status
VNTR	Smoking status	Association with smoking status (lifetime nonsmokers vs. former and current smokers)
VNTR *A644G*	Smoking status Nicotine dependence	Association of *MAOA* gene with smoking status among women and nicotine dependence among men
**TAQ1A*	Smoking status	Association with smoking status Evidence of heterosis in women
VNTR	Nicotine dependence	Association with nicotine dependence
**TAQ1A* *VNTR*	Smoking status Smoking progression	Association of *DRD2* gene with smoking progression in those exposed to nicotine
**TAQ1A*	Smoking status Cigarettes/day	No association with smoking status or cigarettes/day
**RS27072*	Nicotine dependence Age at smoking initiation	No association with nicotine dependence Association with age at smoking initiation among nicotine-dependent smokers only
VNTR	Smoking status Cigarettes/day	No association with smoking status or cigarettes/day
VNTR	Nicotine dependence	Association with nicotine dependence
A1947G (**VAL*/**MET*)	Smoking status	Association with smoking status
**TAQ1B* *A644G*	Smoking status	No association with smoking status, although there was interactive effect between *DRD2* and *MAOB* genes in men
VNTR	Smoking status	Association with smoking status
**TAQ1A* *C1021T*	Smoking status	Association of *DRD2* gene with smoking status Marginal association of *DβH* gene with smoking status
VNTR	Smoking status Daily smoking	Association with smoking status and daily smoking in men
G1368A	Nicotine dependence	Association with nicotine dependence

Table 4.9 Studies of candidate genes for serotonin and smoking behavior

Study (country)	Population		Dominant ancestry
	Study group	Controls	
Lerman et al. 1998 (United States)	268 current smokers	230 lifetime nonsmokers	European and African
Ishikawa et al. 1999 (Japan)	202 current smokers	103 former smokers 82 lifetime nonsmokers	East Asian
Hu et al. 2000 (United States)	177 current smokers	124 former smokers 458 lifetime nonsmokers	European
Lerman et al. 2000 (United States)	185 current smokers	None	European and African
McKinney et al. 2000 (United Kingdom)	225 current smokers	None	European
Lerman et al. 2001 (United States)	249 current smokers	202 lifetime nonsmokers	European
Johnstone et al. 2002 (United Kingdom)	1,524 current smokers	None	European
Ito et al. 2003 (Japan)	147 current smokers	99 former smokers 258 lifetime nonsmokers	East Asian
Mizuno et al. 2004 (Japan)	233 current smokers	135 former smokers 667 lifetime nonsmokers	East Asian
Brody et al. 2005 (United States)	110 current smokers 100 former smokers	275 lifetime nonsmokers	European and African
Gerra et al. 2005 (Italy)	107 adolescents who ever smoked	103 adolescent lifetime nonsmokers	European
Kremer et al. 2005 (Israel)	244 persons who ever smoked	486 lifetime nonsmokers	Other
Munafò et al. 2005a (United Kingdom)	141 current smokers	None	European
Reuter and Hennig 2005 (Germany)	108 current smokers	144 nonsmokers	European

Gene	Polymorphism	Primary phenotype	Main findings
5HTT	*LPR*	Smoking status	No association with smoking status
5HTT	*LPR*	Smoking status	Association with smoking status (current vs. former smokers and lifetime nonsmokers)
5HTT	*LPR*	Smoking status	Association with smoking status (current vs. former smokers and lifetime nonsmokers) among participants with high levels of neuroticism
5HTT	*LPR*	Nicotine dependence	Association of neuroticism with nicotine dependence among those with short allele
MAOA	*C1460T*	Cigarettes/day	Association with cigarettes/day
TPH	*A779C*	Smoking status Nicotine dependence	No association with smoking status or nicotine dependence Association with age at smoking initiation
MAOA	*C1460T*	Cigarettes/day	No association with cigarettes/day
MAOA *MAOB*	*VNTR* *A644G*	Smoking status Nicotine dependence	Association of *MAOA* gene with smoking status among women and with nicotine dependence among men
TPH	*C218A*	Smoking status	No association with smoking status
5HTT	*LPR*	Smoking status Nicotine dependence	No association with smoking status or nicotine dependence
5HTT	*LPR*	Smoking status	Association with smoking status
5HTT	*LPR* *VNTR*	Smoking status Nicotine dependence	Association with smoking status (persons who ever smoked vs. lifetime nonsmokers) No association with nicotine dependence
5HTT	*LPR*	Nicotine dependence	Association with nicotine dependence
TPH	*A779C*	Smoking status Nicotine dependence	Association with nicotine dependence (nonsmokers scored as having zero nicotine dependence)

Table 4.10 Other studies of candidate genes for smoking behavior

Study (country)	Population		Dominant ancestry
	Study group	Controls	
Garciá-Closas et al. 1997 (United States)	315 current smokers	None	European
Comings et al. 2001 (United States)	12 current smokers 326 nicotine-dependent smokers	59 former smokers 120 lifetime nonsmokers 399 nondependent controls	European
Hamajima et al. 2001 (Japan)	126 current smokers	837 nonsmokers	East Asian
Pitha et al. 2002 (Czech Republic)	75 current and former smokers	60 lifetime nonsmokers	European
Uno et al. 2002 (Japan)	124 current smokers	131 former smokers 690 lifetime nonsmokers	East Asian
Füst et al. 2004 (Hungary)	171 persons who ever smoked	140 lifetime nonsmokers	European
Smits et al. 2004 (The Netherlands)	20,938 persons, including current and former smokers and lifetime nonsmokers	NA	European
Beuten et al. 2005 (United States)	990 current smokers 286 nonsmokers	Family-based study	European and African
Liu et al. 2005 (Japan)	213 current smokers	71 former smokers 55 lifetime nonsmokers	East Asian
Ma et al. 2005 (United States)	1,568 current smokers 469 nonsmokers	Family-based study	European and African
Takimoto et al. 2005 (Japan)	109 current smokers	162 nonsmokers	East Asian

Note: **NA** = not applicable.
[a]Pack-years = the number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

dopamine pathway is widely considered to be central in the development of nicotine dependence (see "Pathophysiology of Nicotine Addiction" earlier in this chapter). Releasing dopamine after nicotine administration activates postsynaptic dopamine receptors, including the D2 receptor, whereas DβH is involved in the synthesis of noradrenalin from dopamine (Koob and Le Moal 2001).

The **TAQ1A* ($C^{32806}T$) allele of the *DRD2* gene is associated with reduced numbers of dopamine D2 receptors in the corpus striatum (Thompson et al. 1997), but the functional significance of this variant remains unclear. The **1368A* allele of the *DβH* gene is associated with smoking status (McKinney et al. 2000), although this polymorphism is not considered functional. The nicotine patch was significantly more effective for smoking cessation than was a placebo for carriers of the **A1* allele of the *DRD2* gene but not among those who were homozygous for the more common **A2* allele (Johnstone et al. 2004b). The difference in the effects of treatment in the genotype groups was significant after the first week of

Gene	Polymorphism	Primary phenotype	Main findings
CYP1A1 *GSTM1 *NULL*	**MSP1*	Pack-years[a]	No association with pack-years
CCK	*C-45T*	Smoking status Nicotine dependence	Association with smoking status (current vs. former smokers vs. lifetime nonsmokers) and nicotine dependence (nicotine-dependent smokers vs. nondependent controls)
IL-1β	*C-31T*	Smoking status	No association with smoking status
CD14	*C-159T*	Smoking status	Association with smoking status (current and former smokers vs. lifetime nonsmokers)
IL-1β	*C-31T*	Smoking status	No association with smoking status
TNF2 *C4A* *C4B*	Haplotype Haplotype Haplotype	Smoking status Cigarettes/day	Association of *TNF2* gene with smoking status (persons who ever smoked vs. lifetime nonsmokers)
CYP1A1 *GSTM1* *GSTT1* *GSTP1* *NAT2*	**MSP1* **DEL* **DEL* **ILE/*VAL* **4*	Smoking status	No association with smoking status
$GABA_{B2}$	Haplotype	Nicotine dependence	Association with nicotine dependence
Various	Various	Smoking status	Association of *OGG1, 5HTT, EPHX1, ESR1,* and *CYP17A1* genes with smoking status
DDC	Haplotype	Nicotine dependence	Association with nicotine dependence
CCK *CCKAR*	*C-45T* *T779C* *365 *VAL/*ILE*	Smoking status	Association of *CCK* gene with smoking status

treatment but not at the end of 12 weeks of treatment. The nicotine patch was highly effective among smokers with both the *DRD2 *A1* allele and the *DβH *A* allele, but it was less effective for smokers with other genotypes. This genetic association with treatment response was significant at both 1 and 12 weeks of treatment, which suggests that the short-term efficacy of the nicotine patch may be modulated by *DRD2* and *DβH* genes. Longer follow-up in this analysis supported the association of the *DRD2* variant with abstinence from smoking at 6- and 12-month follow-ups, although this effect was observed only among women and the results for the *DβH* gene were not reported (Yudkin et al. 2004).

The second pharmacogenetic trial of NRT was an open-label trial of the nicotine patch versus nicotine nasal spray. This trial examined the role of the gene for the μ-opioid receptor (*OPRM1*) (Lerman et al. 2004). The opioid receptor is the primary site of action for the rewarding effects of the endogenous opioid peptide β-endorphin (Zadina et al. 1997), which is released in

response to nicotine (Davenport et al. 1990; Boyadjieva and Sarkar 1997). Exon 1 of the human *OPRM1* gene includes a common A118G (*ASN40ASP*) missense SNP. The **ASP40* variant has been associated with reduced messenger RNA (mRNA) and lower protein levels for the receptor (Zhang et al. 2005). Smokers carrying the *OPRM1 *ASP40* variant were significantly more likely than those who were homozygous for the **ASN40* variant to be abstinent from smoking at the end of the treatment phase (Lerman et al. 2004). The differential treatment response among smokers was most pronounced for the nicotine patch, modest and nonsignificant for nicotine nasal spray, and nonsignificant for a placebo, in the bupropion clinical trial described in the next section. A longitudinal analysis in the nicotine patch group revealed a dose-response effect of the nicotine patch. The effect of the genotype in the **ASP40* group was greatest during the nicotine patch treatment of 21 milligrams (mg), but the effect was reduced as the treatment was tapered and disappeared after discontinuation. In addition, smokers who carried the **ASP40* variant gained less weight during the treatment period and reported greater reductions in symptoms of negative mood than did those who were not carriers of the variant. These findings suggest that smokers carrying the **ASP40* variant may be candidates for maintenance therapy with the 21-mg nicotine patch.

Additional investigations provided evidence for an association of the *COMT VAL158 MET* polymorphism with prospective smoking cessation in an NRT open-label trial. Female smokers treated with either the nicotine patch or nicotine nasal spray who carried the low-activity allele, which is associated with a slower degradation of dopamine, were significantly more likely than were those who did not carry this allele to stop smoking independent of the treatment. These findings are consistent with those reported in a retrospective comparison of female current versus female former smokers in a case-control study (Table 4.8) (Colilla et al. 2005).

Bupropion

The first pharmacogenetic analysis of treatment for tobacco dependence was conducted as part of a placebo-controlled clinical trial of bupropion for smoking cessation (Lerman et al. 2002) that focused on *CYP2B6*. Smokers who carried the *CYP2B6* variant, which, to some extent, is associated with slower nicotine metabolism, reported greater increases in craving for cigarettes after the target date for smoking cessation and had significantly higher rates of relapse to smoking than did those without the variant. These effects were modified by a significant interaction among gender, genotype, and treatment, which suggests that bupropion attenuated the effects of genotype among female smokers.

A second report from this clinical trial (Lerman et al. 2006) examined two SNPs that may influence the expression of the DRD2 receptor. These SNPs included an insertion/deletion variant in the promoter region of the *DRD2* gene (*DRD2 -141C *INS/*DEL*). The transcriptional efficiency of the more common **-141C INS C* allele is greater than that of the variant with the **-141C DEL C* allele (Arinami et al. 1997), and a functional synonymous SNP in the *DRD2* (*C957T*) gene decreases mRNA stability and protein synthesis (Duan et al. 2003). At the end of the treatment phase, a statistically significant interaction between the *DRD2 -141C *INS/*DEL* genotype and the treatment indicated a more favorable response to bupropion among smokers homozygous for the **INS C* allele than that for smokers carrying a **DEL C* allele.

One study investigated whether the **TAQ1A* polymorphism in the *DRD2* gene is associated with smoking cessation outcomes after treatment with a combination of bupropion and behavioral counseling in smokers enrolled in an open-label randomized trial of effectiveness (Swan et al. 2005). Compared with women who were homozygous for the **A2* allele, women with at least one **A1* allele were significantly more likely to stop taking bupropion because of side effects from the medication and at 12 months were somewhat more likely to report smoking. However, relapse to smoking by 12 months after treatment was not statistically significant and constituted only a trend. Significant associations or trends were not observed in men.

In addition, another study reported data on 239 smokers who were offered bupropion in a group of general practice physicians in the United Kingdom (Johnstone et al. 2004a). Only 54 of these smokers made an active attempt to stop smoking. Allele frequencies for polymorphisms in the *DRD2*, *DAT*, *DβH*, and *MAOA* genes were reported. However, the sample size was insufficient for formal analysis of the effects of these polymorphisms on smoking cessation.

Varenicline

Varenicline, a partial agonist at the α4β2 nAChR, was approved by FDA as a treatment for smoking cessation in 2006 (USFDA 2006). Several large trials provide evidence that varenicline was more effective than bupropion or placebo as an aid to smoking cessation (Gonzales et al. 2006; Jorenby et al. 2006; Tonstad et al. 2006). Because of the efficacy and relative target selectivity (e.g., targeting a specific receptor subtype) of this compound, pharmacogenetic studies of varenicline are warranted.

Summary and Future Directions

Research on genetic influences on smoking behavior has yielded important insights about the biobehavioral basis of nicotine dependence. There is strong and consistent evidence from studies of twins that smoking initiation and nicotine dependence are influenced by heritable factors. Support for the role of functional genetic variation in nicotine-metabolizing enzymes (e.g., CYP2A6) and genetic variation in nAChR subunit genes (e.g., *CHRNA5*) is largely consistent, although the extent of their contribution to nicotine dependence is unclear. Additional but inconsistent evidence supports the roles of genetic variants in the dopamine pathways. Although the pharmacogenetic approach to smoking cessation holds early promise, larger studies in more diverse populations are required (Lerman et al. 2007). Designs for case-control studies of genetic association are limited, partly by the use of crude measures of smoking behavior phenotypes. This finding supports the importance of future studies to explore associations of candidate genes with endophenotypes, which are intermediate phenotypes of smoking behavior. Some phenotypes are biologically more proximal to their genetic antecedents than are complex behavioral phenotypes, because biologic proximity affords a more homogeneous phenotype and a stronger genetic signal. Endophenotypes that may be relevant to nicotine dependence encompass acoustic startle response, including prepulse inhibition and affective modulation of the acoustic startle (Hutchison et al. 2000); measures of the reinforcing value of nicotine in a paradigm of behavioral choice (Blendy et al. 2005; Ray et al. 2006); various paradigms of craving related to reactivity to cues (Tiffany et al. 2000); measures of attentional bias, such as the modified Stroop task (Munafò et al. 2003) and the dot-probe task (Waters et al. 2003a); and patterns of withdrawal after smoking cessation (David et al. 2003). The list of candidate endophenotypes is growing rapidly, and these may offer powerful measures for genetic analysis, although the role of these putative endophenotypes remains speculative in some cases.

Also deserving of attention is the study of the interaction between genetic variants, nicotine dependence, and disorders comorbid with nicotine dependence (e.g., depression and anxiety). Two studies suggest that smoking behaviors and nicotine dependence are influenced by an interaction between the *5HTT* gene and anxiety-related traits (Hu et al. 2000; Lerman et al. 2000). In one study, however, this association was not replicated (Munafò et al. 2005a). A better understanding of genetic influences on nicotine dependence in different psychiatric populations would be valuable for the development of targeted medications.

Pharmacogenetic investigations of smoking cessation treatments have provided promising initial evidence that genetic variations in drug targets, such as the dopamine system or nAChRs, may predict responses to treatments. Only a few such studies have been conducted, and these have focused on the two FDA-approved approaches for smoking cessation pharmacotherapy: bupropion and NRT. Several additional pharmacotherapies have been tested for efficacy in smoking cessation (Lerman et al. 2005). Although the overall effects of alternate pharmacotherapies, such as fluoxetine and naltrexone, have been modest, it is possible that subgroups of smokers who benefit from such treatments can be identified by genotype. Although pharmacogenetic research on smoking cessation treatments is in the early stages, this research may ultimately be used to tailor pharmacotherapies to smokers most likely to benefit, thereby improving the efficacy. Emerging health policy and ethical issues related to genetically tailored smoking cessation treatments are important to consider (Shields et al. 2004), as are barriers to and facilitators of the integration of genetic tests into smoking cessation in clinical practice (Shields et al. 2004; Munafò et al. 2005b).

Recent studies have begun to provide compelling support for association of some common genetic variants with smoking behavior and related disease phenotypes, such as SNPs within the *CHRNA5/A3/B4* gene cluster (Amos et al. 2008; Hung et al. 2008; Liu et al. 2008; Thorgeirsson 2009); however, the effect sizes described in these studies are very small, and it has been suggested that efforts may need to be directed elsewhere if the genetic architecture of complex traits is to be fully elucidated (Goldstein 2009; Hardy and Singleton 2009; Hirschhorn 2009). In particular, the hypothesis that common phenotypes, such as nicotine dependence, will be explained by common genetic variants has been questioned because the effect sizes observed to date suggest an unrealistically large number of alleles to explain the known heritability of a given phenotype (Goldstein 2009).

A complementary approach may be to seek out less common genetic variations that may have a more profound effect on phenotypes of interest. For example, recent studies have identified a possible role for copy number variants and de novo mutations in the etiology of psychiatric phenotypes such as schizophrenia (Xu et al. 2008) and autism (Sebat et al. 2007). Although no studies have yet investigated the role of copy number variants in smoking behavior, such studies are likely to emerge in the near future. As our understanding of the functional biology of genetic variation continues to develop, so too will the technologies and methods available to dissect the genetic architecture of complex phenotypes such as nicotine dependence.

Prevalence and Trajectory Toward Nicotine Dependence

Genes appear to predispose persons to smoking initiation and persistence and possibly are related to the extent of difficulty a person has in smoking cessation. Genetic transmission may include inheritance of polymorphisms of specific genes that affect responses of the body and the brain to nicotine. These responses include the rate of metabolism of nicotine, receptor sensitivity to nicotine and to certain neurotransmitters, and the levels of neurotransmitters available at neural synapses. These individual differences in response to nicotine are likely to affect the trajectory toward the development of nicotine dependence. Characterization of differences in trajectories has primarily focused on the adolescent population, because most smokers begin smoking cigarettes during this period of life. The next section describes the prevalence of adolescent smoking to increase understanding of the scope for potential development of dependence, differences in trajectory patterns toward dependence, and determinants for developing nicotine addiction. Epidemiologic, laboratory, and clinical studies are described to elucidate the emerging science in this area.

Epidemiology of Adolescent Smoking

A large body of epidemiologic literature has examined the prevalence of smoking, its initiation in adolescence, and the progression among adolescents from experimentation to regular use of cigarettes. This literature includes research on national samples in both school-based studies (University of Michigan 2007) and household studies (Substance Abuse and Mental Health Services Administration 2004). However, compared with an extensive amount of literature that examines adolescent smoking, work on adolescent nicotine dependence is more recent, so there are fewer empirical studies on early antecedents of nicotine addiction than on the antecedents of adolescent smoking (Colby et al. 2000a). Thus, in reviewing existing data, it is important to separate cigarette smoking and nicotine addiction as distinct outcomes (Hughes 2001). In addition, because most studies have focused on adolescent cigarette smoking rather than other forms of tobacco use, this review is restricted to studies of cigarette smoking.

Subsequent data suggest that approximately one in five high school students report "current" smoking, defined as any smoking in the past month (CDC 2008b). Smoking prevalence increases with age throughout adolescence. For example, data from the Monitoring the Future study (Johnston et al. 2007) show that current smoking is reported by 8.7 percent of 8th graders, 14.5 percent of 10th graders, and 21.0 percent of 12th graders. In addition to age, the prevalence of adolescent smoking varies with race and ethnicity. The highest rates were reported by American Indian and Alaska Natives, followed by non-Hispanic Whites, Hispanics, African Americans, and Asians (National Institute on Drug Abuse 2003). Few characteristics of adolescent smoking differed by gender, but adolescents with less-educated parents, lower aspirations for higher education, and rural residence are more likely to smoke cigarettes (Johnston et al. 2007). Finally, some adolescents smoke at high levels of frequency and quantity. For example, daily smoking is reported by 4.0 percent of 8th graders, 7.6 percent of 10th graders, and 12.2 percent of 12th graders; and 1.5 percent of 8th graders, 3.3 percent of 10th graders, and 5.9 percent of 12th graders smoke one-half pack or more of cigarettes per day (Johnston et al. 2007).

Measuring Nicotine Dependence in Adolescents

Colby and colleagues (2000b) summarized the literature on methods of measuring adolescent nicotine dependence. These researchers note that the two major approaches to measurement were formal diagnostic measures, such as interviews based on the *DSM-IV* criteria (APA 1994) and brief self-report measures that were most often modifications of the FTQ (Fagerström 1978). A brief self-report measure, Hooked on Nicotine Checklist (HONC), has been developed and used in longitudinal studies of the early acquisition of nicotine dependence (DiFranza et al. 2002a; O'Loughlin et al. 2003). This measure defines the onset of nicotine dependence as the point of experiencing loss of autonomy over tobacco use (DiFranza et al. 2002a). Although multiple measures have proved useful in predicting aspects of smoking behavior, as previously noted in this chapter, there is no gold standard for assessing nicotine dependence, either in adolescents or adults (Colby et al. 2000a,b; O'Loughlin et al. 2002).

The complexity of assessing adolescent nicotine dependence is evident from the modest correlation found between two of the most common methods for measuring dependence—*DSM*-based diagnoses and FTQ-derived self-report measures—and the fact that these measures do not identify the same adolescents as nicotine

dependent (Kandel et al. 2005). This finding has also been reported for adult smokers (Moolchan et al. 2002). Kandel and colleagues (2005) found a low agreement between *DSM*-based and FTQ-derived measures, except with high cigarette consumption (≥16 cigarettes per day). The *DSM*-based measure identified a higher prevalence of adolescent dependence because smokers met diagnostic criteria at much lower quantities of cigarettes than with the FTQ-derived measure (e.g., 60 versus 19 percent among those adolescent smokers smoking two to five cigarettes per day). Furthermore, for adolescent smokers who smoked a low number of cigarettes per day (e.g., 2.5 cigarettes), increasing depressive symptoms were associated with higher risk for *DSM*-diagnosed dependence (Kandel et al. 2005). This association between *DSM* diagnoses of tobacco dependence and depression has also been reported in adults (Breslau and Johnson 2000) (see "Epidemiology of Tobacco Use and Nicotine Dependence in Adults" later in this chapter). These findings led the investigators to believe that the *DSM* criteria identify a psychological component or behavioral symptoms common to both dependence and depression, which are not found in the FTQ-derived measure. Finally, Kandel and colleagues (2005) examined ethnic differences in dependence and found that non-Hispanic Whites had higher prevalence of dependence than other racial or ethnic groups, but this difference was accounted for by higher prevalence of smoking among this population. Once adjustment was made for differences in prevalence of smoking, differences by ethnicity were attenuated or eliminated. Thus, extensiveness of smoking must be considered when measuring dependence in youth.

Prevalence of Symptoms and Diagnoses in Adolescence

Studies suggest that adolescents report symptoms of dependence even at low levels of cigarette consumption (Colby et al. 2000a,b; Hughes 2001; DiFranza et al. 2002b; Panday et al. 2007). The difference in sensitivity to nicotine in adolescents and adults is also reported in animal models (Slotkin 2002; Adriani et al. 2003; Torres et al. 2008). For example, Levin and colleagues (2003) found that when rats were first exposed to nicotine in adolescence, they self-administered more nicotine than did rats exposed in adulthood. These differences in self-administration by age at first exposure persisted into adulthood. Similarly, Beluzzi and colleagues (2004) found that a single nicotine injection during early adolescence was sufficient to establish conditioned place preference in rats, whereas such injections in late adolescence or adulthood were not sufficient. Thus, paradigms for both self-administration and conditioned place preference in rats suggest that adolescence may be a developmental stage of particular vulnerability to the effects of tobacco exposure. Furthermore, a study by Torres and colleagues (2008), using a conditioned place preference paradigm, showed that adolescent rats not only found lower doses more reinforcing but also found higher doses less aversive compared with adult rats. If so, adolescents may be particularly vulnerable to developing tobacco dependence. DiFranza and colleagues (2002b) concluded that, on average, the onset of an initial symptom of tobacco dependence occurred when adolescents smoked only two cigarettes once a week. Even adolescents who smoked only once or twice in their lives reported an average of 1.3 symptoms on the HONC (1.0 for males and 1.4 for females) (O'Loughlin et al. 2003). As a cautionary note, the interpretation of the results relies on whether the HONC reflects valid symptoms of dependence.

Kandel and Chen (2000) examined a proxy measure of *DSM* diagnosis of nicotine dependence in data from the National Household Survey on Drug Abuse (now the National Survey on Drug Use & Health). They reported that, compared with adults, adolescents met the criteria for dependence at lower levels of cigarette consumption. Some researchers have suggested that these age differences reflect a greater sensitivity to nicotine among adolescents than among adults (Kandel and Chen 2000). However, researchers have also noted that these age differences can reflect cohort effects (Breslau et al. 2001; Hughes 2001). That is, given the national reductions in smoking prevalence are accompanied by greater social proscriptions against smoking, smoking among more recent (younger) cohorts may represent more "hard core" smoking with greater levels of dependence (Breslau et al. 2001), although other researchers have questioned whether a "hardening of smokers" has actually occurred (O'Connor et al. 2006).

Reported prevalence of nicotine dependence among current adolescent smokers varies depending on whether heavy or light smokers are considered. In one study, 19.4 percent of adolescents who smoked weekly were considered to be dependent on the basis of an analog measure from the *ICD* criteria (O'Loughlin et al. 2003). Even less-than-weekly tobacco use may result in progression toward nicotine dependence. A later study found that the most susceptible youth lose autonomy over tobacco within one or two days of first inhaling from a cigarette. The appearance of tobacco withdrawal symptoms and failed attempts to stop smoking can precede daily smoking dependence, as defined by *ICD-10*, and typically appears before consumption reaches two cigarettes per day (DiFranza et al. 2007). One study using data from the National Survey on Drug Use & Health reports a 28-percent prevalence

of last-year nicotine dependence (based on symptoms approximating *DSM-IV* dependence criteria) among adolescents aged 12 through 17 years who smoked during the last month, which was only slightly lower than the prevalence for adults (e.g., 30 to 32 percent among those aged 18 through 49 years) (Kandel and Chen 2000). The majority of adolescent daily smokers meet criteria for nicotine dependence. For example, Kandel and colleagues (2005) found that 87 percent of adolescent daily smokers met *DSM* criteria and 63 percent met the modified FTQ criteria (score >3). Similarly, O'Loughlin and colleagues (2003) found that 65.9 percent of seventh graders who smoked daily met *ICD* criteria.

There has also been interest in whether adolescents experience withdrawal symptoms on the discontinuation of smoking, either as part of an attempt to stop smoking or during periods when they cannot smoke. Colby and colleagues (2000a) summarized six retrospective studies in which adolescent smokers recalled their experiences during periods of nonsmoking. Most adolescents reported at least one symptom of withdrawal. Craving was the most commonly reported symptom upon abstinence. Fernando and colleagues (2006) analyzed data from the National Youth Tobacco Survey and reported that 63 percent of adolescents who smoked five or fewer cigarettes per day reported at least one withdrawal symptom. Hanson and colleagues (2003) examined the effects of the nicotine patch on adolescent-reported withdrawal symptoms. Compared with the placebo group, the nicotine patch group had lower scores for withdrawal symptoms.

Killen and colleagues (2001) recruited adolescents from alternative high schools and from a homeless shelter who smoked at least 10 cigarettes per day. There were two assessment sessions. Participants were randomly assigned to the nicotine patch or the placebo patch for the second assessment. The researchers found a decrease in heart rate across sessions only for the placebo condition. However, they found significant increases in self-reported withdrawal symptoms for both the nicotine patch and the placebo patch conditions. The most intense withdrawal symptoms were craving and anxiety, which were not relieved by the nicotine patch. Finally, some adolescents who believed they had worn a nicotine patch had expectancy effects; they reported less craving and frustration and a greater ability to concentrate. Together, these results suggest that adolescent smokers experience withdrawal symptoms but that expectancy effects also influence findings. Prokhorov and colleagues (2005) suggest caution about interpreting nonspecific symptoms such as irritability, depression, insomnia, and trouble concentrating, which can have multiple causes besides tobacco withdrawal.

Some animal data suggest that adolescents experience a dampened withdrawal response compared with that in adults (O'Dell et al. 2004, 2006). O'Dell and colleagues (2004) precipitated withdrawal with mecamylamine in rats receiving long-term administration of nicotine versus saline and found mecamylamine-induced withdrawal in adult rats but not in adolescent rats. These findings in animal studies, combined with limited clinical data, indicate the need for further studies of differences in withdrawal symptoms by age.

Trajectories of Smoking from Adolescence to Adulthood

Cigarette smoking shows age-related trends with typical initiation of smoking occurring in early adolescence. Retrospective data from the 1999 National Survey on Drug Use & Health (Kopstein 2001) suggest that the average age at first use of cigarettes is 15.4 years and the average age at initiation of daily smoking is 18 years. Data from both retrospective and longitudinal studies suggest that smoking prevalence or incidence of daily smoking in adolescents increases over time, peaks in young adulthood, and then declines (Chen and Kandel 1995; Breslau et al. 2001). However, these data are limited in that they describe a single "average" trajectory of age-related changes in smoking behavior, which obscures substantial heterogeneity among smokers. For example, there is variation in age at smoking initiation (Breslau et al. 1993a; Chassin et al. 2000) in the time it takes to progress to daily smoking, and in the time to develop dependence symptoms (DiFranza et al. 2002b).

Advances in mixture modeling (Nagin 1999; Muthén and Muthén 2000) have enabled longitudinal studies to identify multiple age-related trajectories of smoking behavior. Some of these studies conducted follow-up on participants through adolescence (Colder et al. 2001; Audrain-McGovern et al. 2004b; Abroms et al. 2005). Wills and colleagues (2004) performed cluster analysis rather than mixture modeling. These studies have all identified multiple trajectory groups, which typically include a group with early-onset (7th grade) regular smoking (smoking at least a few times a week); a group with experimental smoking (smoking occasionally each year); nonsmokers; and a group with intermediate- (regular smoking in 9th grade) and late-onset (regular smoking in 10th grade) regular smoking. These studies do not assess tobacco dependence, and even the late-onset groups were younger than age 18 years. Karp and colleagues (2005) studied only adolescents who had started to smoke. Most of their participants remained at low levels of smoking, but there was heterogeneity in the speed at which the others escalated their cigarette use, and youth across all rates of escalation were more likely to show symptoms of nicotine dependence than those individuals who maintained low levels

of cigarette use. Soldz and Cui (2002) conducted follow-up on participants through 12th grade. They identified the following groups: nonsmokers, experimental smokers, smokers with early or late escalation of smoking, and stable continuing smokers. Their findings are noteworthy for identifying a group who stopped smoking, which was absent in other studies.

Several studies had follow-up from adolescence to adulthood. White and colleagues (2002b) recruited 374 adolescents in New Jersey through random telephone sampling. The participants were interviewed five times from age 12 years to age 30 or 31 years. The investigators identified three trajectory groups: (1) nonsmokers and experimental smokers; (2) occasional smokers and smokers whose smoking peaked at 18 years of age and then declined; and (3) heavy smokers and regular smokers. Predictor variables distinguished between nonsmoking and smoking trajectories but could not predict heavy smoking among smokers. Predictor variables were disinhibition items from the Zuckerman Sensation Seeking Scale, low school grades, and use of other drugs. Chassin and colleagues (2000) recruited 8,556 adolescents in 6th through 12th grades in a midwestern county school system and surveyed them annually in 1980 through 1983. Additional follow-ups were conducted in 1987 and 1993 and identified a greater number of groups reflecting smoking trajectory. The groups included nonsmokers, experimental smokers, persons with early smoking initiation who became stable smokers, persons with late smoking initiation who became stable smokers, and persons who stopped smoking. On average, persons with early smoking initiation who became stable smokers were smoking daily by 15 years of age and averaged more than one-half pack of cigarettes per day by 18 years of age. In contrast, persons with late smoking initiation who became stable smokers averaged weekly smoking at age 18 years but less than one-half pack per day. Thus, the stable group with early initiation was also at particular risk for heavy smoking. This group was characterized by (1) a high frequency of parental smoking, perhaps reflecting both genetic and environmental risk factors; (2) less parental support; and (3) greater attitudinal tolerance for deviant behavior ("deviance proneness").

Orlando and colleagues (2004) identified similar groups: nonsmokers; triers (never exceeding one or two cigarettes per year, increasing slightly in early adolescence, then decreasing to very low levels in young adulthood); late-onset increasers (started at a low smoking rate, but increased smoking steadily with the sharpest increase occurring between 18 and 23 years); decreasers (smoked a few times per month at age 13 years but decreased to once or twice a year by age 23 years); and early increasers (started out at low level of smoking at age 12 years but rose sharply to weekly smoking by age 14 years with continuing increases in smoking). These researchers also identified a group of heavy smokers throughout the age range of 13 through 23 years. The studies by Chassin and associates (2000) and Orlando and colleagues (2004) both found that the group with late initiation seemed to be protected in adolescence by family factors, including (across the two studies) less familial smoking, more parental support, intact families, and higher levels of parental education. However, Orlando and colleagues (2004) found that the trajectory groups of the stable heavy smokers, the persons with early initiation who increased cigarette consumption, and those with late initiation who increased cigarette consumption all converged to a similar point of heavy smoking by 23 years of age. Thus, these studies identify a group of persons with early initiation and sharply escalating cigarette consumption who are at high risk for heavy smoking. However, late initiation of smoking does not necessarily imply protection against heavy smoking. Divergence among these groups may occur at ages older than 23 years, which were not represented in the study by Orlando and colleagues (2004).

Several studies focused on African Americans. Juon and colleagues (2002) conducted follow-up on inner-city participants who had low socioeconomic status (SES) and divided them into nonsmokers, former smokers, smokers with late initiation (after age 18 years), and smokers with early initiation. The group with early initiation was more aggressive in childhood, more likely to have lax parental supervision, and had more drug problems. White and colleagues (2004) modeled trajectories of the number of cigarettes smoked each day. They identified nonsmokers, light smokers, and heavy smokers and found that African Americans started smoking later and had lower cigarette consumption than did White participants. Similarly, Blitstein and colleagues (2003) found that progression of smoking was more likely to be slow among African Americans. Finally, Brook and colleagues (2006) modeled trajectories for African American and Puerto Rican adolescents from age 14 to 26 years and identified the following groups: nonsmokers, persons whose smoking peaked at 18 years of age and then declined, smokers with late initiation, and smokers with early initiation. Although there are few studies, these findings suggest that the age at smoking initiation and the speed of progression in cigarette consumption may differ by ethnicity. This hypothesis should be considered in describing smoking trajectories from adolescence to adulthood.

Another important consideration is that none of these longitudinal studies spanning adolescence and adulthood directly assessed nicotine dependence. Therefore, the extent to which predictors of early progression to heavy smoking are predictors of nicotine dependence

is unknown. However, Storr and colleagues (2004) performed a latent class analysis of nicotine dependence symptoms by using data from the National Survey on Drug Use & Health. The findings indicated that early smoking initiation leads to a higher probability of experiencing nicotine dependence features within two years of smoking onset compared with those smokers who initiated smoking after age 20 years.

Determinants of Nicotine Addiction

Researchers have described the progression of cigarette smoking as a process of multiple stages, including precontemplation, contemplation or preparation, initial trying, experimental or irregular smoking, and established daily smoking (Mayhew et al. 2000). Researchers have also suggested that movement across these stages is determined by different factors (Flay et al. 1983). For example, social factors such as peer modeling and opportunities to experiment may have a greater influence on initial experimentation with smoking, whereas factors such as genetic risk, negative affect, and propensity to develop tolerance to nicotine have been hypothesized to play a greater role in determining movement across later stages of smoking (Flay et al. 1983). However, the empirical evidence for such stage-specific predictors is weak. Mayhew and colleagues (2000) reviewed this literature and found that few studies tested for stage-specific predictors. Rather, most studies aggregated data across stages, predicting any progression in smoking or predicting broad categories such as "regular" smoking, which ranges from smoking a single cigarette a month to daily heavy smoking. Moreover, much of the research on adolescent smoking initiation is motivated by an interest in smoking prevention. Therefore, many studies focus on the initiation of smoking or experimental smoking. Few studies have examined predictors of nicotine dependence or daily heavy smoking. For these reasons, little is known about stage-specific predictors of nicotine dependence.

Some studies have used genetically informed designs to examine the extent to which adolescent tobacco dependence is related to additive genetic influences, shared environmental influences that make siblings more alike, and unshared environmental influences that make siblings different (Boomsma et al. 2002). From the extensive literature on the genetics of adolescent smoking, several studies are selected for review, because they focus on heavy smoking or nicotine dependence in adolescence. McGue and colleagues (2000) report that 44 percent of the variance in nicotine dependence among 17-year-old twins was associated with additive genetic influence. However, shared environment also played an important role, accounting for 37 percent of the variance in nicotine dependence. Similarly, a study that focused on high frequency of smoking rather than nicotine dependence reports that both additive genetic and shared environmental influences were important (Rende et al. 2005). One study reported differences by gender in heritability for "problem" tobacco use (Rhee et al. 2003). Heritability was a stronger influence, and shared environmental factors were a weaker influence for female than for male adolescents. Thus, studies of behavioral genetics in relation to adolescent heavy smoking or nicotine dependence suggest the importance of both genetic and environmental influences, although in an adult study population, tobacco dependence seems to be more strongly influenced by genetics (see "Genetics" earlier in this chapter).

Researchers have also associated maternal smoking during pregnancy with the later development of tobacco dependence in offspring. Buka and colleagues (2003) examined a sample (aged 17 to 39 years) from the Providence (Rhode Island) cohort of the National Collaborative Perinatal Project. They found an elevated risk for tobacco dependence when the mother smoked more than one pack of cigarettes per day during pregnancy. However, the investigators note that these results could also be explained by genetic influences. Moreover, because postnatal maternal smoking was not considered, social environmental mechanisms of intergenerational transmission of nicotine dependence (e.g., role modeling) could also influence findings. For example, Cornelius and colleagues (2005) found that the relationship between prenatal exposure and adolescent smoking was not significant after adjustment for factors such as the mother's current smoking and the smoking of friends.

Studies have also associated child and adolescent psychopathology with nicotine dependence and heavy smoking. Using data from the Yale Longitudinal High-Risk Study, Dierker and colleagues (2001) found a significant association of nicotine dependence with anxiety disorder, affective disorder, conduct disorder, oppositional defiant disorder, substance dependence, and parental substance dependence. The investigators reported that affective disorders and drug use disorders remained unique predictors of nicotine dependence after adjustment for confounding comorbidities. These relationships were found only for nicotine dependence and not for distinguishing between nonsmoking and experimentation or between regular smoking and a combined group of earlier stages of smoking progression. Clark and Cornelius (2004) also examined adolescents with or without parental substance use disorder. They found that substance use disorders and daily smoking in parents, as well as conduct disorder, oppositional defiant disorder, and attention-deficit/hyperactivity disorder in offspring predicted progression to daily smoking. However, these researchers found no significant

relationship between anxiety or depressive disorders in adolescents and progression to daily smoking.

In a longitudinal study of a large sample of adolescents recruited from high schools, Rohde and colleagues (2004) report a finding similar to that of Clark and Cornelius (2004). Externalizing disorders (e.g., attention-deficit/hyperactivity disorder, disruptive behavior disorders, and alcohol and drug use disorders) are more strongly and consistently associated with smoking cigarettes than are internalizing disorders (e.g., mood and anxiety disorders). In a multivariate analysis that included familial psychopathology, familial smoking, and composite variables of internalizing and externalizing disorders, only the externalizing disorders predicted both progression to daily smoking and to nicotine dependence among daily smokers. Thus, these studies show a consistent support for externalizing disorders, but less consistent support for internalizing disorders, as predictors of frequent smoking or nicotine dependence. The inconsistent effects of internalizing disorders may reflect variation in study samples and methods and, particularly, differences in the choice of which variables are statistically controlled in models of multiple predictors. Inconsistent results may also reflect the presence of moderating variables. For example, Patton and colleagues (1998) found that depression and anxiety were significant predictors of transition to daily smoking only when there were high levels of peer smoking.

Finally, Lloyd-Richardson and colleagues (2002) used data from a cross-sectional study—the National Longitudinal Study of Adolescent Health—to compare adolescents who were at different smoking stages. The smoking stages compared were persons who never smoked; experimental smokers, who tried a cigarette but had not smoked in the past 30 days and had never smoked daily; intermittent smokers, who reported some smoking but no daily smoking in the past 30 days; and regular smokers, who smoked daily for the past 30 days. The investigators examined whether predictor variables had different effects at different smoking stages. For example, a variable might be particularly important at early stages of smoking and thus would differentiate persons who never smoked from those who experimented with smoking but would not significantly differentiate among the other groups. The results showed some stage specificity of predictors. Peer smoking and low level of school connectedness more strongly differentiated between regular smokers and persons who never smoked, experimental smokers, and intermittent smokers than differentiated among persons who never smoked, experimental smokers, and intermittent smokers. Thus, according to the investigators, peer smoking and low school connectedness were more influential in later stages of smoking than in early stages. Alcohol use showed the opposite pattern and so was thought to be more influential in the early stages of smoking. However, there was also evidence that predictors were not stage specific. For example, depression, delinquency, parental smoking, and family connectedness significantly differentiated among all the smoking groups, and thus these variables were not found to be stage-specific predictors.

Summary and Future Directions

The literature on adolescent nicotine addiction is relatively recent and less extensive than that resulting from the years of research that has been conducted on adolescent smoking. Some data suggest that compared with adults, adolescents display nicotine addiction at lower levels of cigarette consumption and so may be particularly vulnerable to addiction when exposed to tobacco. To both replicate and explain this phenomenon, there is a critical need for systematic assessment of how adolescents differ in their experience of different aspects of addiction—development of tolerance, withdrawal, reinforcing effects, associative learning—which makes this population more vulnerable to addiction compared with adults. The developing brain may be especially susceptible and receptive to acute or repeated doses of nicotine (Adriani et al. 2003; Schochet et al. 2005) and potentially other tobacco-related constituents and to associative learning processes.

Multiple trajectories of smoking from adolescence to adulthood have been identified, with one subgroup showing early initiation and a steep escalation of smoking associated with familial smoking and lack of parental support and with risk for chronic heavy smoking in adulthood. Further studies are needed to identify the genetic and environmental contributions to such trajectories, as well as the endophenotypes underlying the genetic contributions. Epidemiologic studies are particularly useful in providing an understanding of the critical environmental influences that may interact with specific genes to enhance the risk for developing nicotine dependence.

Another risk factor for nicotine addiction may be the diagnosis or symptoms of externalizing disorders. Previous research has been focused on the common neurosubstrates associated with nicotine addiction and depression (see "Psychiatric Comorbidity" earlier in this chapter). However, a better understanding of the relationship and the neurophysiology that links smoking to externalizing disorders is needed. In summary, future research needs to focus on the complex interactions among genes, environment, social and neurodevelopmental phases, and their influence on the trajectory toward nicotine dependence.

Epidemiology of Tobacco Use and Nicotine Dependence in Adults

Prevalence of Cigarette Smoking and Nicotine Dependence

According to one study, the prevalence of current smoking among adults (aged ≥18 years), as assessed by the National Health Interview Survey, was approximately 19.8 percent, or 43.4 million U.S. adults (CDC 2008a). According to the survey, 77.8 percent of current smokers smoked every day and 22.2 percent smoked on some days. (Current smokers are defined as those who smoked ≥100 times during their lifetime and who are smoking every day or on some days.) This high prevalence of daily smokers indicates the highly addictive nature of cigarettes. More men (22.3 percent) than women (17.4 percent) reported current smoking. For the racial and ethnic groups, the lowest prevalence of smoking was among Asians (9.6 percent), and the highest prevalence was among American Indians and Alaska Natives (36.4 percent). Across educational levels and SES, the highest prevalence of smoking was among persons with low levels of education—44.0 percent of those with a General Educational Development diploma and 33.3 percent of those with 9 to 11 years of education, versus 6.2 percent of those with graduate degrees—and persons with the lowest levels of income—28.8 percent of adults living below the poverty level and 20.3 percent of those living at or above the poverty level. The prevalence of smoking was lowest among persons aged 65 years or older (10.2 percent) and highest among those aged 18 through 24 years (23.9 percent).

In adults, the diagnosis of nicotine dependence or addiction in population surveys has largely been based on *DSM* 3rd ed. (rev) (*DSM-III-R*), *DSM-IV* (APA 1987, 1994, 2000), and *ICD-10* (WHO 1992) diagnostic criteria. The adult survey instruments used to make the diagnosis have included the National Institute of Mental Health Diagnostic Interview Survey and the Composite International Diagnostic Interview-Substance Abuse Module (Colby et al. 2000b). Researchers also have used data from other population surveys, such as the National Survey on Drug Use & Health to assess symptoms of tobacco dependence. That survey includes terms or phrases such as (1) "reported daily use of the product for two weeks or longer," (2) "have tried to cut down on smoking," (3) "unable to cut down or quit or experienced difficulty quitting," (4) "felt a need for more tobacco for the same effect," (5) "felt dependent," or (6) "felt sick or experienced withdrawal symptoms when stopping smoking." Results have been reported on the percentage of smokers who indicated one or more of these symptoms of dependence or experienced at least one of the withdrawal symptoms, psychoactive effects (e.g., "it relaxes or calms me"), or difficulty with smoking cessation, as a sign of potential tobacco dependence (CDC 1994, 1995a,b). Researchers have also used the presence of a specified number of these symptoms as a proxy measure for *DSM-IV* criteria for nicotine dependence (Kandel et al. 1997).

The prevalence of nicotine dependence based on these measures in population- or community-based samples from studies conducted in the United States are shown in Table 4.11. The variability in the prevalence of nicotine dependence can be mostly attributed to the characteristics of the population surveyed and the diagnostic tools used. The lifetime prevalence of *DSM-III-R* diagnosis of nicotine dependence in the general U.S. population ranges from 20 to 24 percent, and past-year prevalence of *DSM-IV* diagnosis of nicotine dependence is 9 to 13 percent. By virtually any measure, the prevalence of lifetime nicotine dependence is higher for cigarette smoking than for any other category of substance abuse (Anthony et al. 1994; Giovino et al. 1995). The results from Table 4.11 also illustrate that almost one-third of persons who have ever tried smoking cigarettes became dependent on nicotine.

Examination of self-reports of specific symptoms by adult daily or dependent smokers (Table 4.12) shows that in the majority of studies that assessed these symptoms, the least frequently reported symptoms include tolerance, withdrawal, and giving up activities as a result of tobacco use. The most frequently reported symptoms include efforts to reduce smoking and the inability to reduce smoking; feeling dependent; using more cigarettes than intended; and perhaps, continuing to smoke cigarettes despite experiencing problems. Therefore, the symptoms of nicotine dependence most likely to be reported among adults tend to be behavioral or a loss of control over smoking, and the least reported items appear to be physiological (e.g., symptoms of tolerance and withdrawal). In a study by Kandel and Chen (2000), a higher proportion of adolescents reported experiencing symptoms of tolerance (22.2 percent) and/or physical and psychological problems (27.0 percent) resulting from tobacco use, compared with the proportion of adults aged 18 through 49 years (14.4 and 20.3 percent, respectively) and adults aged 50 years or older (9.9 and 11.0 percent, respectively). These results may reflect either the cohort effect or the effect described previously as higher sensitivity in adolescents than that in adults to the effects of nicotine on physiological symptoms of dependence.

Table 4.11 Lifetime and current prevalence of nicotine dependence in population studies in the United States

Study	Design/sample	Diagnostic measure	Prevalence (%)	Population characteristics
Hughes et al. 1987	1,006 middle-aged male smokers from Multiple Risk Factor Intervention Trial screening 1980	*DSM-III* FTQ score ≥7	90.0 36.0	Smokers (82% smoked ≥15 cigarettes/day, mean cigarettes/day ± standard deviation = 28.0 ± 12.8)
Breslau et al. 1991, 1993a	Random sample aged 21–30 years Large health maintenance organization N = 1,007 of 1,200 1989–1990 (follow-up)	NIMH-DIS *DSM-III-R*[a]	20.0 27.0 51.0	Total sample Ever smoked Ever smoked daily for 1 month Lifetime prevalence
Anthony et al. 1994	Population survey of noninstitutionalized persons aged 15–54 years National Comorbidity Survey N = 4,414 1990–1992	CIDI *DSM-III-R*[b]	24.1 31.9	General population Ever smoked[c] Lifetime prevalence
Centers for Disease Control and Prevention 1995b	NHSDA population survey of noninstitutionalized civilians aged ≥12 years N = 61,426 1991 and 1992	NHSDA (≥1 indicator of dependence) *DSM-IV*[d]	75.2 90.9	Smoked ≥1 time in past 30 days Daily smokers Smoked daily for ≥2 consecutive weeks in past 12 months
Cottler et al. 1995	Field trial using random-digit telephone dialing methods for general population sample N = 260 daily smokers 1990–1991	CIDI-SAM *DSM-III-R*[b] *ICD-10* *DSM-IV*[d]	 71.0 77.0 66.0	Daily smoking for 1 month Lifetime prevalence
Kandel et al. 1997, 2001; Kandel and Chen 2000	NHSDA population survey of noninstitutionalized civilians aged ≥12 years N = 87,915: 1991–1993 N = 39,994: 1994–1996	NHSDA *DSM-IV*[d]	8.6–10.5 28.0 28.5	General population Used tobacco product in past year Smoked last month Prevalence in past year
Breslau and Johnson 2000	Random sample aged 21–30 years Large health maintenance organization N = 238 daily smokers 1989–1990 (follow-up)	NIMH-DIS *DSM-III-R*[a] FTND score ≥4	 66.4 75.0 55.5 57.1	 Daily smokers Daily smokers with FTND score ≥4 Daily smokers with FTND score <4 Daily smokers Lifetime prevalence
Breslau et al. 2001, 2004a	4,414 respondents to National Comorbidity Survey, Tobacco Supplement Aged 15–54 years 1990–1992	CIDI *DSM-III-R*[b]	24.0 48.0	Total population Daily smokers Lifetime prevalence

Table 4.11 Continued

Study	Design/sample	Diagnostic measure	Prevalence (%)	Population characteristics
Grant et al. 2004	NESARC population survey of noninstitutionalized civilians aged ≥18 years N = 43,093 2001–2002	NIAAA Alcohol Use Disorder and Associated Disabilities Interview Schedule *DSM-IV*[e]	12.8	Total sample Prevalence in past year

Note: **CIDI** = World Health Organization's Composite International Diagnostic Interview; **CIDI-SAM** = CIDI Substance Abuse Module; ***DSM-III*** = *Diagnostic and Statistical Manual of Mental Disorders,* 3rd ed.; ***DSM-III-R*** = *DSM,* 3rd ed. (rev); ***DSM-IV*** = *DSM,* 4th ed.; **FTND** = Fagerström Test for Nicotine Dependence; **FTQ** = Fagerström Tolerance Questionnaire; ***ICD-10*** = *International Classification of Diseases, Tenth Revision*; **NESARC** = National Epidemiology Survey on Alcohol and Related Conditions; **NHSDA** = National Survey on Drug Use & Health; **NIAAA** = National Institute on Alcohol Abuse and Alcoholism; **NIMH-DIS** = National Institute of Mental Health Diagnostic Interview Schedule.

[a]NIMH-DIS included ever smoking daily for ≥1 month plus *DSM-III-R* criteria for dependence with ≥3 of the following symptoms persisting for ≥1 month: greater use than intended; unsuccessful efforts to control use; important activities given up; continued use despite social, psychological, or health problems; tolerance; withdrawal symptoms; and use to avoid withdrawal symptoms. Excluded 2 symptoms listed in the general *DSM-III-R* criteria for psychoactive substance use disorders: (1) great deal of time spent in activities necessary to acquire substance or recover from effects and (2) frequent intoxication or withdrawal symptoms when expected to fulfill major role obligations.

[b]CIDI criteria included daily smoking for ≥1 month plus *DSM-III-R* criteria for dependence with ≥3 of criteria with symptoms persisting for ≥1 month.

[c]Data on persons who ever smoked estimated from synthesis with NHSDA data.

[d]*DSM-IV* criteria for dependence with ≥3 of the following symptoms within a 12-month period: tolerance; withdrawal; using larger amounts or longer than intended (assessed as needed or if smoker felt dependent on nicotine); unsuccessful efforts to cut down; negative social, occupational, and physical consequences; and persistent physical and psychological problems. Excluded spending significant amount of time to obtain substance; instead, quantity (smoking ≥2 packs daily in past 30 days) was examined in relation to dependence.

[e]NIAAA used *DSM-IV* criteria modified as follows: use of nicotine to relieve or avoid withdrawal as operationalized by using the following four symptom items: (1) use of nicotine on awakening, (2) use of nicotine after situation in which use was restricted, (3) use of nicotine to avoid nicotine withdrawal symptoms, and (4) waking up in middle of the night to use tobacco. "Giving up activities in favor of nicotine use" was assessed as (1) giving up or cutting down on important activities, such as associating with friends or relatives or attending social activities, because tobacco use was not permitted at activity and (2) giving up or cutting down on activities that were of interest or that gave pleasure because tobacco use was not permitted. The "great deal of time spent using tobacco" criterion was assessed by single symptom item, chain-smoking. The "using tobacco more than intended" criterion was operationalized as having a period when tobacco was used more than intended. Nicotine dependence was assessed for any tobacco product, including cigarettes, cigars, pipes, chewing tobacco, and snuff.

However, on the basis of animal studies, withdrawal symptoms would be presumed to be fewer in adolescents than in adults (O'Dell et al. 2004, 2006), yet more adolescents are endorsing physical problems than do adults. As pointed out previously, factors other than withdrawal may be associated with higher endorsement of withdrawal symptoms among adolescents. Another possibility is that questions on physical dependence, particularly on tolerance, are not asked in a manner that is understood by or relevant to adult smokers.

The symptoms most frequently reported by adults appear to be less specific to the diagnosis of nicotine dependence. For example, Breslau and colleagues (1994) observed that (1) 88.6 percent of dependent smokers reported the symptom of dependence described as "smoking more than intended" (p. 747) and (2) 93.6 percent reported "unsuccessful attempts to quit" (p. 747). However, these items were also reported by a substantial percentage of nondependent smokers (47.9 and 25.2 percent, respectively) who smoked daily for a month or more during their lifetime but never met criteria for nicotine dependence. However, 87 percent of dependent smokers as opposed to only 12 percent of nondependent smokers reported one or more of the three physiological indicators of dependence (tolerance, withdrawal symptoms, and/or cigarette use to avoid withdrawal symptoms).

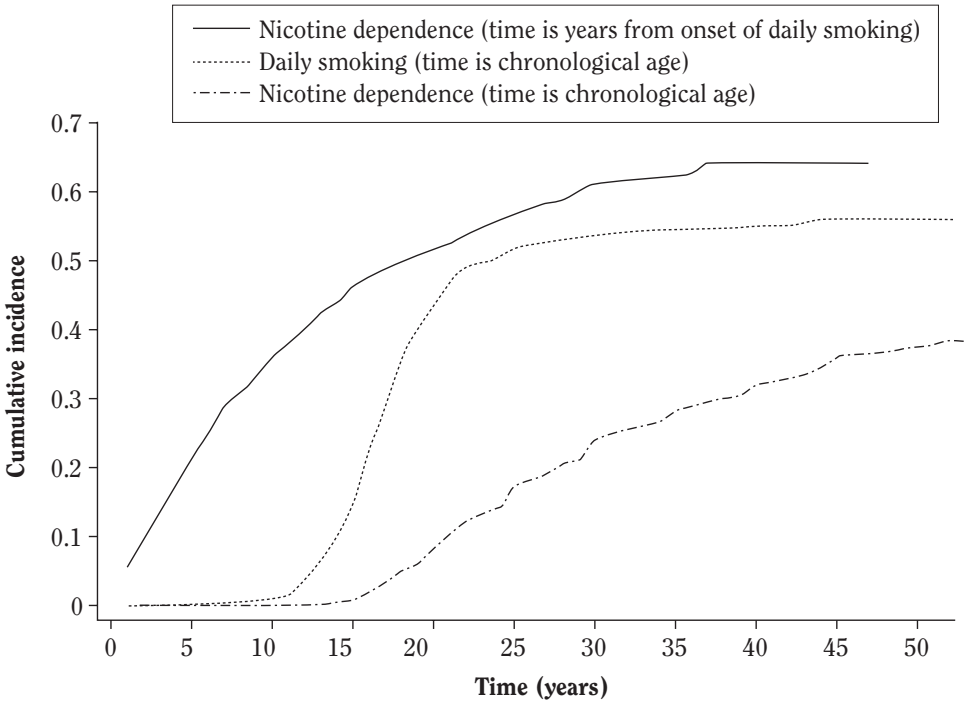
With regard to the onset of nicotine dependence relative to daily smoking, one study of data from the

National Comorbidity Survey showed that the highest rates of becoming nicotine dependent, as defined by *DSM-III-R*, occurred in the first 16 years from the year after progression to daily smoking, whereas in the subsequent 10 years the progression to nicotine dependence declined and continued at a slower rate (Figure 4.5) (Breslau et al. 2001). Thus, nicotine dependence generally followed daily smoking, although 5.4 percent of nicotine dependence began before or in the same year as progression to daily smoking. In most cases, the onset of nicotine dependence occurred one or more years after the initiation of daily smoking. These results appear somewhat contrary to results described in "Prevalence of Symptoms and Diagnoses in Adolescence" earlier in this chapter, which indicates that dependence symptoms may occur even earlier in a person's history of smoking. The discrepancies in results may be a function of how nicotine dependence was diagnosed or defined, that is, whether one was examining symptoms or a diagnosis of dependence or cohort effects.

Prevalence by Dose, Duration, and Subpopulations

The results from Table 4.11 also show that the more a person smokes, the greater is the likelihood of a diagnosis of nicotine dependence (CDC 1995b). Kandel and Chen (2000) observed a linear dose-response relationship between the number of cigarettes smoked in the past month and the percentage of smokers with nicotine dependence in the last year. This finding was based on self-reporting of symptoms approximating *DSM-IV* criteria for dependence and was confirmed in other studies (Kawakami et al. 1998). The percentage of male and female smokers with a diagnosis of dependence rose sharply and significantly as the amount of smoking increased from less than one cigarette per day, to one to five cigarettes per day, and to one-half pack per day. Thereafter, the increase in the percentage of smokers with a diagnosis of dependence tended to rise minimally; however, at

Figure 4.5 Cumulative incidence curves of daily smoking and nicotine dependence in the National Comorbidity Survey



Source: Breslau et al. 2001. Reprinted with permission from American Medical Association, © 2001.
Note: Participants included 4,144 daily cigarette smokers and 2,136 smokers who were nicotine dependent.

Table 4.12 Prevalence of selected symptoms of nicotine dependence reported in selected studies

Study	Population	Used daily for ≥2 weeks	Tried to cut down	Unable to cut down/ unsuccessful attempts to control use (%)	Felt need for more/ tolerance (%)
Henningfield et al. 1990	NHSDA				
	Used at least once (N = 5,105)	51.1	54.2		11.7
	≥1 pack/day (N = 1,010)	91.2	84.3		23.9
Breslau et al. 1994	Random sample				
	Health maintenance organization				
	Aged 21–30 years (N = 1,200)				
	All smokers[a] (N = 394)			60.4	27.4
	Dependent[b] (N = 202)			93.6	45.5
	Nondependent[c] (N = 194)			25.2	8.3
Centers for Disease Control and Prevention 1995b	NHSDA 1991–1992				
	Aged ≥12 years				
	All responders (N = 14,688)	78.4	64.4	76.6	14.0
	Daily users in past year (N = 10,343)	NA	74.9	79.6	17.5
Kawakami et al. 1999[d]	Current male smokers			64.2	
	Volunteers (N = 58)				
	Smoking cessation patients (N = 151)			65.5	
	Health Risk Assessment survey sample (N = 194)			59.3	
Storr et al. 2004	NHSDA				
	1995–1998				
	Recently initiated			21.7	16.0

Note: **NA** = data not available; **NHSDA** = National Survey on Drug Use & Health.
[a]Smoked daily for ≥1 month in their lifetime.
[b]*Diagnostic and Statistical Manual of Mental Disorders,* 3rd ed. (rev) *(DSM-III-R)* criteria for nicotine dependence.
[c]Has never met *DSM-III-R* criteria for nicotine dependence.
[d]Conducted in Japan.

numbers higher than one and one-half packs of cigarettes per day, females showed a higher prevalence of dependence than did males. The duration of cigarette smoking has also been related to the prevalence of nicotine dependence (Kandel and Chen 2000).

Kandel and Chen (2000) also found that among persons who smoked in the last month, the prevalence of nicotine dependence in middle-aged adults was similar to that in adolescents. After adjustment for the quantity of cigarettes smoked, the prevalence of dependence was generally higher among adolescents than among adults, particularly at lower levels of cigarette consumption. Several reasons that may account for this finding (i.e., cohort effects) have been discussed previously (see "Prevalence of Cigarette Smoking and Nicotine Dependence" earlier in this chapter). The lowest rates of nicotine dependence were in adults aged 50 years or older; this finding was attributed to lower sensitivity to increased quantity of nicotine intake. The investigators also found that the prevalence of nicotine dependence was higher among females than among males, even after adjustment for the number of cigarettes smoked. However, this difference was observed only among persons 18 through 49 years of age. The prevalence of dependence was also higher among Whites than among Blacks, and this difference was particularly evident at the lower levels of cigarette consumption.

Other studies have found no differences by gender in the prevalence of nicotine dependence (Breslau et al. 1991; Anthony et al. 1994) but have confirmed differences by race when *DSM* criteria were used to diagnose nicotine dependence (Breslau et al. 1994, 2001). However, when time to the first cigarette was used as an indicator of dependence, more Blacks than Whites reported smoking

Felt dependent (%)	Felt sick when stopped/ withdrawal symptoms (%)	Greater use than intended (%)	Use despite problems (%)	Use to avoid/ relieve withdrawal (%)	Activities given up (%)	Salience (drug involvement) (%)
37.9	16.5					
79.2	33.3					
	30.5	68.8	44.4	26.6	6.6	
	58.9	88.6	72.3	49.0	12.9	
	0.3	47.9	15.1	3.1	0.0	
68.9	34.9					
85.0	37.4					
55.2	67.2	84.5	65.5	60.3	10.3	
54.7	73.0	73.0	56.1	63.5	17.6	
36.1	58.2	67.5	42.8	49.0	8.2	
		17.9	4.7–5.3		4.9	20.1

within 10 minutes of awakening even though Blacks had lower or similar levels of cigarette consumption (Royce et al. 1993). In another study, Blacks also reported shorter time to the first cigarette than did Whites (Ahijevych and Gillespie 1997). Differences in nicotine metabolism and blood concentrations of cotinine may contribute to differences in the prevalence of dependence among Blacks and Whites (Benowitz et al. 1999). Among smokers who ever smoked daily, nonnicotine-dependent Blacks were 2.5 times more likely to persist in smoking than were nondependent Whites (Breslau et al. 2001). These findings suggest a weakness in diagnostic systems categorized by differences in ethnic and racial groups, differences in sensitivity to nicotine across groups, or differences in sociocultural factors (e.g., extent of cigarette promotion or smoking restrictions) that contribute to persistence in smoking across groups.

Nicotine Dependence and Psychiatric Comorbidity

As described in the previous sections, studies have found a strong association between nicotine dependence and comorbid disorders that warrants further discussion. It is estimated that nearly one-half of all cigarettes sold in the United States (44 percent) are consumed by people with mental illnesses or substance abuse disorders. In addition, the prevalence of tobacco use among those with either addictions and/or mental illness is between 38 to 98 percent, as opposed to 19.8 percent for the general population (Schroeder 2009). Breslau and colleagues (1991) have conducted several studies. One earlier population-based study in Michigan observed that young adults with a diagnosis of nicotine

dependence reported higher prevalence of alcohol and drug dependence and major depression and anxiety disorders than did persons who had never experienced nicotine dependence (Breslau et al. 1991). The relationships between each disorder and nicotine dependence were observed even when adjustments were made for confounding comorbidities. These findings are similar to those observed for adolescent smokers described earlier (Dierker et al. 2001) (see "Determinants of Nicotine Addiction" earlier in this chapter). However, the results were contrary to other findings among adolescents (Clark and Cornelius 2004; Rohde et al. 2004). Other population-based research and clinical studies have also pointed to the strong relationship between daily smokers or nicotine-dependent smokers (as opposed to lifetime nonsmokers or nondependent smokers) and substance use disorders, anxiety disorders, and depression, with higher prevalence of comorbid psychiatric disorders among nicotine-dependent smokers and higher prevalence of nicotine-dependent smokers among persons with comorbid disorders. For example, in a U.S. population-based survey, Grant and colleagues (2004) observed that the prevalence of alcohol use disorders, current mood disorders, or current anxiety disorders among adult respondents with diagnoses of nicotine dependence during the past year ranged from 21 to 23 percent compared with 9 to 11 percent in the general population. Conversely, other studies have shown the percentage of persons with nicotine dependence among respondents with these comorbid disorders ranging from 25 to 35 percent and as high as 52 percent among respondents with drug use disorders compared with 12.8 percent in the general population (Glassman et al. 1990; Breslau et al. 1994, 2004b; Lasser et al. 2000; Degenhardt and Hall 2001; Kandel et al. 2001; Isensee et al. 2003; Schmitz et al. 2003; Grant et al. 2004; John et al. 2004).

Furthermore, studies have shown that the more severe the nicotine dependence, the more likely was the association with comorbid disorders. For example, John and colleagues (2004) found that the greater the number of nicotine-dependent symptoms or nicotine withdrawal symptoms and the higher the total FTND scores, the higher the odds ratios for psychiatric disorders. Nonetheless, even nonnicotine-dependent smokers, compared with nonsmokers, had significantly higher prevalence of alcohol and drug dependencies, but not of major depression or anxiety disorders (Breslau et al. 1991, 1994, 1996). This result suggests that smoking may either physiologically or perhaps more critically, socially, lower the threshold for substance abuse disorders. Conversely, the greater the number of psychiatric disorders experienced by the individual, the higher the prevalence or odds of smoking, particularly daily or heavy smoking (Lasser et al. 2000; Breslau et al. 2004b) and of diagnosis of nicotine dependence (Breslau et al. 2004b; John et al. 2004).

The relationship of major depression or anxiety disorders with nicotine dependence is complex and not extensively explored. Breslau and colleagues (1993b) examined the relationship between depression and nicotine dependence in a prospective investigation of 14 months. The investigators found that major depressive disorder increases the risk of progression to nicotine dependence and more severe levels of dependence. These results were confirmed in a subsequent analysis of cross-sectional data from the National Comorbidity Survey in which preexisting major depressive disorders, several anxiety disorders (e.g., phobias, generalized anxiety disorders, and posttraumatic stress disorders), and substance use disorders had resulted in an increased risk for progression to daily smoking or onset of nicotine dependence among daily smokers (Breslau et al. 2004b). Of the anxiety disorders assessed, neither preexisting agoraphobia nor panic disorder predicted a subsequent progression to daily smoking, and panic disorder did not increase the relative risk of transition to nicotine dependence. Similar findings had also been observed in earlier epidemiologic cross-sectional studies of adults (Breslau and Klein 1999) and in longitudinal studies with follow-up of adolescents into young adulthood (Johnson et al. 2000; Isensee et al. 2003).

Conversely, Breslau and colleagues (1993b) also observed that a history of nicotine dependence increased the risk for a subsequent first incident or recurrence of major depressive disorder. Daily smoking or nicotine dependence increased the risk of a subsequent onset of drug use, anxiety disorders, major depression, or dysthymia both in epidemiologic studies (Breslau et al. 1998, 2004a; Breslau and Klein 1999) and in population-based longitudinal studies (Kendler et al. 1993; Isensee et al. 2003). In a population-based longitudinal cohort study, adolescents who smoked one or more packs of cigarettes per day had higher odds of the onset of anxiety disorders (e.g., generalized anxiety disorders, panic disorder, and agoraphobia) in adulthood than did adolescents who smoked less than one pack a day (Johnson et al. 2000). Analysis of cross-sectional data from the National Comorbidity Survey found no differences between nicotine-dependent and nondependent daily smokers in the likelihood of a subsequent first onset of a psychiatric disorder (Breslau et al. 2004a). Therefore, daily smoking appears to be just as important a risk factor as a diagnosis of nicotine dependence. This finding may reflect the limitations of the criteria for a diagnosis of nicotine dependence.

This bidirectional finding in relation to cigarette smoking and some of the mood and substance use disorders can be considered either causal or a reflection of an underlying factor that is common to the predisposition to both disorders. For example, psychiatric disorders may lead to self-medication with nicotine, which targets

the neurosystems that have mood-altering effects, or long-term exposure to nicotine may alter neurobiologic substrates, leading to the development of psychiatric comorbidities. Another possibility is that psychiatric disorder and nicotine addiction share genetic or environmental vulnerabilities or risk factors.

Few studies have been directed toward providing evidence for whether these factors are responsible for the relationships between smoking and psychiatric disorders. Support for self-medication of psychiatric disorders would come from three findings that show (1) smokers with psychiatric disorders have rates of smoking cessation lower than those for smokers who do not have these disorders; (2) remission of disorders is less likely to predict progression to daily smoking, because there is no need for self-medication, but preexisting active disorders are associated with increased risk for smoking and/or nicotine dependence; and (3) prevalence of smoking is higher among persons with remission of disorders than among those who continue to experience psychiatric symptoms because smoking reduced the psychiatric symptoms.

To date, the data show that the impact of psychiatric disorders on smoking cessation is equivocal (see "Trajectory of Recovery or Relapse" later in this chapter). However, these studies are limited to the disorders of major depression and alcohol abuse or dependence. Major depressive disorder is the only psychiatric disorder to meet the first two characteristics associating cigarette smoking with self-medication (findings 1 and 2) (Romans et al. 1993; Breslau et al. 2004a) (see "Trajectory of Recovery or Relapse" later in this chapter).

If the development of psychiatric disorders were caused by the effects of cigarette smoking or nicotine exposure, then findings to support this hypothesis would show that (1) a longer and higher exposure increases a smoker's odds of developing a psychiatric disorder; (2) longer abstinence from smoking leads to reduced risk for psychiatric disorder, unless the effects are irreversible; and (3) current but not former smoking is associated with higher risk for psychiatric disorder. The only disorders that appear to meet these characteristics are panic disorders and agoraphobia (Breslau and Klein 1999; Johnson et al. 2000; Isensee et al. 2003; Breslau et al. 2004a).

Support for common factors, hereditary or acquired, would be based on findings that show (1) both current and former daily smoking increase the risk for psychiatric disorders, (2) both active disorders and disorders in remission or only disorders in remission predict daily smoking or a progression to nicotine dependence, and (3) familial or genetic vulnerability is shared across nicotine dependence or smoking and psychiatric disorders. The greatest support for shared common factors is for substance abuse disorders and smoking.

Remission of substance abuse disorders has been a predictor of daily smoking and progression to nicotine dependence (Breslau et al. 2004b). Results of studies on families and twins support a shared familial and genetic vulnerability across substance use disorders (Bierut et al. 1998; Merikangas et al. 1998; Tsuang et al. 1998). The data on common factors for major depressive disorders and smoking are conflicting, showing both support (Breslau et al. 1994; Kendler and Gardner 2001; Johnson et al. 2004) and lack of support (Dierker et al. 2002; McCaffery et al. 2003). Researchers have attributed inconsistency in these results to differences in levels of cigarette consumption, definitions of depression, study methods, and analytic approaches (Johnson et al. 2004). The use of antidepressant treatments for both depression and smoking cessation, regardless of a history of depression, would support the concept of shared substrates that mediate nicotine dependence and depression (see "Pathophysiology of Nicotine Addiction" earlier in this chapter).

As a caveat, the strong relationship between nicotine dependence and some psychiatric disorders may be a function of the method used to diagnose nicotine dependence. For example, in another study conducted by Breslau and Johnson (2000), nicotine dependence, as defined by the FTND score, was not related to major depression. These researchers attributed the strong relationship between the *DSM-III-R* definition of nicotine dependence and major depression to the numerous behavioral symptoms associated with the diagnosis of nicotine dependence.

Summary and Future Directions

The effects of dose, age, race, and gender may be related to the prevalence of nicotine dependence. The number of cigarettes smoked per day and the duration of smoking are positively related to the percentage with diagnosis of nicotine dependence. Prevalence of nicotine dependence among adolescent smokers may be higher than that among adult smokers, particularly for those who smoke fewer cigarettes per day. Conflicting study results suggest that prevalence of nicotine dependence, as defined by *DSM* criteria, is higher among Whites than among Blacks but that prevalence is lower in Whites when time to the first cigarette of the day is the criterion for dependence. It is unclear whether the prevalence of nicotine dependence differs by gender. These results suggest the need for further research to explore reasons for the inconsistent findings across subgroups of smokers. A significant association also exists between psychiatric disorders and smoking, but the nature of this association is unclear. Depending on the disorder, the relationship may be causal; for example, smoking may increase the odds of

panic disorder and major depressive disorder and may lead to self-medication with tobacco use. On the other hand, this association may result from common underlying factors that involve fundamental psychological or physiological processes, such as intolerance to states of negative affect or neurotransmitter dysfunction in a common pathway, which lead to nicotine dependence, substance abuse, and possibly depression. To date, understanding the causal relationships has relied predominantly on cross-sectional data sets. Prospective studies have been limited and have examined only a few psychiatric disorders, but this type of study is necessary to lend stronger evidence for any bidirectional causality or for common underlying causes of cigarette smoking and nicotine dependence with specific psychiatric disorders. A clearer understanding of these relationships will result in a deeper understanding of the pathophysiology of nicotine addiction. Moreover, the studies of adults are limited in that the focus has been primarily on internalizing rather than externalizing disorders. In studies of adolescents, externalizing disorders may play an even greater role than do internalizing disorders in the development of nicotine addiction (see "Determinants of Nicotine Addiction" earlier in this chapter). Therefore, studies encompassing a broader range of diagnoses are warranted.

Trajectory of Recovery or Relapse

Studying recovery from smoking can provide valuable information on the nature of tobacco addiction and the factors affecting it. Every year about 45 percent of daily smokers in the United States stop smoking for 24 hours, but only 5 percent or less achieve long-lasting abstinence (CDC 2002, 2004). Thus, relapse is the principal limiting factor in the transition from smoking to nonsmoking status. This finding underscores the need to understand the nature of relapse and the factors affecting it.

Relapse: Definitions and Limitations of the Literature

Integration of information about relapse is difficult because definitions of critical events differ among studies. For instance, it seems useful to distinguish a lapse from a relapse. A lapse refers to an occurrence of smoking or tobacco use that takes place after an attempt to stop smoking but is not part of an ongoing pattern of consistent use (Brandon et al. 1986). Relapse refers to the point after an attempt to stop smoking when tobacco use becomes ongoing and persistent (Brandon et al. 1986). Although standards have been offered for defining "relapse" (Hughes et al. 2003), many reported results are based on idiosyncratic standards. In addition, there is no formally accepted definition of a "lapse." For instance, some studies define a lapse as only the first use of tobacco after an attempt to stop smoking, and other studies use broader definitions. Because of this diversity, this review reports results according to the definitions used by the investigators in each study. In addition, some investigators distinguish between relapse and failure of smoking cessation, with relapse occurring only after a period of abstinence (e.g., after 48 hours) (Hughes et al. 2003). Again, few studies make such a distinction. Therefore, to render the bulk of the evidence comparable, this review uses the concept of return to smoking after a cessation attempt as an index of vulnerability to relapse, regardless of the duration of abstinence. In general, no distinction is made between cessation failure and relapse. Finally, some of the reviewed studies predict the likelihood of relapse while others predict relapse latency. In this review, either prediction is taken to reflect a higher level of vulnerability to relapse.

Natural History of Relapse

Prevalence

Two key characteristics of relapse are its high prevalence and its rapidity. Past reviews have consistently reported that persons who decide to stop smoking on their own and those who receive placebos in clinical trials achieve 6- to 12-month abstinence rates of only 3 to 5 percent (Cohen et al. 1989; Hughes et al. 2004c). Thus, within one year of an attempt to stop smoking, about 95 percent of persons who try to stop without a pharmacologic aid continue to smoke or resume smoking. Reviews of efficacious treatments reveal that 20 to 25 percent of those who tried to stop smoking succeeded for six months (Fiore et al. 2008). This finding means that about 75 percent of persons who try to stop smoking by using evidence-based treatments return to smoking within six months. The risk of relapse, however, does not end 6 to 12 months after the attempt at smoking cessation. Findings in studies of

long-term outcome suggest that relapse ultimately claims 30 to 40 percent of smokers who stop smoking for one year (Eisinger 1971; Gilpin et al. 1997; Krall et al. 2002). For instance, Yudkin and colleagues (2003) found that about one-half of the smokers who had stopped smoking for one year relapse to smoking within the subsequent seven years. However, roughly 50 percent of those who have ever smoked eventually become long-term former smokers (Husten 2005) because many make repeated attempts to stop smoking until they are successful.

Rapidity

Most smokers who ultimately relapse resume smoking early after their attempt to stop. This pattern of early lapsing has been reported in persons receiving treatment (Kenford et al. 1994), as well as in those who decide on their own to stop smoking and in smokers who receive placebos (Hughes et al. 2004c). For example, Kenford and colleagues (1994) found that 80 to 90 percent of those who were smoking at six months after trying to stop had resumed smoking in the first two weeks of the attempt to stop. Other studies report similarly high rates of early lapsing in populations of treated and untreated smokers (Garvey et al. 1992; Gulliver et al. 1995; Westman et al. 1997; Hughes et al. 2004a). Women who stop smoking during pregnancy, however, tend not to relapse early in the attempt to stop, but rather tend to relapse after delivery, which is often weeks or months after initial cessation (Fingerhut et al. 1990; USDHHS 1990; Floyd et al. 1993; Stotts et al. 2000; Colman and Joyce 2003).

Lapse-Relapse Relationship

The odds of an eventual relapse are especially high among those who lapse or engage in initially isolated smoking episodes after the cessation date. Data suggest that lapsing is the single best predictor of an ultimate relapse (Brandon et al. 1990; Hughes et al. 1992; Kenford et al. 1994; Nides et al. 1995). Moreover, the risk of an ultimate relapse appears to increase with the number of lapse events (Wileyto et al. 2004). Nevertheless, even multiple lapses do not inevitably lead to a relapse (Nides et al. 1995). This finding attests to the wide variation in the course of both relapse and successful cessation in a population of smokers attempting to stop smoking.

The pattern of a return to regular smoking varies considerably across individuals and typically occurs over days and weeks rather than hours. On average, smokers have a second lapse three or four days after the first lapse (Shiffman et al. 1996b). Almost one-half of smokers have the second lapse within 24 hours of the first lapse (Brandon et al. 1990). On average, the latency between the first lapse to a relapse is three to five weeks (Brandon et al. 1990; Shiffman et al. 1996a,b; Gwaltney et al. 2005a), which suggests that there is time after an initial lapse to engage in additional treatment to prevent progression to full relapse.

Risk Factors

To promote more precise thinking about the time courses and interactive and cumulative effects of different types of influences on relapse, several reviews recommend an organizational framework for categorizing forces that influence a relapse (Shiffman et al. 1986; Shiffman 1989a; Piasecki et al. 2002). In general, such recommendations have proposed three factors as important influences on relapse: person factors, emergent processes, and situational instigators. Person factors are stable characteristics that preexist the attempt to stop smoking and endure (e.g., gender and history of or proneness to depression). Emergent processes are dynamic factors that unfold over time and emerge sometime during the postcessation period. Such processes tend not to be bound to context. For example, although these processes may arise in response to an episodic event such as stress, they can persist for days or weeks. Withdrawal is an example of a dynamic variable that arises gradually in response to falling blood concentrations of nicotine (Hughes et al. 1990b; Piasecki et al. 2003a). Although situational factors may affect withdrawal symptoms (McCarthy et al. 2006), the symptoms persist well beyond the situational influences and are not wholly explained by them. Situational instigators are factors such as cues, contexts, or events that give rise to short-lived (phasic) reactions lasting from seconds to hours. Such reactions might comprise affective reactions to a stressor, such as an argument, or to exposure to smoking cues, such as seeing someone smoke.

Thus, this organizational scheme reflects the instigator of the process, such as a contextual cue, as well as the time course of vulnerability associated with relapse. Such categorization is complex, because the distinction among the time courses of influences is somewhat arbitrary and various influences may interact (Piasecki et al. 2002; Gwaltney et al. 2005b). These influences are not mutually exclusive or independent, which adds to the complexity of this organizational method. For example, person factors may affect situational reactions or emergent patterns of symptoms. The categorization scheme described here is only one approach to conceptualizing the causes of relapse. This approach has, however, allowed researchers to identify factors that consistently predict relapse and is consistent with a greater body of research and theory showing that person factors, phasic reactions, and contexts powerfully affect behavior (Mischel 2004).

Person Factors

Cognitive and Attitudinal Influences

There is evidence that relatively stable attitudinal variables affect the vulnerability to relapse of smokers. For example, precessation assessments of expectations that smoking will alleviate distress (e.g., negative moods and stress) predict the subsequent likelihood of a relapse (Wetter et al. 1994; Brandon et al. 1999). In addition, multiple studies conclude that baseline measures of confidence in the ability to stop smoking can also predict outcomes (Condiotte and Lichtenstein 1981; Baer et al. 1986; Shiffman et al. 2000). Other findings indicate that confidence before attempts to stop smoking and positive expectations may interact to predict risk of relapse to smoking. Smokers with low confidence and high expectations for smoking reinforcement are especially likely to relapse (Shadel and Mermelstein 1993; Dijkstra and Brosschot 2003). Finally, high levels of motivation, based on health concerns (Nides et al. 1995; Dijkstra and Brosschot 2003) or other reasons (Turner and Mermelstein 2004), may foster cessation and protect against relapse. However, motivation tends to be less effective than other factors, such as level of tobacco dependence or self-efficacy, that is, self-confidence in the ability to stop smoking cigarettes (Hyland et al. 2004; University of Michigan 2006).

Other cognitive variables are less consistently related to lapse and relapse. For instance, expectations about the negative effects of smoking (e.g., risk of disease) appear to predict the motivation or intention to stop smoking but not the likelihood of a relapse (Wetter et al. 1994; Brandon et al. 1999). Also, one study found that a strong commitment to continuing abstinence from smoking was related to reduced rates of relapse, but this finding was obtained in a population that comprised persons who abused opiates and alcohol in addition to smokers, and this condition made the relevance to smoking per se unclear (Hall et al. 1990).

Finally, cognitive dimensions such as expectations or motivation are sometimes hard to classify. For example, motivational structures and attitudes may affect behavior over many years (Etter et al. 2003b; Beltman and Volet 2007). However, motivational phenomena change over time and can be affected by contextual factors (Beltman and Volet 2007; McCaul et al. 2007; Sanderson et al. 2008; Weiss-Gerlach et al. 2008). Therefore, cognitive and motivational factors are discussed both as person factors and emergent processes, with the distinction reflecting the time course of their emergence.

Other data show that the attentional salience of smoking cues also predicts vulnerability to relapse. Using the Stroop paradigm, researchers presented smoking-related and neutral words to 158 volunteers for a smoking cessation program (Waters et al. 2003b). Results show that if words related to smoking attracted the attention of smokers, an early relapse was more likely within a three-month follow-up interval. In theory, the attention-grabbing properties of words related to smoking reflect the motivational potency of smoking that could then account for the greater likelihood of a relapse.

Tobacco Dependence

Measures of tobacco dependence predict the likelihood that a smoker will achieve long-term abstinence from tobacco use. For instance, self-report measures of dependence tend to predict cessation and relapse (Breslau and Johnson 2000; Piper et al. 2004; Shiffman et al. 2004a). However, the various self-report measures of dependence often do not show good agreement with one another (Breslau and Johnson 2000; Moolchan et al. 2002). This finding is consistent with emerging evidence that nicotine dependence is multifactorial (Hudmon et al. 2003; Piper et al. 2004; Shiffman et al. 2004b). More recent evidence suggests that some dependence factors are more predictive of dependence than are others. In particular, self-report measures of tobacco dependence that assess heavy automatic smoking that is not discriminated on time or context are most consistently associated with heightened risk of relapse (Transdisciplinary Tobacco Use Research Center 2007; Piper et al. 2008). This finding is consistent with the observation that objective measures of a high rate of smoking, such as expired carbon monoxide levels and serum concentrations of cotinine, are often related to the likelihood of a relapse (Nørregaard et al. 1993; Faue et al. 1997; Kenford et al. 2002). Even in the best circumstances, however, measures of tobacco dependence account for only modest amounts of variation in risk of relapse. This finding is consistent with the notion that relapse is a function of multiple person factors, emerging processes, and contextual factors.

In addition to dependence, the sensitivity of a smoker to a nicotine reinforcement predicts a shorter latency to relapse (Perkins et al. 2002a). In contrast, formal laboratory measures of tolerance to the effects of nicotine do not appear to be significantly related to relapse (Perkins et al. 2002a).

Demographic and Lifestyle Variables

Studies have related numerous variables of demographic factors and lifestyle to vulnerability to relapse. For example, researchers have related an increased likelihood of relapse to younger age (Nides et al. 1995; Ockene et al. 2000; Hyland et al. 2004), a low SES or a low level of education (Nides et al. 1995; Ockene et al. 2000; Wetter

et al. 2005b), being unmarried (Nides et al. 1995; Ockene et al. 2000), higher levels of tonic stress, and more stressors or the perception of a higher stress level (Swan et al. 1988; Wewers 1988; Cohen and Lichtenstein 1990; McKee et al. 2003). Of these factors, low SES and low educational status appear to be especially strong and consistent predictors of ability to abstain from smoking on a continuing basis (Mullen 2004; Wetter et al. 2005a; Fernández et al. 2006; Lee and Kahende 2007; Letourneau et al. 2007). In addition, some data from clinical trials and population samples indicate that women may be less likely than men to maintain abstinence from tobacco use (Hubert et al. 1987; Bjornson et al. 1995; Community Intervention Trial for Smoking Cessation 1995; Wetter et al. 1999; Smith et al. 2003; Hyland et al. 2004). However, such relationships are not consistently found across different data sets. For instance, as noted above, numerous data sets reveal that females are more likely to relapse to tobacco use than are males. However, a substantial number of studies fail to find such a relationship (Gritz et al. 1998; Killen et al. 2002; Westmaas and Langsam 2005; Velicer et al. 2007; Walsh et al. 2007). Besides the issue of consistency, additional topics deserve greater research attention. These topics include exploration of how the various person factors "work together" to affect the success or failure of smoking cessation. In addition, it is important to determine whether the different person factors are associated with different sorts of relapse mechanisms or processes; that is, regardless of the likelihood of relapse in different smoker groups, it is important to determine whether relapse processes "unfold" differently in such groups.

Research suggests that men and women may differ in sensitivity to environmental events. There is evidence, for instance, that environmental or conditioned cues related to use of nicotine, such as seeing information about nicotine dose, seeing others smoking, or receiving cues previously paired with nicotine, tend to elicit stronger motivational response to use the drug in women than in men (Pomerleau et al. 2005; Perkins et al. 2006; Leventhal et al. 2007; Walsh et al. 2007). These data agree with animal research data showing that nicotine-paired environmental cues are more effective in eliciting self-administration of nicotine in female rats than in male rats (Chaudhri et al. 2005). Complementary data suggest that men are more likely to be responsive to actual nicotine dose and other pharmacologic properties than are women (Perkins et al. 2006). If men are indeed more sensitive to nicotine's pharmacologic properties than are women, this could explain why men who use NRT sometimes achieve higher levels of success with smoking cessation than do women who use NRT (Wetter et al. 1999; Perkins 2001; Cepeda-Benito et al. 2004) and why this finding did not hold for use of psychosocial interventions (Velicer et al. 2007).

Other studies show additional differences by gender. Data from study of a community-based population sample suggest that financial stressors may be more likely to inhibit smoking cessation in women than in men and that negative health events are more likely to prompt cessation in men (McKee et al. 2003). Other research shows that male smokers tend to be more reactive to relatively minor stressful events (i.e., hassles) than are women (Wetter et al. 1999; Delfino et al. 2001; Todd 2004). Although there is mounting evidence of differences by gender in reaction to nicotine or environmental cues (Perkins et al. 1999), and in motivation to use tobacco or nicotine, these differences have not been definitively linked with either relapse or differences by gender in relapse. Even less is known about the relationship of factors such as low SES or educational attainment to likelihood of smoking cessation (Wetter et al. 2005a).

One innovative approach to unraveling the complex interrelationships among the multiple person factors and relapse is to conduct classification or decision-tree analyses. These analyses have been used to determine whether categories of person factors (e.g., male versus female) comprise smoker subgroups that can be distinguished on the basis of their risk profiles for cessation failure. One example of this approach generated six subgroups of women smokers (Swan et al. 2004). For some subgroups, cessation failure appeared to be related to educational attainment and the number of previous attempts to stop smoking; for others, failure was more strongly related to body mass index and family history of depression (Swan et al. 2004). In contrast, male smokers comprised subgroups more highly distinguished by variables related to nicotine dependence, such as FTND score (Heatherton et al. 1991) and the number of years of smoking. In addition, male subgroups were distinguished on the basis of previous NRT and a history of depression. This type of classification or decision-tree analysis is useful because it has the potential to reveal factors that are highly predictive of cessation outcome in a subgroup of smokers, even if a factor is not important over an entire sample (Swan et al. 1997, 1999). Further research is needed to assess the replicability of such findings.

Psychiatric and Affective Dimensions

Some researchers have reported that the vulnerability to failure of smoking cessation or relapse to smoking is positively related to a history of depression, alcohol intake, a tendency toward negative affect, and an intolerance of psychological distress. As with most other individual differences, these relationships are either small in

magnitude, inconsistent, or both. For example, both studies of population samples and clinical trials indicate that a history of depression or depressive symptoms predicts a greater likelihood of a relapse or a failure to stop smoking (Anda et al. 1990; Romans et al. 1993; Ferguson et al. 2003; Smith et al. 2003; Japuntich et al. 2007). However, one meta-analysis of data from 15 clinical trials failed to find such an effect (Hitsman et al. 2003). Studies in this meta-analysis generally excluded participants who were currently depressed or taking antidepressant medication.

One hypothesis is that if depression is correlated with vulnerability to relapse, the correlation may be attributable to the presence of two specific subpopulations of persons who have depression. Hitsman and colleagues (2003) observed that several studies have found a relationship between recurrent (multiple episode) depression and heightened risk of failure to stop smoking (Glassman et al. 1993; Covey et al. 1999; Brown et al. 2001). Haas and colleagues (2004) also found that a high rate of failure to stop smoking was associated with a history of multiple, but not single, episodes of depression. There also is evidence that current depression is more strongly associated with relapse than is past depression (Niaura et al. 2001; Japuntich et al. 2007; Turner et al. 2008). These results suggest that associations between depression and relapse may be attributable to subpopulations with depression, that is, those who are either currently depressed or who are prone to recurrent depression. These types of depression may be linked to risk of relapse because both were associated with recurrent or chronic negative mood (Niaura et al. 2001; Haas et al. 2004; Japuntich et al. 2007), and negative mood has repeatedly been linked with increased likelihood of relapse to smoking among persons with depression (Kahler et al 2002; Leventhal et al. 2008). However, it is possible that the heightened risk of relapse presented by current or recurrent depression is caused by other factors, such as poor coping skills or low self-efficacy.

There is also mixed evidence as to whether a history of alcohol abuse or dependence increases vulnerability to relapse to smoking. Some studies show an elevated risk of relapse (Hughes 1993; Breslau et al. 1996), but in others risk is not elevated (Covey et al. 1993; Hurt et al. 1995). Perhaps the best characterization of the evidence is the finding that active abuse of or dependence on alcohol constitutes a risk factor for relapse to smoking (Hurt et al. 1994; Kalman et al. 2001, 2002). However, there may be little or no risk if problems with alcohol are in remission (Hughes and Callas 2003). Evidence also shows that an active consumption of alcohol enhances the risk of relapse to smoking (Krall et al. 2002; McKee et al. 2003). Thus, the risk of relapse posed by alcohol use is not attributable to alcohol being a marker for a trait-like vulnerability to relapse but rather is attributable to the immediate (situational) effects of intoxication. However, there is modest evidence that another syndrome of disinhibition, attention-deficit/hyperactivity disorder, is associated with elevated risk of relapse to smoking (Humfleet et al. 2005).

An additional affective dimension that has been studied and may contribute to a heightened risk for relapse is the ability of a person to tolerate distress or to persist in a distressing task. Hence, several studies have associated measures of distress tolerance among smokers with the likelihood of or latency to relapse. In these studies, smokers with low vulnerability to relapse showed a greater persistence in tasks such as breathholding and mental arithmetic than did smokers with high vulnerability to relapse (Hajek et al. 1987; Brown et al. 2002). This finding provides evidence that characteristics such as an inability or unwillingness to tolerate distress is linked to a vulnerability to relapse. An inability to tolerate negative affect may be especially related to early relapse to smoking (Zvolensky et al. 2004; Brown et al. 2008).

In summary, the person factors that yield the strongest or most consistent prediction of relapse are measures of tobacco dependence and cognitive and attitudinal variables such as expectation of smoking reinforcement. In addition, measures of low SES and low educational attainment are also fairly consistently related to risk of relapse. Other relatively stable person factors are more modestly or inconsistently related to smoking relapse. Predictors of relapse vary from study to study, probably reflecting differences in the populations studied, different mixes of predictors included in the studies, and diverse methods and measures of the same target constructs. In addition, much of the variation in vulnerability to relapse is no doubt caused by other factors not measured in most studies—for example, exposure to episodic events and reactions to smoking cessation (Shiffman et al. 1996a,c; Kenford et al. 2002; Gwaltney et al. 2005a,b; McCarthy et al. 2006). Also, other variables may account for apparent direct associations between person factors and relapse. For instance, persons who drink heavily may be especially likely to socialize with other smokers, and an exposure to smokers may cause heightened risk of relapse.

Emergent Processes

Emergent processes are reflected in rapid changes in symptoms or behaviors that occur within several days before a lapse or relapse. Researchers have typically studied emergent processes across two temporal windows: one that begins at the time of smoking cessation and therefore captures initial responses to the event and a second that starts close in time to a lapse in cessation and captures changes in behaviors or symptoms leading up to the event. Both types of analyses provide evidence that

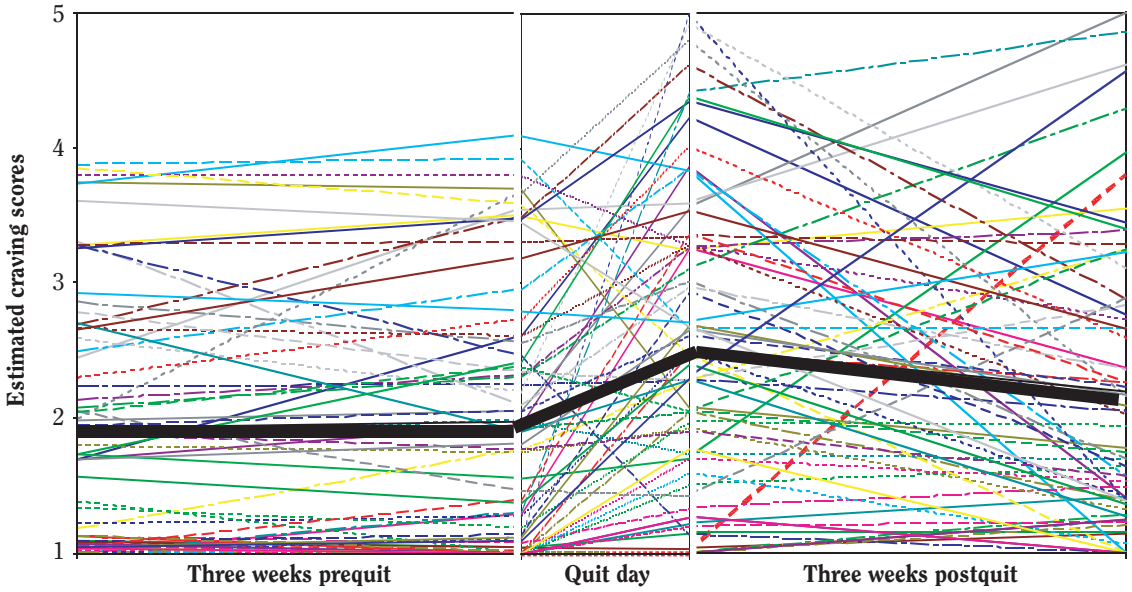
emergent processes set the stage for smoking lapses and relapses. In general, emergent processes do not depend on the sort of treatment or cessation strategy used—for example, they occur in smokers receiving active or placebo pharmacotherapy.

Tobacco Withdrawal and Affective Symptoms

Perhaps the strongest evidence that emergent processes affect vulnerability to relapse comes from research on the tobacco withdrawal syndrome. Until recently, major reviews concluded there was little evidence that withdrawal symptoms were consistently related to the likelihood of a relapse (Hughes et al. 1990b; Patten and Martin 1996). However, in the decade ending in 2004, research has shed light on the nature of withdrawal, as well as its relationship to a relapse (Hughes 2007). First, in many smokers, perhaps most of those attempting to stop smoking, withdrawal symptoms are persistent and often remain elevated for months after an attempt to stop smoking (Gilbert et al. 1998, 2002; Piasecki et al. 1998, 2000). Second, withdrawal results (1) in great heterogeneity of symptoms, both in and across smokers, and (2) in volatile changes in affect and craving (see Figure 4.6 for craving pattern) (Piasecki et al. 2003a; McCarthy et al. 2006). Third, withdrawal results in vulnerability to more severe symptoms in reaction to environmental events than those that occur before smoking cessation (Figure 4.7) (McCarthy et al. 2006). In addition, research shows that some of these symptomatic effects of tobacco withdrawal are associated with an increased vulnerability to relapse. In general, smokers are more likely to relapse if withdrawal symptoms after smoking cessation are severe, increase in severity over time, or are highly variable (Piasecki et al. 1998, 2000, 2003b; McCarthy et al. 2006). Research also shows that withdrawal symptoms indicate vulnerability to relapse, as the result of either immediate increases in symptoms in response to abstinence from smoking or emergent changes in symptoms that occur across the days preceding a lapse in smoking cessation (Figure 4.8) (Piasecki et al. 2003b; McCarthy et al. 2006).

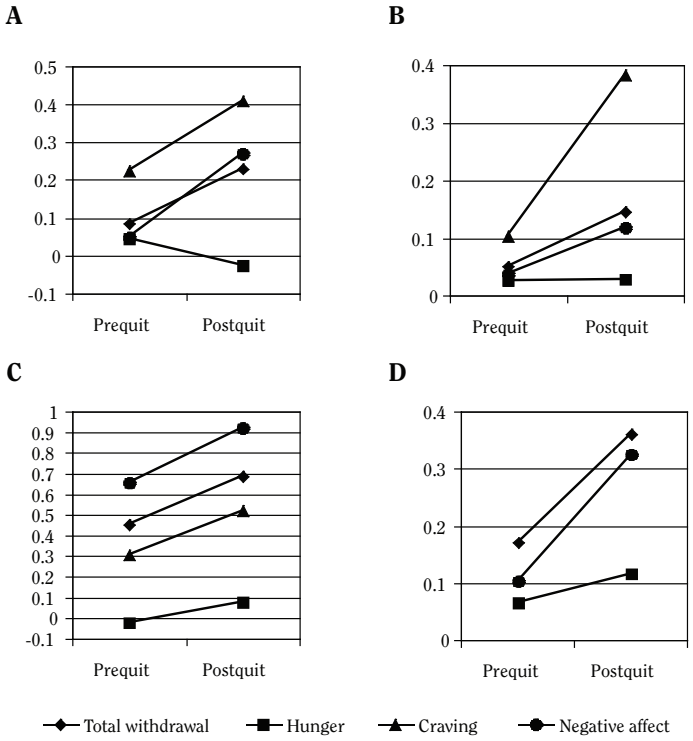
Withdrawal measures tap a variety of symptoms, but research suggests that self-reported craving and negative affect are the symptoms most predictive of relapse (West et al. 1989; Killen et al. 1991; Swan et al. 1996; Killen and Fortmann 1997; Piasecki et al. 1998; McCarthy et al.

Figure 4.6 Individual estimated slopes in craving ratings over three weeks prequit, from just before to just after midnight on the quit date, and over three weeks postquit



Source: McCarthy et al. 2006.
Note: The synthesized trajectories are based on multiple daily ratings made in real time with electronic diaries. The heavy black line represents the mean trend in craving ratings across all individuals. All other lines represent the slopes or trajectories of craving ratings for individual smokers and show how variable withdrawal symptoms can be across smokers across time.

Figure 4.7 Reactions for the three-week period before the quit date and the three-week period after the quit date



Source: McCarthy et al. 2006.
Note: Data are from 70 smokers making a quit attempt. The *y*-axis depicts the magnitude of the average standardized coefficient derived from multivariate, multilevel models. Episodic event coefficients were estimated separately in the prequit and postquit periods. The beta weights shown reflect the degree of symptom change (in overall withdrawal, hunger, craving, and negative affect) associated with the presence versus absence of an episodic event. (A) Symptom coefficients associated with smoking in the past 15 minutes in models of overall withdrawal. (B) Symptom coefficients associated with recent exposure to smoking behavior. (C) Symptom coefficients associated with exposure to recent stressful events. (D) Symptom coefficients associated with recent strong urges and temptations. Results suggest greater symptomatic reactivity to events after quitting than before quitting.

2006). Other elements of the withdrawal syndrome, such as sleep disturbances or weight gain, are less consistent indices of a vulnerability to relapse (Wetter et al. 1995; Borrelli et al. 2001).

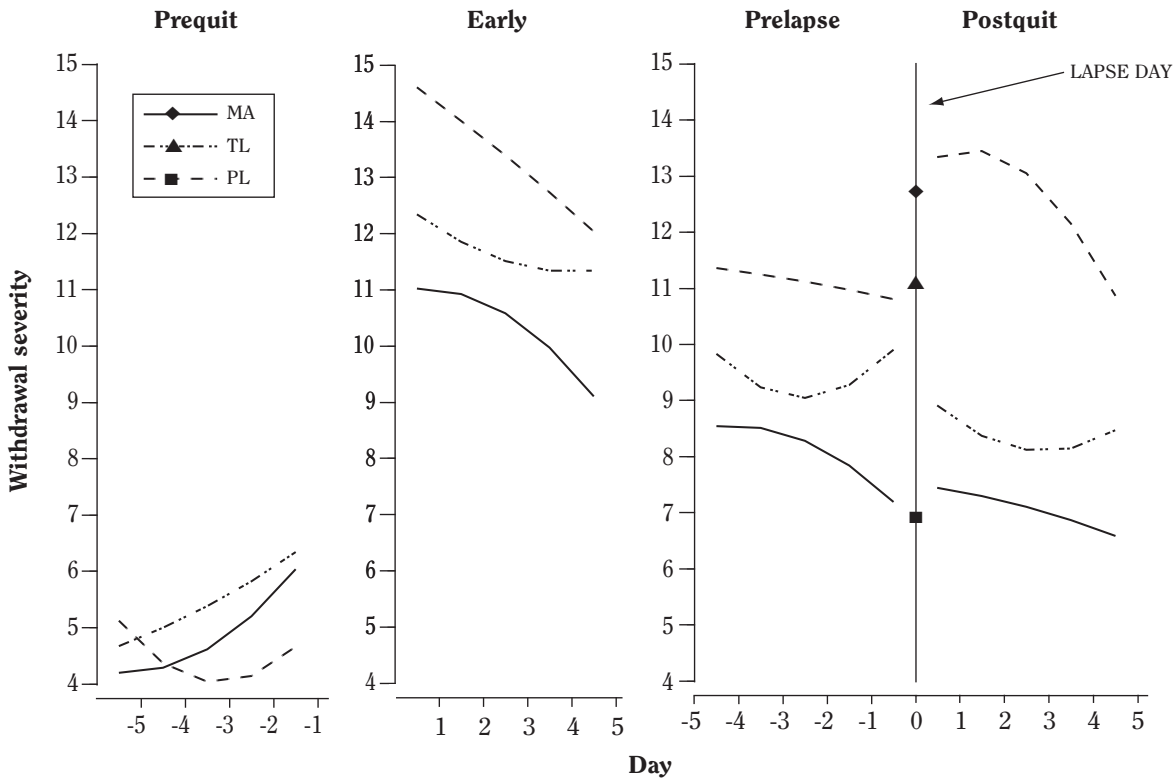
One piece of evidence that supports the role of withdrawal in precipitating relapse is research showing that withdrawal suppression appears to mediate the effects of pharmacologic treatments for smoking cessation (McCarthy et al. 2006; Shiffman et al. 2006). Statistical tests suggest that nicotine replacement and bupropion treatments reduce relapse risk to the extent that they suppress withdrawal symptoms. These studies suggest only partial mediation, however, consistent with the notion that other factors also influence relapse.

Although it is clear that emergent trends can set the stage for lapses and relapses to smoking, much remains to be learned about these associations. The time course by which emergent symptoms anticipate lapses, for example, needs more focused examination, because a gradual emergence of symptoms would permit the delivery of preventive interventions. Several studies show that craving and exacerbation of withdrawal symptoms precede lapses by several days (Piasecki et al. 2003b; McCarthy et al. 2006; Allen et al. 2008). However, as noted earlier in this section, other research shows that lapse-provoking increases in negative affect unfold within hours rather than days (Figure 4.9) (Shiffman and Waters 2004).

Cognitive and Attitudinal Influences

Emergent cognitive and attitudinal processes may also enhance vulnerability to relapse. For instance, one study used real-time data recording to show that low

Figure 4.8 Withdrawal severity and lapse behavior among smokers who abstained for the first five days of a quit attempt



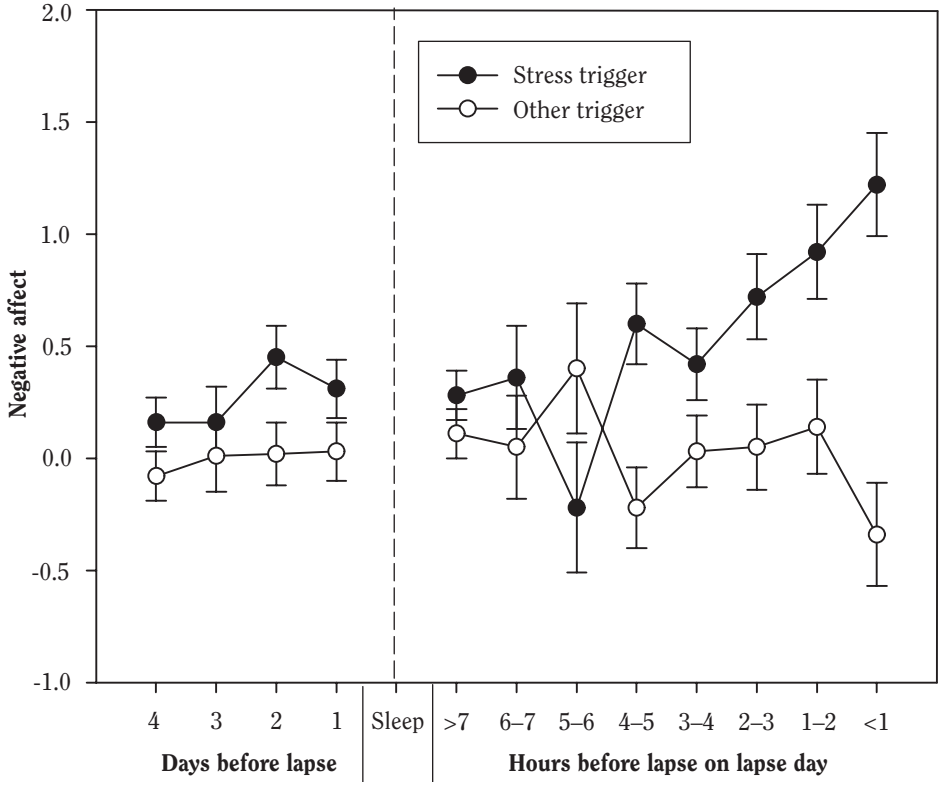
Source: Piasecki et al. 2003b.
Note: Matched abstainers (MAs; n = 152) had never smoked during the follow-up period. Transient lapsers (TLs; n = 124) had lapsed but did not immediately resume regular smoking. Protracted lapsers (PLs; n = 28) had immediately returned to regular smoking upon lapsing. The figure shows predicted withdrawal severity growth functions for these three groups over several periods: baseline (prequit: prior to day 0 in the first panel), the first five days of the quit attempt, the five days preceding and following the lapse dates of the lapsers (TL and PL participants); and last five days of the quit attempt (when TL and PL participants were smoking and MA participants were abstinent). Each lapsed participant was paired with an MA to produce temporal equivalence across the prelapse and postlapse windows. To compare the symptoms of lapsers with those of nonlapsers, the investigators randomly matched each lapser with a person who did not lapse, then compared the predicted symptom trajectories of these individuals over the same postquit periods of time defined by when a lapse actually occurred.

abstinence and self-efficacy estimates, along with high expectations of smoking reinforcement, predicted a lapse to smoking that occurred on the following day (Gwaltney et al. 2005a). These effects were independent of scores for these measures on the day of smoking cessation, suggesting that the effects reflect emergent processes and not trait differences. Other research shows that persons who lapse to smoking appear to experience a marked dip in motivation during the week leading up to a lapse (Hedeker and Mermelstein 1996).

Timing and Motivational Significance of Emergent Processes

As previously noted, both symptomatic and attitudinal changes emerge across the period after smoking cessation and predict a relapse. Such changes may occur in the first few hours after cessation or in the hours or days just before a lapse to smoking (Figures 4.8 and 4.9) (Hedeker and Mermelstein 1996; Gwaltney et al. 2005a). Emergent symptoms may occur at any time during the postcessation period. However, research shows that symptoms that occur early in this period (e.g., in the first 24 hours) may

Figure 4.9 Negative affect in the days and hours preceding the first lapse for smokers who attributed their first lapse to a stressor or bad mood (stress trigger) or to some other type of event (other trigger)



Source: Adapted from Shiffman and Waters 2004 with permission.
Note: Stress trigger, n = 29; other trigger, n = 61. These data suggest that increasing negative affect is a risk factor for lapsing for some smokers. Error bars show one standard error.

be more tightly linked to outcomes than are later symptoms. For instance, in the Killen and Fortmann (1997) research, 2,600 smokers were entered into three studies through population-based recruitment. Across all three studies, craving ratings gathered early in the attempt to stop smoking (e.g., 24 hours postcessation) predicted relapses across the first year after cessation. Smokers with ratings in the highest quartile for craving were twice as likely to relapse as were smokers in the lowest quartile (31 versus 16 percent, respectively, averaged across all three studies). This research agrees with a wealth of other evidence that appearance of symptoms early in the attempt to stop smoking is negatively related to an ability to remain abstinent and to avoid a relapse (Killen et al. 1991; Doherty et al. 1995; McCarthy et al. 2006).

These data supported a large amount of evidence showing that various types of self-reports become markedly more predictive of ultimate outcomes as soon as persons have some experience in the attempt to stop smoking (Kenford et al. 2002; Gwaltney et al. 2005a). This evidence suggests that even though smokers have experience with abstinence from smoking and have memories of previous attempts to stop smoking, many are still unprepared for the forces unleashed by abstinence, which ultimately lead to a relapse.

Situational Instigators

A large body of research shows that lapses and relapse are associated with a limited set of contextual or situational features. Studies that use remote data collection techniques, in which data are gathered long after the lapse or relapse occurred, show that the contexts of lapses are characterized by features such as negative affect, urges to smoke, alcohol consumption, and cues to smoke (O'Connell and Martin 1987; Brandon et al. 1990).

Research using real-time data acquisition shows that situations in which lapses occur (lapse situations) can be distinguished from temptations, that is, instances in which smoking did not actually occur, and from random occasions on the basis of the negative moods that occur in relation to lapses (Shiffman et al. 1996c). Negative moods are significantly more likely to co-occur with lapses than with temptations without smoking or to occur alone at randomly determined times. These negative moods tend to be strongly associated with reports of interpersonal stress such as arguments.

Shiffman and colleagues (1996c) also found that lapse situations can be distinguished from temptation situations and random occasions in that lapses are more likely to be accompanied by alcohol intake and strong urges to smoke that occur later in the day. Considerable additional evidence demonstrates that alcohol intake sets the stage for lapses (Borland 1990; Brandon et al. 1990). Also, both lapses and temptation situations tend to co-occur in the presence of other persons who are smoking. Thus, the availability of cigarettes and the modeling of smoking are associated with an increased desire to smoke. However, such cues do not reliably distinguish between the desire to smoke and the occurrence of smoking. Finally, the smoker is not a passive party in the progression to relapse. The data show that the execution of a coping response is more characteristic of temptation than of lapse occasions, suggesting that coping detoxifies temptation situations (Shiffman et al. 1996c).

Attesting to the powerful influence of contextual factors, recent research shows that smoking policies or the numbers of smokers in the person's environment reliably predict likelihood of relapse or success in cessation (Letourneau et al. 2007). For instance, risk of relapse or rapidity of relapse is heightened by the number of smokers in a person's social network, whether the person's partner smokes (Mullen 2004; Letourneau et al. 2007; Macy et al. 2007; Solomon et al. 2007), and whether there are smoking restrictions at the person's place of work or at home (Gilpin et al. 1999; Lee and Kahende 2007; Macy et al. 2007). However, some data suggest that bans in social contexts or restaurants may not be related to the success of cessation (Albers et al. 2007).

In general, research on situational indicators suggests that temptations to smoke and smoking lapses are contingent on internal symptoms of withdrawal (e.g., urges to smoke), alcohol use, and environmental signals of smoking, including the availability of cigarettes and the status of smoking restrictions. These findings are consistent with theories that drug availability and distress both constitute potent prods to motivation for drug use (Niaura et al. 1988; Skjei and Markou 2003; Baker et al. 2004).

Integration Across Relapse Influences

Person factors, situational cues, and emergent processes all influence risk of relapse. Moreover, research suggests that relapse risk reflects an interaction among these types of influences (Shiffman 1989a; Piasecki et al. 2002). For example, the intensity of the urge to smoke during temptation events predicts the likelihood of a lapse (Shiffman et al. 1997). However, this relationship depends on the level of urges to smoke reported on the day of smoking cessation. Thus, situational ratings are related to trait characteristics, such as tobacco dependence or emergent trends (e.g., withdrawal) that affect ratings for the urge to smoke on the day of smoking cessation. The relationship between the type of lapse situation and an emergent negative affect are shown in Figure 4.9. Data also show that the intensity of the urge to smoke during temptation episodes grows in the days leading up to a lapse (Shiffman et al. 1997). These data provide further evidence for the role of emergent processes in affecting situational reactions that, in turn, are related to lapse events. Finally, this same research shows that the level of the urge to smoke reported by persons on awakening predicted the likelihood of a lapse later on the same day. For some reason, urges to smoke in the morning, as opposed to urges reported at other times, tended to provide the most powerful predictions of lapses. In sum, research on the urge to smoke shows that the likelihood of a lapse reflects the interaction of trait factors, emergent processes, and situational cues.

Other data suggest interactive influences on the likelihood of a lapse. For example, Gwaltney and colleagues (2005b) found that persons who have low levels of trait-like self-efficacy at baseline show marked declines in self-efficacy in situations that produce strong urges or negative affect. Hence, trait measures capture a person's vulnerability to succumb to situational challenges. A chief goal of future research is to elucidate how various types of influences on relapse interact to produce a relapse in a particular person at a particular time.

Transition from Lapse to Relapse or Recovery

Exploration of the factors that transform lapses into relapses is vital, because initial incidents of tobacco use routinely usher in a return to regular smoking (Baer et al. 1989; Garvey et al. 1992; Kenford et al. 1994). Study of the factors that influence the lapse-relapse progression is also important, because it seems that factors affecting this progression differ from factors that affect the occurrence of the lapse itself. For instance, Wileyto and colleagues

(2005) found that the likelihood of lapse in a smoker was relatively unaffected by his or her dependence level (FTND score) or symptoms of depression. However, both of these factors were associated with greater difficulty in recovering from a lapse—that is, reestablishing abstinence for at least 24 hours.

Researchers have found that the probability or the latency of a relapse after a lapse can be predicted by nicotine dependence (Shiffman et al. 1996b, 1997) and by features of the lapse situation, such as the failure to make a coping response, feelings of hopelessness, and stronger urges to smoke during the lapse (Shiffman et al. 1996b). In addition, postlapse declines in self-efficacy of abstinence indicate a greater likelihood of or a faster progression to a relapse (Gwaltney et al. 2005b). Thus, it appears that individual capitulation in the cessation attempt and high levels of nicotine dependence foster the progression to a relapse.

Lapses appear to play a causal role in precipitating a relapse. This finding is indicated by the report that smokers randomly assigned to experimental lapse events resume smoking more rapidly than do smokers not assigned to such lapse experiences (Chornock et al. 1992).

Summary and Future Directions

The data suggest that factors contributing to a relapse are multidimensional and involve many processes associated with addiction, including personal traits, past experiences with nicotine, associative learning and conditioning, and the manifestation of withdrawal symptoms. Development of treatments to prevent lapses (occasional smoking) is important, because these events so frequently lead to a relapse. In addition, this review suggests that treatments should target specific phenomena that may motivate lapses and relapses: (1) increases in withdrawal symptoms, especially urges to smoke and negative affect that occur in the first 48 hours of smoking cessation (Figures 4.6 and 4.8); (2) emergent increases or spikes in negative affect and urges that occur at any point after smoking cessation (Figures 4.8 and 4.9); (3) the drop in self-confidence or the increase in urges engendered by a lapse; (4) urges that occur shortly after awakening that may or may not reflect conditioned withdrawal effect (Figure 4.6); (5) a trait-like intolerance of distress; (6) increased urges to smoke and withdrawal symptoms prompted by smoking-related cues or stressful events (Figure 4.7); and (7) alcohol consumption and its effects on cognitive and motivational processes. Although relapse has also been associated with relatively stable demographic factors such as SES and educational status, it is unclear why these factors are associated with failure of smoking cessation and which treatment strategies could be used to counter them. Future research should be focused on further refining types for relapse and recovery, understanding genetic and neurobiologic underpinnings, and developing effective treatments for these types.

Evidence Summary

The 1988 Surgeon General's Report, *The Health Consequences of Nicotine Addiction,* concluded that "nicotine is the drug in tobacco that causes addiction" (USDHHS 1988, p. 9). Studies show that animals self-administer or prefer nicotine over saline and that many people smoke to regulate blood concentrations of nicotine. For example, if smokers are given cigarettes with lower nicotine yields than their usual brands, they tend to smoke more intensely or to cover the filter ventilation holes to increase their nicotine intake. The VTA region of the brain and the mesocorticolimbic dopamine neurons originating in this brain site are primarily responsible for the positive reinforcing aspects of nicotine. An increase in levels of dopamine is mediated by nicotine directly stimulating nAChRs, primarily α7 homomeric and α4β2-containing nAChRs within the VTA, thus increasing activity of VTA neurons projecting to the nucleus accumbens and the frontal cortex. Nicotine stimulates α7 nAChRs on glutamatergic terminals that release glutamate, an excitatory neurotransmitter, which results in increased release of dopamine in the nucleus accumbens, amygdala, and frontal cortex. Nicotine also excites nAChRs on GABA-releasing terminals. Thus, levels of GABA, an inhibitory neurotransmitter, are also increased by nicotine. However, the interplay between the quick desensitization of nAChRs on the GABA neuron and the higher doses of nicotine required to desensitize nAChRs on the glutamate neuron result in a greater increase in dopamine levels.

The neurophysiology associated with withdrawal symptoms may be based on the type of symptoms experienced (e.g., somatic versus affective). It appears that nAChRs differ in their involvement in both the somatic and affective components of nicotine withdrawal and dependence. As seen in animal studies, β4 nAChRs play an important role in the somatic signs of withdrawal, whereas β2 nAChRs play an important role in the affective, but not

somatic, aspects of withdrawal. The role of α4 nAChRs is unclear, but these receptors may play a role in both the affective and somatic withdrawal effects of nicotine addiction. The α7 nAChRs appear to be involved only in some of the somatic signs of nicotine withdrawal.

The amount and speed of nicotine delivery also plays a critical role in the potential for abuse of tobacco products. The speed and amount of nicotine delivered to the brain depend on the amount of nicotine in the product, the alkalinity of the product, and the route of administration. Nicotine, 3-(1-methyl-2-pyrrolidinyl)pyridine, is a volatile alkaloid in the tobacco plant, and its absorption and renal secretion is highly dependent on pH. Products with higher alkalinity are associated with greater amounts of nicotine in the nonionized or free base state, which can vaporize more easily into the gas phase, can be deposited directly on the lung tissues, and crosses cell membranes more rapidly than ionized nicotine. Tobacco products can contain constituents such as ammonia to increase the conversion of nicotine to the nonionized or free base state. Physical design features such as filter-tip ventilation also increase the free base fraction of nicotine (see Chapter 3, "Chemistry and Toxicology of Cigarette Smoke and Biomarkers of Exposure and Harm"). The fastest rate of nicotine delivery is through smoking cigarettes. Nicotine, when inhaled, enters the lungs, which present a large surface area of small airways and alveoli, undergoes dissolution in pulmonary fluid at a high pH, is transported to the heart, and then immediately passes to the brain. This rapid and bolus delivery of nicotine through cigarettes leads to greater control over the amount of nicotine delivered to the brain and results in higher abuse potential than do other tobacco- or nicotine-containing products.

Nicotine in the tobacco product and its kinetic profile are not the only factors that might contribute to a tobacco product's potential for addiction. Other constituents may also serve as reinforcers or may enhance blood levels of nicotine or its effects. For example, animal studies have shown that nornicotine, a secondary tobacco alkaloid, functions as a reinforcer, but at less potency than nicotine. The effect of nornicotine in humans is unclear. Acetaldehyde, another constituent in tobacco smoke, which results from burning sugars and other materials in the tobacco leaf, may play a role in increasing the reinforcing effects of nicotine. In animal studies, acetaldehyde enhanced the acquisition of nicotine self-administration among adolescent rats but not adult rats. Extracts from flue-cured tobacco that appear to inhibit MAO activity in the brain may be another contributory factor to the reinforcing effects of cigarettes. Increased MAO inhibition results in increased levels of catecholamines. Current smokers have lower levels of MAO than do nonsmokers or former smokers.

Tobacco product design and ingredients contribute to the risk of addiction by reducing noxious effects such as the unpleasant taste of nicotine and unpleasant sensory effects (see Chapter 2, "The Changing Cigarette"). Such designs include ventilation to cool the smoke and ingredients such as menthol and chocolate that make nicotine inhalation more pleasant. Other nonnicotine factors can also contribute to addiction potential. These factors include the associative learning processes (internal and environmental cues linked with nicotine administration) that develop with repeated tobacco use. This associative learning can be as powerful as the direct effects of nicotine. For example, presenting smokers with sensory aspects of smoking without nicotine has resulted in a decrease in craving for cigarettes, a decreased subset of withdrawal symptoms, and short-term reinforcing efficacy similar to that of cigarettes containing nicotine (see Chapter 3, "Chemistry and Toxicology of Cigarette Smoke and Biomarkers of Exposure and Harm").

Typically, smoking initiation occurs during adolescence. Research shows that adolescent smokers report some symptoms of dependence even at low levels of cigarette consumption, and animal studies show that sensitivity to nicotine in adolescents differs from that in adults. For example, results from the paradigms of self-administration and conditioned place preference in rats demonstrate that adolescence may be at a stage of development with higher sensitivity to nicotine exposure than that in adults. Using mixture modeling, longitudinal studies have identified multiple age-related trajectories of smoking behavior. These trajectories typically include smokers with early initiation of smoking and steep acceleration of smoking, persons who engage in experimental or light smoking, smokers with late initiation and accelerated progression of smoking, persons who stopped smoking, and those who never smoked. The group with early initiation and steeply escalating and persistent smoking has been associated with familial smoking, which reflects genetic and/or environmental risk factors, less parental support, and a risk for chronic heavy smoking in adulthood. Ethnic differences have also been observed for the age at initiation of smoking and the speed of progression in smoking. These studies showed that African Americans were more likely to have slower progression of smoking and a lower number of cigarettes smoked than do Whites. Studies that have looked at predictors for developing nicotine addiction or heavy smoking suggest the importance of both genes and environmental influences. Parental smoking, parental substance abuse disorders, and externalizing disorders (attention-deficit/hyperactivity, disruptive behavior, and alcohol and drug abuse) have been found to be predictive of nicotine dependence and/or daily smoking.

Initiation and persistence of smoking and nicotine dependence show strong heritability. Most coefficients of reported heritability range from less than 0.3 to more than 0.8 and vary on the basis of the smoking behavior phenotype examined and the social or environmental factors such as prevalence of smoking. The balance of evidence suggests that the risk of smoking initiation is influenced by both genetic and environmental factors, whereas the risk of smoking persistence may have a stronger genetic component. Although some genetic influences on smoking initiation and persistence are common, there are also separate and unique genetic influences for initiation and for persistence. Studies also suggest that the ability to stop smoking is under a strong genetic influence, and some consider this phenotype to be the key behavioral phenotype for nicotine dependence. Molecular genetic studies have been conducted to examine the specific genetic factors and biologic mechanisms involved in nicotine addiction. Most of the candidate gene studies have focused on genetic variation in nAChRs, relevant neurotransmitter pathways, or genes for nicotine-metabolizing enzymes. Candidate gene studies are association-based studies comparing prevalence of candidate gene variants in two unrelated groups—for example, nicotine-dependent versus nondependent persons. Examples of candidate gene variants that have been examined include nAChR subunits, such as *CHRNA4* and *CHRNA5*; dopamine receptors D2 and D4 (*DRD2* and *DRD4*) and dopamine transporter (*DAT*) genes; tryptophan hydroxylase, which is associated with serotonin biosynthesis; serotonin transporter *5HTTLPR*, which is associated with genes that code for serotonin reuptake; *MAOA* and *DβH* genes, which affect norepinephrine pathways; genes in the endogenous opioid pathway (e.g., *OPRM1*); and genes involved in the metabolism of nicotine (e.g., *CYP2A6*).

To date, the only candidate genes with consistent evidence of an association with smoking behavior or nicotine dependence are *CYP2A6* and *5HTT* and SNPs in the *CHRNA5/A3/B4* gene cluster. More research has been conducted on the effects of *CYP2A6*. Variants of P-450 *CYP2A6* associated with **NULL* or reduced activity are associated with reduced levels of the CYP2A6 enzyme and slower rates of nicotine metabolism, leading to higher plasma levels of nicotine for a given dose of nicotine. Persons who carry these variants with **NULL* or reduced activity tend to have lower risk for becoming smokers, reduced cigarette consumption, and possibly higher likelihood of successful smoking cessation than that for persons with wild-type genotypes and higher rates of nicotine metabolism. Research in this area will be greatly enhanced when there is agreement in the field on phenotypes for smoking initiation, trajectory toward nicotine dependence, and nicotine dependence. One area of research that has provided promising initial evidence is the pharmacogenetics of treatment to aid in smoking cessation, which included examining genetic variations in drug-metabolizing enzymes and variations in drug targets to predict responses to treatment. It is important to recognize that although genes may play an important role in the various aspects of smoking behavior, the risk for smoking exists in persons without the gene variants, and it is predominantly exposure, rather than the host, that leads to smoking-related illnesses.

Studying recovery from smoking can provide valuable information on the nature of tobacco addiction and the factors that affect it. Relapse to smoking occurs at a high rate, and most smokers who ultimately relapse resume smoking early after the attempt to stop smoking. The risk for relapse is particularly high among those who lapse or engage in a single episode of smoking after their first day of cessation. The pattern of return to smoking varies across individuals. However, on average, a second lapse occurs within 24 hours of the first lapse, and lapse to relapse occurs three to five weeks after the cessation attempt. Several multidimensional factors may be associated with relapse. These factors include the expectations that the effects from smoking will be rewarding, confidence in the ability to stop smoking, educational status, and degree of tobacco dependence. Situational indicators suggest that temptations to smoke and smoking lapse and relapse are associated with alcohol use and environmental signals such as the sight of others smoking and the availability of cigarettes.

Evidence supports the relationship of tobacco withdrawal syndrome with vulnerability to relapse. Studies show three important findings for many smokers: (1) withdrawal symptoms are persistent and often severe for several months after an attempt to stop smoking, (2) the heterogeneity in withdrawal symptoms is great, and (3) features such as the severity, variability, and the course of withdrawal symptoms confer increased risk for relapse. Craving and negative affect are the withdrawal symptoms most predictive of relapse, including urges to smoke that are experienced immediately after awakening in the morning. Research suggests complex interrelationships within and across the different types of influences. Future research is needed to elucidate these interactions.

Conclusions

1. Nicotine is the key chemical compound that causes and sustains the powerful addicting effects of commercial tobacco products.

2. The powerful addicting effects of commercial tobacco products are mediated by diverse actions of nicotine at multiple types of nicotinic receptors in the brain.

3. Evidence is suggestive that there may be psychosocial, biologic, and genetic determinants associated with different trajectories observed among population subgroups as they move from experimentation to heavy smoking.

4. Inherited genetic variation in genes such as *CYP2A6* contributes to the differing patterns of smoking behavior and smoking cessation.

5. Evidence is consistent that individual differences in smoking histories and severity of withdrawal symptoms are related to successful recovery from nicotine addiction.

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