Appendix 1

Background on Nicotine Pharmacology

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I. EVOLUTION OF THE DEFINITION OF ADDICTION

The scope of the definition of addiction and dependence has evolved over the years. Until the 1960's, the terms addiction and habituation were used to describe conditions associated with repeated substance use. In the U.S., use of the term addiction primarily implied the existence of a personality weakness.[1] Internationally, the term addiction was used to describe the combination of psychic and physical dependence on a drug.[2] The characteristics of addiction consisted primarily of tolerance, compulsive drug use, and psychological and physical dependence.[3] Damage to society as a result of drug use was also considered to be a component of addiction.[4] Opiates, barbiturates, and alcohol were regarded as addiction-producing drugs.[5]

In contrast, habituation was used to describe repeated but nondependent drug use for psychic effect and perhaps damage to the individual user but not to society. A habit-forming drug was defined as "one which is or may be taken repeatedly without the production of all of the

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[1] APA, 1952, at p. 39.
USDHEW, 1964, at p. 351.
USDHHS, 1988, at p. 248.

[2] WHO, 1950, at p. 6-7.
WHO, 1957, at pp. 9-10, 12
WHO, 1993, at p. 4.

[3] USDHEW, 1964, at p. 351.
WHO, 1957, at p. 10.

[4] WHO, 1957, at p. 10
USDHEW, 1964, at pp. 351, 356.
USDHHS, 1988, at p. 10.

[5] WHO, 1950, at pp. 3-14.
Royal Society of Canada, at p. 2.

characteristics outlined in the definition of addiction . . . "[6] Cocaine, amphetamines, and nicotine were viewed as habit-forming.[7] Cigarette smoking was considered an habitual behavior.[8]

The problem with these characterizations of addiction and habituation is that they did not take into account the fact that people on opiates for chronic pain may have developed tolerance or experienced withdrawal when stopping the drug but did not develop compulsive-use behavior.[9] On the other hand, no explanation was given for the fact that cocaine could produce all of the characteristics defined as constituting addiction.[10] In addition, difficulties were encountered in distinguishing addictive from habitual use.[11] Further, it was noted that damage to society resulted from habitual use of drugs, especially cigarettes, in the form of health care costs and lost work and productivity associated with drug- and smoking-related illnesses.[12] In 1964 the World Health Organization (WHO) recommended that the terms addiction and habituation be abandoned in favor of the term dependence in order to reduce the confusion between disorders, shift the focus away from the moral and social issues associated with addiction, and put more emphasis on

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[6] WHO, 1957, at p. 12.

[7] Royal Society of Canada, at p. 2.

[8] USDHEW, 1964, at p. 354.

[9] APA, 1987, at p. 166.

[10] Royal Society of Canada, at p. 2.

[11] Royal Society of Canada, 1989, at p. 9.

[12] USDHHS, 1988, at p. 252.
Royal Society of Canada, 1989, at p. 3.

behavioral aspects.[13] Although there has been widespread acceptance of the term dependence to describe addictive behavior, some authorities continue to use the term addiction. The terms dependence and addiction have been used interchangeably.[14]

Today, several major medical organizations have essentially similar definitions of addiction. All definitions share the common view that addiction or dependence occurs when a psychoactive substance begins to control behavior despite risk of injury to self or others.[15] (Psychoactive is defined as having the ability to alter mood, anxiety, behavior, cognitive processes, or mental tension.[16])

There is a consensus among the medical organizations that nicotine is addictive. A summary of the views of the major scientific organizations follows.

A. The Office of the U. S. Surgeon General

The Office of the U.S. Surgeon General first reported that nicotine was addictive in its 1986 assessment of smokeless tobacco.[17] The report cited numerous studies demonstrating nicotine's abuse liability. Studies by Griffiths, Hughes, Rosecrans, and many others showed that

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[13] WHO, 1964, at p. 9.
USDHHS, 1988, at p. 11.

[14] USDHHS, 1988, at p. 7.

[15] USDHHS, 1988, at p. 248.
Royal Society of Canada, 1989, at p. 6.

[16] Stedman's, 1990, at p. 1284.

[17] USDHHS, 1986, at p. 144.

nicotine from cigarettes affected the central nervous system.[18] The effects of nicotine obtained from cigarettes were similar to those obtained from smokeless tobacco.

Although in 1964 the Surgeon General described tobacco smoking as habituating rather than addicting, studies on nicotine's effects on the brain were not available for consideration.[19] The 1964 report concluded that habitual tobacco use was primarily driven by psychological and social forces. It acknowledged, however, that the habit was reinforced by the pharmacological effects of nicotine on the central nervous system and that nicotine-free tobacco did not satisfy the needs of those who had a tobacco habit.[20]

The 1964 Surgeon General's report applied the contemporary definitions developed by the 1957 World Health Organization Expert Committee on Addiction-Producing Drugs to addiction and habituation.[21] Addiction was defined as a state of intoxication accompanied by a compulsion to use the drug, a tendency to increase the dose of the drug, a psychological and physical dependence on the drug's effects, and detrimental effects on the individual and on society.[22]

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[18] Griffiths et al., 1982, at pp. 260-263.
Hughes et al., 1986, at pp. 289-294.
Nemeth-Coslett et al., 1986, at pp. 420-425.
Rosecrans et al., 1981, at pp. 497-501.

[19] USDHHS, 1988, at pp. 6-7, 11.

[20] USDHHS, 1988, at p. 10.
USDHEW, 1964, at p. 354.

[21] WHO, 1957, at p. 9-10.
USDHEW, 1964, at pp. 350-351.

[22] USDHEW, 1964, p.351.
WHO, 1957, at p. 9.

Habituation, on the other hand, was defined as a condition which resulted from the use of the drug. Indicators of habituation included a desire, but not compulsion, to take the drug, little tendency to increase the dose, some psychic but no physical dependence on the drug, and detrimental effects primarily on the individual.[23] From this definition, chronic tobacco smoking was characterized as habituation, similar to the habitual use of coffee and tea.[24]

In the 1988 report *"Health Consequences of Smoking: Nicotine Addiction,"* the Surgeon General concluded that cigarette smoking is addictive and that nicotine is the substance in tobacco that causes addiction.[25] By that time, considerable research had emerged that cigarettes and other forms of tobacco were addicting, even using the earlier definitions. Monographs published in the 1970's by the National Institutes on Drug Abuse (NIDA) considered tobacco use to be a form of drug dependence.[26] In particular, by the late 1980's, new evidence was emerging that nicotine was psychoactive and that laboratory animals would work to self-administer the drug[27] Self-administration is a distinguishing characteristic of the potential of a drug to cause dependence.[28] Consequently, the Surgeon General's Report concluded that cigarette smoking was addictive.

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[23] WHO, 1957, at p. 9-10.

[24] USDHEW, 1964, at pp. 351-352.

[25] USDHHS, 1988, at p. 9.

[26] USDHHS, 1988, at p. 12.

[27] Garcha et al., 1986.
Goldberg et al., 1981, at pp. 573-575.
Goldberg et al., 1982, at pp. 216-220.
Goldberg et al., 1989, at pp. 295-302.
Griffiths et al., 1979, at pp. 163-208.

[28] USDHHS, 1988, at p. 277.

The 1988 Report described compulsive or habitual use of a drug as a characteristic of dependence but made the distinction that dependence differed from habitual behavior when it involved the use of a psychoactive drug that was capable of reinforcing the drug-taking behavior. Addictive behavior included use despite harmful effects, a return to use following a drug-free interval (relapse following a period of abstinence), and recurrent persistent urges to use the drug (craving). Dependence-producing drugs were characterized as producing tolerance, physical dependence, and reinforcing pleasant effects.[29]

B. The World Health Organization

The World Health Organization first recognized that tobacco was dependence-producing in 1974; however, tobacco was not included with other dependence-producing drugs until 1992, when the 10th edition of the *International Classification of Diseases* (ICD-10) was published.[30] Dependence syndrome in ICD-10 was defined as follows:

> *A cluster of physiological, behavioural, and cognitive phenomena in which the use of a substance or a class of substances takes on a much higher priority for a given individual than other behaviours that once had greater value. A central descriptive characteristic of the dependence syndrome is the desire (often strong, sometimes overpowering) to take psychoactive drugs (which may or may not have been medically prescribed), alcohol, or tobacco. There may be evidence that return to substance use after a period of abstinence leads to a more rapid reappearance of other features of the syndrome than occurs with nondependent individuals.*[31]

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[29] USDHHS, 1988, at p. 8.

[30] WHO, 1974a, at pp. 15-16.
WHO, 1992, at p. 324.

[31] WHO, 1992, at pp. 75, 321.

Under the diagnostic guidelines for dependence syndrome, an individual must meet three or more of the criteria to be diagnosed as dependent on a psychoactive substance.[32]

Previously, in ICD-8 (1968), drug dependence was defined as:

> *a state, psychic and sometimes also physical, resulting from taking a drug, and characterized by behavioural and other responses that always include a compulsion to take the drug on a continuous or periodic basis in order to experience its psychic effects, and sometimes to avoid the discomfort of its absence. Tolerance may or may not be present. A person may be dependent on more than one drug.*[33]

Based on the research and literature available at the time, tobacco/nicotine use did not fit this definition.

ICD-9 (1978) recognized tobacco dependence but classified the disorder as a nondependent abuse because tobacco was considered different from other drugs of dependence in that it did not produce "psychotoxic" effects.[34] ICD-9's category of nondependent abuse of drugs included:

> *cases where a person, for whom no other diagnosis is possible, has come under medical care because of the maladaptive effect of a drug on which he is not dependent and that he has taken on his own initiative to the detriment of his health or social functioning.*[35]

C. The American Psychiatric Association

The American Psychiatric Association first recognized tobacco as dependence-producing in 1980

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[32] WHO, 1992, at p. 75.

[33] WHO, 1974b, at pp. 47-48.

[34] WHO, 1978, at p. 43.

[35] WHO, 1978, at p. 43.

in the third edition of the *Diagnostic and Statistical Manual* (DSM-III).[36] In DSM-III, either tolerance or withdrawal (not both) must have been present to demonstrate dependence for most drugs; while intoxication was a descriptor for abuse, it was not necessary for dependence. DSM-III also added a new criterion to its previous definition of dependence: unsuccessful attempts to decrease or stop the use of the drug.

The DSM-III (1980) identified specific criteria for tobacco dependence and withdrawal but not for tobacco intoxication or abuse. The definition of tobacco dependence was based primarily on users' unsuccessful attempts to quit and their continued use of tobacco despite medical problems exacerbated by its use. Intoxication was identified as an element of abuse; the DSM-III did not list tobacco as causing intoxication or abuse.[37] ICD-9 (1978), however, categorized tobacco dependence as nondependent abuse because it differed from other drugs of abuse with respect to psychotoxic effects.[38]

Dependence as described in DSM-III-R (1987) did not necessarily imply physiological dependence.[39] Although the indicators of tolerance and withdrawal were broadened, neither tolerance nor withdrawal were now required for a diagnosis of dependence. The new definition of dependence included a group of behaviors and symptoms that indicated impaired control of the

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[36] APA, 1980, at p. 99.

[37] APA, 1980, at pp. 92-100.

[38] WHO, 1978, at p. 43.

[39] Reid et al., 1989, at p. 34.

substance use and continued use of the substance despite adverse consequences.[40]

The DSM-III-R definition of dependence was expanded from the three criteria used in DSM-III to nine criteria. DSM-III-R also differed from DSM-III in that more than one criterion was needed for a diagnosis of dependence; however, only three of the nine criteria in the new version had to be met.[41] The DSM-III-R criteria included the following: 1)substance taken in larger amounts or over a longer period of time than the person intended; 2) persistent desire or one or more unsuccessful efforts to cut down or control substance use; 3) a great deal of time spent to get the substance, or recovering from its effects; 4) frequent intoxication or withdrawal symptoms when expected to fulfill major role obligations at work, school, or home, or when substance use is physically hazardous; 5) important social, occupational, or recreational activities given up or reduced because of substance use; 6) continued substance use despite knowledge of having a persistent or recurrent social, psychological, or physical problem that is caused or exacerbated by the use of the substance; 7) marked tolerance: need for markedly increased amounts of the substance in order to achieve intoxication or desired effect, or markedly diminished effect with continued use of the same amount; 8) characteristic withdrawal symptoms; 9) substance often taken to relieve or avoid withdrawal symptoms. As with DSM-III, the DSM-III-R recognized two conditions associated with tobacco use: nicotine dependence and nicotine

[40] APA, 1987, at p. 166.

[41] APA, 1987, at pp. 166-167.
APA, 1980, at p. 99.
Reid et al., 1989, at p. 98.

withdrawal.[42]

The list of criteria for dependence in DSM-IV (1994) varies slightly from that in DSM-III-R. The criteria have been reduced from nine to seven, although it remains the case that only three must be met in order to diagnose substance dependence. Additionally, the DSM-IV has specifiers to measure the degree of dependence, eliminates any reference to intoxication, and uses tolerance and withdrawal as indicators of physiological dependence. DSM-IV continues to describe nicotine dependence and nicotine withdrawal. For a diagnosis of nicotine dependence, all dependence-defining criteria may not be applicable, but DSM-IV describes how nicotine satisfies more than three of the criteria necessary for dependence: tolerance; a well-defined withdrawal syndrome; a desire to quit smoking; a great deal of time using the substance (exhibited by chain smoking); and continued use despite knowledge of medical problems.[43]

D. Other Scientific and Medical Associations

Other scientific and medical associations worldwide identify nicotine as an addicting or dependence-producing drug. The American Medical Association states, "The AMA identifies alcohol and nicotine as drugs of addiction which are gateways to the use of other drugs by young people."[44] In a July 1988 statement before the U.S. House Subcommittee on Health and the Environment, the American Psychological Association concurred with the findings of the 1988

[42] APA, 1987, at pp. 150, 181.

[43] APA, 1994, at p. 243.

[44] AMA, 1993, at p. 35.

A) CNS MECHANISMS

The addictive properties of nicotine are produced through its actions in the central nervous system. Nicotine affects many areas of the brain, and investigations have not determined conclusively if the addictive properties are mediated solely by a unitary circuit spanning different brain centers or whether multiple, interrelated circuits are involved.[49]

Most of the biological effects produced by nicotine are caused by its actions on specific receptors called nicotinic cholinergic receptors (nicotinic receptors). Nicotinic receptors are distributed over most organs of the body, including much of the peripheral and central nervous systems. Many important bodily functions, including mood regulation, are produced or modulated by the action of acetylcholine, a naturally-occurring substance, on nicotinic receptors. In the brain, nicotine activates nicotinic receptors located on dopaminergic neurons to cause the neurons to release more dopamine.[50]

Most scientists agree that nicotine's addictive effects, like other drugs of abuse (e.g. cocaine, morphine and amphetamine) are the result of nicotine's action on the mesolimbic system. The mesolimbic system is located in the midbrain and projects onto two forebrain regions called the nucleus accumbens and the olfactory tubercle.[51] The mesolimbic system consists of a field of neurons and pathways thought to be important in emotions and in reinforcing wide-ranging activities like eating, sex, and drug dependence.

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[49] Stolerman et al. 1991, at p. 472.

[50] Reavill et al., 1990, at pp. 315-322.

[51] Pomerleau et al. 1984, at p. 506.
Stolerman et al. 1991, at p. 472.

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[51] Pomerleau et al. 1984, at p. 506.
Stolerman et al. 1991, at p. 472.

Nicotine and other drugs of abuse produce their rewarding or reinforcing effects by stimulating the release of dopamine from dopaminergic neurons within the mesolimbic system. Dopamine plays a major role in regulating mood and pleasurable sensations. Nicotine stimulates the release of dopamine by binding to nicotinic receptors located on the cell bodies of these dopaminergic neurons. Dopamine then acts on dopaminergic receptors to produce the positive reinforcing effects of nicotine.[52]

Stimulation of the mesolimbic dopaminergic system has been shown to produce rewarding or reinforcing effects in laboratory animals. Drugs such as amphetamine, cocaine, and nicotine stimulate this system to produce reinforcing effects.[53] These effects are due to an increase in the amount of dopamine available to stimulate dopaminergic receptors.[54] Although the cellular actions by which amphetamine, cocaine, and nicotine increase dopamine release from mesolimbic neurons are different, their stimulant effects on dopamine receptors that produce rewarding or reinforcing properties are very similar.[55]

As noted previously, nicotinic receptors are distributed widely in the body. Evidence suggests that the positive reinforcing effect of nicotine in both humans and animals is activated by

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[52] Wise et al., 1989, at pp. 191-214.
Clarke, 1990, at p. 154.

[53] Imperato et al., 1986, at pp. 337-338.
Corrigall and Coen, 1991a, at pp. 167-170.

[54] Wise et al., 1989, at pp. 191-214, 219.

[55] Wise et al., 1989, at pp. 214-219.
Rowell et al., 1987, at pp. 1451-1453.
Imperato et al., 1986, pp. 337-338.

a portion of these receptors.[56] Specifically, some addiction researchers believe that the nicotinic receptors residing on dopaminergic nerve terminals within the nucleus accumbens activate the positive reinforcing effects of nicotine.[57]

Laboratory and clinical studies strongly suggest a link between the positive reinforcing effects of nicotine and its action on the nucleus accumbens. In vitro studies have shown that small concentrations of nicotine, similar to the amounts in the plasma of cigarette smokers, selectively enhance release of dopamine in the nucleus accumbens.[58] Experiments have shown similar effects on the nucleus accumbens in vivo after systemic administration of nicotine. In these studies, dopamine is released when nicotine is infused directly into the nucleus accumbens.[59] Conversely, nicotine's effects are reduced when access to dopaminergic receptors is reduced. Lesions of the mesolimbic dopaminergic system reduce the number of nicotine binding sites as well as weaken self-administration in rats.[60] Similarly, chemicals that block dopamine receptors (i.e., antagonists) can alter some of the effects produced by nicotine in animals.[61]

In summary, most researchers believe that nicotine produces its addicting effects through

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[56] USDHHS, 1988, at pp. 88-120.

[57] Clarke, 1990, at pp. 159-160.

[58] Rowell, et. al., 1987, at p. 1451.

[59] Imperato et al., 1986, at pp. 337-338.
Brazell et al., 1990, at pp. 1177, 1179, 1183.

[60] Singer et al., 1982, at pp. 580-581.
Clarke, 1990, at p. 160.
Clarke et al. 1988, at pp. 701-708.

[61] Clarke, 1990, at pp. 155-157.

its action on the mesolimbic dopaminergic system. Specifically, nicotine is thought to interact with nicotinic receptors on the dopamine nerve cell endings located in the nucleus accumbens. Release of dopamine is thought to activate the drug-reinforcing effects produced by nicotine and by other stimulant drugs such as amphetamine and cocaine.

B. PHYSIOLOGICAL EFFECTS

1. Dose-Response

The relationship between the dose of nicotine and the resulting response (dose-response relationship) is complex and is a function of the specific response measured. In low doses nicotine causes nerve stimulation; in high doses, it blocks the nerve after a period of brief stimulation. This type of pattern is referred to as "biphasic." Dose-response characteristics in humans are often biphasic.[62] For example, at low doses of nicotine, similar to those seen during cigarette smoking, cardiovascular effects appear to be activated by the central nervous system. The result is an increase in blood pressure and heart rate. At higher doses, nicotine may act directly on the peripheral nervous system and produce nerve stimulation and the release of adrenal catecholamines that transmit indirect chemical signals to the brain. With high doses and rapid administration, nicotine produces slowing of heart rate.[63]

2. Tolerance

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[62] Comroe, 1960, at pp. 48-49.

[63] Henningfield et al., 1985 at pp. 4-6.

Tolerance occurs when a consistent dose of a drug produces a less intense effect over time or when an increasing dose over time is required to achieve a specified response. Functional tolerance occurs when a particular drug concentration at a receptor site produces less effect than it did from a prior exposure. If the tolerance develops within one or two doses, it is referred to as acute tolerance. If tolerance develops after more prolonged use, the tolerance is referred to as acquired or chronic tolerance.

Differences among individuals sensitivity to the first dose of a drug also occurs frequently. Individuals who exhibit a reduced response to a specified drug dose or require a greater dose to elicit a specified level of response may be said to be tolerant to the drug. This form of tolerance is referred to as first-dose tolerance or lower drug sensitivity.

The term tolerance will be used in this document to describe a reduced response to nicotine during the course of, or following a previous, exposure. Acute drug sensitivity will be used to describe increased responsiveness to an initial dose.

Studies on nicotine tolerance began in the late 19th century and, in general, focused on tolerance which develops as a result of chronic administration. These studies have been important to the understanding of the nervous system and the drug properties of nicotine. Scientists using repeated nicotine administration in a variety of animal species and on in vitro tissue preparations concluded the following: 1) with repeated dosing, physiological responses diminished to nearly negligible levels; 2) after tolerance occurred, responses could be restored by increasing the size of the dose; 3) after a few hours without nicotine, responsiveness was partially or fully restored.[64]

[64] US DHHS, 1988, at p. 45.

After smoking a cigarette, naive smokers usually experience a number of effects that are generally uncommon among experienced smokers. For example, retrospective reports by smokers indicate that while initial exposure to tobacco smoke produced dizziness, nausea, vomiting, headaches, and dysphoria, these effects disappear with continued smoking and are rarely reported by chronic smokers. Nicotine tolerance develops quickly. During the course of nicotine poisoning, tolerance may develop to toxic effects, such as nausea, vomiting, and pallor, despite persistence of nicotine in the blood in extremely high concentrations.[65] Tolerance to nicotine is never complete, however. Even the heaviest smokers experience symptoms of toxicity such as nausea and vomiting when they suddenly increase their smoking rates.[66]

a. Acute Tolerance

Smoking a single standard cigarette after 24 hours of abstinence causes an increase in heart rate from baseline. However, repeated smoking of a standard cigarette in the usual manner throughout a normal day causes less increase in heart rate compared to the first cigarette smoked after an abstinence period.[67] In one example, an individual developed complete tolerance to nausea and vomiting over 8 hours during the course of an accidental nicotine poisoning. Tolerance also develops to the effect nicotine on arousal level, heart rate, and blood pressure. Heart rate and blood pressure responses are significantly greater after more prolonged abstinence.

[65] Benowitz et al., 1987, at pp. 119-120.

[66] Danaher, 1977, at pp. 151-155.

[67] West and Russell, 1987, at pp. 118-121,

Considerable tolerance persists throughout the daily smoking cycle but is lost with prolonged abstinence. Tolerance, at least after abstinence for one week, is rapidly reestablished with subsequent exposure.[68]

b. Chronic Tolerance

Chronic tolerance may be related to lower blood levels of tolerance or to a decrease in sensitivity of the brain tissue to the drug. Considerable differences exist among humans in the rate of nicotine metabolism. Nicotine metabolism is faster in smokers than in nonsmokers.[69] Chronic tolerance to nicotine may also be due to the desensitization of nicotinic receptors following chronic nicotine exposure. Although there is an increase in the number of brain nicotinic receptors following chronic exposure, there is a decrease in the absolute number of receptors capable of being activated.[70]

C. CARDIOVASCULAR EFFECTS

The baseline heart rate is increased during daily cigarette smoking. Catecholamine concentrations in the plasma are increased. This is consistent with the data that cigarette smoking

[68] Lee et al., 1987, at pp. 476-478.

[69] Kyermaten et al., 1982, at pp. 769-779.
Kyermaten et al., 1983, at pp. 205-209.

[70] Marks et al., 1983, at p. 823.
Schwartz et al., 1985, at pp. 428-429.

produces sustained or persistent sympathetic neural activation.[71] Persistent sympathetic activation would be expected to result in the following effects: 1) changes in lipid metabolism; 2) increased platelet aggregation and coagulation; 3) narrowing of blood vessels and coronary spasm; and 4) increased heart rate and contraction of the heart wall muscle producing an increase in the oxygen demands of the heart and of circulating catecholamines, which can promote irregular heart rhythms.[72] These factors could accelerate fatty deposits in the arteries and contribute to myocardial infarction.

D. PERFORMANCE EFFECTS

Nicotine may alter cognition and performance through brain receptor activity or through interaction with skeletal muscle and hormonal systems, respectively. Nicotine and smoking produce inconsistent effects on human performance. Sensory abilities appear to be enhanced by nicotine, but the majority of studies are confounded because the testing is done in tobacco-deprived smokers. Such nicotine deprived smokers are in a state of withdrawal, a state that is associated with decreased performance. Therefore, the "performance enhancement" reported by some studies may merely be the result of reducing the performance deficit associated with withdrawal. Finger tapping rate is modestly, yet reliably, increased by nicotine, whereas hand steadiness and tremor are impaired. The largest amount of research in this area has involved the measurement of attention. Over half of these studies reported that nicotine and smoking had no

[71] Benowitz, 1986b, at p. 1640.

[72] Benowitz, 1986a, at pp. 26-28.

effect on attentional behavior. There is evidence that nicotine prevents the loss of attention typically observed on tests of sustained attention; however, these data do not indicate that performance was enhanced over baseline levels. Nicotine's effects on cognition are also inconsistent. Studies show a range of responses from no effect to evidence of improved or impaired responses in the same study.[73]

E. PHYSICAL DEPENDENCE

After several weeks of nicotine exposure, physical dependence to nicotine develops. When nicotine-dependent people are deprived of nicotine for more than a few hours, withdrawal symptoms are reported. Early studies showed that smokers who are abruptly switched to cigarettes containing less nicotine experience behavioral and physiological withdrawal signs, including discomfort and the seeking of regular cigarettes.[74] Common self-reported withdrawal effects include increased irritability anxiety, difficulty concentrating, restlessness, impatience, insomnia, and craving for tobacco.[75]

Physiological changes after cigarette deprivation include decreased heart rate, decreased arousal evidenced by drowsiness, and CNS hypersensitivity.[76]

Some studies have reported insomnia and sleep disturbance following tobacco deprivation.

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[73] Heishman et al., 1994, at pp. 345-395.

[74] USDHHS, 1988, at p. 198.

[75] Hughes et al., 1986, at pp. 289-294.

[76] West et al., 1984, at pp. 217-218.

Tobacco-deprived smokers' total sleep time and sleep patterns may be altered during withdrawal.[77]

Another physical change reported among tobacco-deprived smokers is increased weight. This is likely attributed to decreased metabolism and decreased energy expenditure.[78]

III. BEHAVIORAL EFFECTS OF NICOTINE

Nicotine is a psychoactive (mood altering) drug that can cause addiction.[79] The previous section discussed the mechanisms of nicotine addiction, including tolerance and physical dependence.[80] This section addresses the properties of nicotine that can cause compulsive use of nicotine, including its pleasurable effects and its ability to control behavior (reinforcing effects). Substances that can produce compulsive drug-seeking and drug-taking behavior in humans:

> *have two fundamental commonalities: (a) . . . they are voluntarily self-administered by non-human mammals, and (b) . . . they acutely enhance brain reward mechanisms.*[81]

This section documents how nicotine maintains self-administration behavior and reinforces that behavior through brain reward mechanisms.

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[77] Jarvik and Schneider, 1992, at p. 342.

[78] Wack et al. 1982, at pp. 366-380
Glauser et al. 1970, at pp. 377-381.

[79] USDHHS, 1988, p 215

[80] USDHHS, 1988, at p. 215

[81] Gardner, 1992, at p. 86.

A. DISCRIMINATIVE STIMULUS PROPERTIES OF NICOTINE

The ability of a drug to function as a stimulus that can be discriminated or distinguished from another drug is an objective measure of a drug's psychoactivity that can be tested in animals. The discriminative stimulus properties of a drug are evaluated in a drug discrimination studies. Drug discrimination studies are routinely used in the preclinical assessment of the abuse potential of drugs and are considered to be an animal model to evaluate the subjective effects in humans. Frequently, there is a strong correlation between the results in the laboratory animal and humans. Drugs that elicit similar subjective effects in humans generally produce similar discriminative stimulus effects in animals.[82]

1. Nicotine Discrimination Studies in Animals

The ability of laboratory animals to identify nicotine in drug discrimination studies was first reported in 1969 and has been well documented since. In the 1969 study, rats were able to distinguish that the subjective effects of nicotine were different from those of other drugs, including amphetamine, pentobarbital, and caffeine. A nicotine-appropriate response was attenuated when rats were subcutaneously pretreated with mecamylamine prior to the nicotine injection. However, when the rats were given a subcutaneous injection of chlorisondamine prior to nicotine, a nicotine-appropriate response was elicited. This study confirmed that nicotine's effects occur in the central nervous system since mecamylamine is a nicotinic receptor antagonist

[82] Overton, 1988, at pp. 176-198.
Schuster and Johanson, 1988, at pp. 161-175.
Stolerman et al., 1988, at pp. 32-43.

that crosses the blood-brain barrier to prevent nicotine from producing an effect. Chlorisondamine, on the other hand, is a quaternary ganglion blocker that does not enter the brain and therefore does not block central nicotinic receptors. [83] Similar studies confirmed that mecamylamine reduced the ability of rats to discriminate subcutaneously administered nicotine, and other antagonists that do not enter the brain, such as hexamethonium, did not interfere with the rats' ability to distinguish nicotine from saline.[84]

These findings have been confirmed by other investigators using a variety of drug discrimination paradigms.[85] In one study using a T-maze apparatus, rats learned to enter one arm of the T-maze in the presence of nicotine and enter the opposite arm following the administration of placebo. [86]

The discriminative stimulus properties of nicotine are highly specific. Nicotine analogues, drugs similar to nicotine that inhibit binding of nicotine in vitro, and nicotine metabolites have been shown to elicit nicotine-like discriminative stimulus effects.[87] These findings support the

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[83] Morrison et al., 1969, at pp. 351-360.

[84] Schechter and Rosecrans, 1971, at pp. 821-832.
Meltzer et al, 1980, at pp. 283-286.

[85] Chance et al., 1977, at pp. 19-26.
Schechter and Rosecrans, 1971, at pp. 821-832.
Schechter and Rosecrans, 1972, at pp. 379-387.
Stolerman, 1989, at pp. 131-138.

[86] Schechter and Rosecrans, 1971, at pp. 821-832.
Schechter and Rosecrans, 1972, at pp. 379-387.

[87] Romano et al., 1981, at pp. 310-315.
Pratt et al., 1983, at pp. 54-60.
Stolerman et al., 1984, at pp. 413-419.
Garcha et al., 1986, at p. 298.

concept that there are specific receptors in the brain for nicotine.

Several investigators provided additional evidence that the discriminative stimulus effects of nicotine occur in the central nervous system. The studies reported that when nicotine is administered directly into the lateral ventricles of the brain, it produces the same subjective effects as does nicotine administered subcutaneously.[88] Additionally, when nicotine is injected bilaterally into the hippocampus and unilaterally into the medial reticular formation, nicotine-appropriate responding is elicited.[89]

2. Discriminative Stimulus Properties of Nicotine in Humans

Human studies on nicotine's discriminative stimulus effects have substantiated the findings obtained in animal studies. One of the first human studies utilizing the drug discrimination procedure was a study of nicotine discrimination in experienced smokers. Kallman et al reported that humans could discriminate between research cigarettes that varied in nicotine level but had been equated for taste, water content, tar, and puff counts (draw strength) and that the degree and rate of acquisition of the discrimination appeared dose-dependent. Twenty-two males, aged 20-45 (mean 31.2) years who smoked at least one pack per day, were recruited from a university

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Reavill, et al., 1987, at pp. 789-792.
Takada et al., 1989, at pp. 208-212.
Goldberg et al., 1989, at pp. 295-302

[88] Schechter, 1973, at pp. 327-335.
Rosecrans et al., 1977, at pp. 155-185.
Romano et al., 1981, at pp. 316-315.

[89] Rosecrans and Meltzer, 1981, at pp. 497-501.

campus for the study. Ninety-four per cent of the subjects readily learned to discriminate between two types of cigarettes that contained either 0.14 mg or 1.30 mg of nicotine. Only 27% of the subjects were able to discriminate between cigarettes that contained 0.28 and 0.69 mg of nicotine respectively.[90] These findings are consistent with earlier reports that human volunteers can differentiate between cigarettes that differed substantially in nicotine contents.[91]

Perkins et al also reported on the ability of nicotine to function as a discriminative stimulus in humans following intranasal administration. Subjects were trained to discriminate 12 μg/kg nicotine administered by measured dose-spray. The subjects were able to distinguish the lowest dose of nicotine (2 μg/kg) from placebo; 50% and 30% nicotine appropriate responding was elicited by the male and female subjects, respectively.[92]

B. NICOTINE SELF-ADMINISTRATION

The self-administration model is widely used in both humans and animals to assess the reinforcing efficacy of drugs and to quantitate their abuse liabilities. This model enables a researcher to assess the role of the variables in the reinforcing efficacy of a drug, such as dose, schedule of availability, and pharmacologic interactions with other products. A general finding is that drugs of abuse serve as reinforcers in drug administration models.[93]

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[90] Kallman et al., 1982, at pp. 211-218.

[91] USDHHS, 1988, at p. 176
Goldfarb et al., 1976, at pp. 767-772.

[92] Perkins et al. 1994, at p. 111.

[93] Henningfield and Goldberg, 1983, at pp. 989-992.

1. Self Administration Studies in Animals

Early nicotine self-administration studies employed a fixed-ratio schedule for nicotine reinforcement[94] Some of these studies demonstrated that nicotine, when compared to cocaine using similar schedules, was a weak reinforcer. Other studies demonstrated that nicotine was only slightly more reinforcing than saline.

Between 1981 and 1987, however, several laboratories independently evaluated the reinforcing properties of nicotine under a variety of intermittent schedules of reinforcement. Other drugs of abuse (e.g. cocaine) were known to function as positive reinforcers using the interim schedule that closely resembles the patterns of human cigarette smoking behavior. A desired nicotine level can be maintained by taking intermittent small doses (like a puff) with a time interval between puffs and cigarettes.[95]

In 1981, Goldberg et al, confirmed that nicotine was self-administered in primates. Other studies around this time period also provided an explanation for the failure of earlier studies to demonstrate more potent reinforcing effects of nicotine. The reinforcing properties of nicotine are dependent on the time intervals at which it is administered. Goldberg and colleagues were the

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[94] USDHHS 1988, at pp. 181-192
Lang et al., 1977, at pp. 65-70.
Singer et al., 1978, at pp. 387-389.
Hanson et al., 1979, at pp. 70-90.
Latiff et al., 1980, at pp. 209-213.
Deneau et al., 1976, at pp. 277-279.
Yanagita, 1977, at pp. 231-242.
Griffiths et al., 1979, at pp. 163-208.
Ator et al., 1983, at pp. 993-1003.

[95] USDHHS, 1988. at pp. 181-192.
Henningfield, 1984, at pp. 131-210.

first to demonstrate that nicotine could maintain high rates of response. Squirrel monkeys trained under second-order schedules responded to a visual stimulus (light) that was intermittently associated with nicotine injection. When the light was removed, the animals would not press levers as frequently as when the visual stimulus was present. The overall rate at which the monkeys responded and pressed the lever for more nicotine was high, similar to the rate seen in studies using cocaine.[96] In addition, the rates of responding were about twice as high when the brief stimulus was presented as when it was not.[97] The results show that nicotine can function as an effective reinforcer under a second-order schedule of drug self-administration and that an environmental stimulus associated with nicotine intake can contribute to the maintenance of persistent drug-seeking behavior.[98]

2. Self-Administration in Humans

Under controlled laboratory conditions, it has been shown that cigarette smoking behavior is an orderly behavioral-pharmacological process. Cigarette smokers individualize their nicotine doses by the types of cigarette they smoke (high vs low nicotine and tar); by their smoking rates; and by their smoking topographies (number of puffs, puff duration, puff size, depth of inhalation, and the amount of tobacco smoked). Smoking behavior changes depending on variables such as

[96] Goldberg et al., 1981, at pp. 573-575.

[97] Goldberg et al, 1981, at p. 575.

[98] Goldberg et al, 1981, at p. 573.

the length of deprivation and the nicotine dose being received.[99]

Griffiths et al studied the patterns of cigarette smoke self-administration in seven volunteer human subjects with a history of regular smoking. They reported that cigarette smoking was an orderly spaced behavior and that when the number of puffs per cigarette and the time between cigarettes varied, smokers adjusted their smoking pattern to maintain a desired level of nicotine.[100]

It is widely accepted that nicotine functions as the primary reinforcer and that cigarette smoking is an efficient vehicle for nicotine self-administration. The role of nicotine as the positive reinforcer in cigarettes has been supported in several studies. A study by Goldfarb et al has shown that it is the level of nicotine as opposed to the level of tar that is responsible for the maintenance of cigarette smoking behavior. In this study, ratings of "strength" and "satisfaction" were directly related to the nicotine content. As the nicotine level in the cigarette increased, the rating of strength and satisfaction increased. Also, when cigarette smokers were given cigarettes with a high nicotine content, the numbers of cigarettes smoked decreased.[101]

A similar study showed that cigarette smokers modify smoking behavior when the amount of nicotine available is changed. Nine volunteers who smoked an average of 18.5 cigarettes per day were given their own brand in whole, half, quarter, and one-eighth lengths to smoke in random order. Each session was two hours in duration and the subjects were allowed to smoke ad lib. Each cigarette was smoked through a modified plastic holder that recorded the number of

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[99] Griffiths and Henningfield, 1982, at pp. 260-263.

[100] Griffiths et al., 1981, at pp. 256-265.

[101] Goldfarb et al., 1976, at pp. 767-772.

puffs per cigarette. The results showed that as the cigarette length decreased, the number of puffs increased and the number of cigarettes smoked significantly increased. Also, the subjects' satisfaction rating significantly increased as the cigarette length increased.[102]

In the same study, 28 subjects were given whole or quarter length cigarettes that delivered 0.2 or 2.0 mg of nicotine per cigarette. During the two-hour session, the subjects were allowed to smoke ad lib. Subjects smoked a significantly greater number of the low-nicotine (0.2 mg) cigarettes than the high-nicotine (2.0 mg) cigarettes. Also, subjects took more puffs when smoking the low-nicotine content cigarette. Consistent with the results from the first study, the subjects smoked significantly more quarter-length cigarettes than full-length cigarettes.[103]

Cigarette smokers tend to engage in compensatory behaviors in an attempt to counteract the blocking effects of mecamylamine.[104] Stolerman et al reported that cigarette smokers pre-treated with mecamylamine increased the number of cigarettes smoked and the total number of puffs during a two-hour session. Consistent with the findings in drug discrimination studies which showed that the reinforcing effects of nicotine occurred in the brain, pretreatment with the antagonist pentolinium, which does not enter the brain, did not alter rates of cigarette smoking.

Nemeth-Coslett and her colleagues further characterized the effects of mecamylamine on cigarette smoking. Eight volunteers who smoked an average of 33 cigarettes a day for an average of 15 years were allowed to smoke ad lib during 90-minute sessions on Mondays, Wednesdays,

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[102] Jarvik et al., 1978, at pp. 303-306.

[103] Jarvik et al., 1978, at pp. 303-306.

[104] Stolerman et al., 1973, at pp. 247-259.

and Fridays. One hour prior to each session, the subjects were given varying doses of oral mecamylamine. The presence of mecamylamine changed smoking behavior. Because mecamylamine blocks the nicotinic receptors and reduces the effect of nicotine, smokers increased the numbers of puffs per cigarette, the puff duration, and the number of cigarettes per session. These increases varied with the dose of mecamylamine.[105]

Pomerleau et al also demonstrated that cigarette smokers engage in compensatory behaviors to overcome the blocking effects of mecamylamine. Eight male smokers, who had smoked at least 20 cigarettes per day and for at least five years, were administered either placebo or 12.5 mg of mecamylamine orally prior to their smoking session. In comparison to placebo treatment, the mecamylamine treated subjects' plasma nicotine levels were significantly higher after smoking two high nicotine research cigarettes.[106]

Henningfield et al examined whether cigarette smokers would self-administer intravenous nicotine in place of cigarettes. Six male cigarette smokers participated in three-hour experimental sessions that were conducted one to three days apart. During each session, ten responses on one lever produced an injection of nicotine or saline; responses on the other lever did not produce an injection. Both the subjects and research staff were blind to which product was being delivered. Both nicotine and saline were self-injected by all subjects. However, nicotine self-injection occurred in a regular/orderly pattern, and the rate of self-administration was inversely related to the nicotine dose delivered. When saline was substituted for nicotine, saline self-injection mainly

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[105] Nemeth-Coslett et al., 1986, at pp. 420-425.

[106] Nemeth-Coslett et al., 1986, at pp. 420-425.

occurred early in the session, and the pattern of self-administration was erratic. Low response rates were observed when saline was available. Subjects with a history of illicit drug use identified nicotine as cocaine. Interestingly, subjects continued to self-administer nicotine in spite of reporting that nicotine produced dysphoric effects (i.e., burning sensations at injection site, momentary shortness of breath accompanied by the feeling of fear, coughing and nausea). In addition, it was observed that three of the subjects reduced subsequent cigarette smoking behavior.[107]

C. SUBJECTIVE EFFECTS OF NICOTINE

Several studies have demonstrated that human subjects can distinguish between nicotine doses following intravenous administration. Johnston (1942) was the first to evaluate the subjective effects of intravenous nicotine in 35 volunteers. Johnston reported that the "psychic" effects of nicotine were dose-dependent, the subjective effects of nicotine were specific and distinguishable from those of cocaine and codeine, smokers reported that nicotine was pleasurable, and approximately 0.11 mg of nicotine (i.v.) appeared to produce subjective effects equivalent to that obtained from one "deep" inhalation of cigarette smoke.[108]

Johnston's findings have been confirmed by several investigators.[109] Jones and colleagues

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[107] Henningfield et al., 1983b, at pp. 887-890.

[108] USDHHS, 1988, at pp. 176-177.

[109] USDHHS, 1988, at pp. 176-177.
Jones et al., 1978, at pp. 202-208.
Rosenberg et al., 1980, at pp. 517-522.
Henningfield et al., 1985, at pp. 1-12.

and Rosenberg et al demonstrated that humans could differentiate intravenous nicotine at doses similar to those found in cigarettes. In a study by Henningfield and colleagues, the subjective effects of intravenous and inhaled nicotine were studied in heavy cigarette smokers (30 - 40 cigarettes/day) with histories of drug abuse. Eight male subjects were tested with three doses of intravenous nicotine (0.75, 1.5, and 3.0 mg/10-sec infusion) and placebo each test day; on alternate test days the subjects received three doses of inhaled nicotine in the form of research cigarette smoke (0.4, 1.4, and 2.9 mg estimated yield). The subjective effects of nicotine were qualitatively similar following intravenous or inhalation administration; however, intravenous nicotine presented more striking dose-related effects. Using the Morphine-Benzedrine Group of the standard euphoria scale of the Addiction Research Center Inventory, nicotine was classified as a euphoriant by the subjects. High doses (1.5 and 3.0 mg) of intravenous nicotine were identified respectively as cocaine and amphetamine in six out of eight and one out of eight subjects. The 3.0 mg dose of i.v. nicotine was described as being similar to the initial "rush" or "high" that one feels with cocaine or morphine (except that the effect of dissipated more quickly). In addition, the subjects also mentioned that this dose produced a feeling of fear or anxiety. When given inhaled nicotine, the same seven subjects identified the 2.9 and 1.4 mg dose as being cocaine or amphetamine. Three subjects identified inhaled nicotine as marijuana at all three doses.[110]

It has been show that nicotine-induced subjective effects can be blocked by mecamylamine. Four male subjects were tested with three intravenous doses of nicotine hydrogen tartrate (0.75, 1.5, and 3.0 mg). A dose-dependent increase in self-reported "drug-liking" and

[110] Henningfield et al., 1985, at pp. 1-12.

drug dose strength scores was measured. Intravenous nicotine effects were identified as being cocaine or amphetamine on the Addiction Research Center, Single Dose Questionnaire. Mecamylamine (2.5, 5.0, and 10.0 mg) given at 60 minutes prior to nicotine administration attenuated nicotine-induced subjective effects. All doses tested blocked nicotine's subjective effects.[111]

IV. NONPHARMACOLOGICAL BEHAVIORAL EFFECTS OF TOBACCO USE

Nicotine does not account for all of the behavioral aspects of smoking. Reports by Butschky et al and Pritchard and Robinson report that some measure of gratification is at least transiently derived by the act of smoking, even in the absence of nicotine delivery. Some studies have indicated that smoking behavior may be reinforced by sensory stimulations while others have shown that emotion, personality, and advertising can influence smoking behavior.[112]

A. THE IMPACT OF ORAL SENSORY STIMULATION ON SMOKING BEHAVIOR

Several studies have shown that smoking behavior can be influenced by sensations produced by smoke in the back of the mouth, pharynx, and tracheo-bronchial areas. Rose et al demonstrated a reduction in cigarette craving when the sensory input from tobacco smoke was blocked by the administration of an anesthetic.[113] It has also been demonstrated that ascorbic acid

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[111] Henningfield et al., 1983a, at pp. 259-265.

[112] Butschky et al., 1995, at pp. 91-96.
Pritchard et al., 1994 (abstract).

[113] Rose et al., 1984, at p. 214.

that is inhaled can simulate some of the sensations produced by inhaling cigarette smoke.[114] Likewise, black pepper extract has been shown to produce mouth, throat, and respiratory tract sensations similar to cigarette smoke and to temporarily reduce cravings among cigarette smokers.[115] In some studies, low-nicotine or nicotine-free products that replicate the taste, flavor, or throat and chest sensations of cigarette smoking can, in the very short term, reduce certain nicotine withdrawal symptoms, including craving for cigarettes.[116]

Significantly, however, many of the positively perceived aspects of the harsh taste and flavor of commercial tobacco products are due to "secondary reinforcement." This is a phenomenon by which smokers associate the irritant effects of nicotine in the mouth and throat with desired psychoactive effects that occur immediately thereafter.[117] These irritant effects are then judged favorably, because they are associated with the delivery of the psychoactive properties of nicotine. The conditioning process is similar to that which occurs for other dependence-producing drugs in which effects that are disliked upon initial exposure come to be associated with desired psychoactive effects.[118] Experienced smokers can use the irritant effects

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[114] Levin et al., 1993, at p. 211.

[115] Rose and Behm, 1994, at pp. 225-229.

[116] Rose and Behm, 1987.
Levin et al., 1990b.
Rose and Behm, 1994, at pp. 225-229.

[117] Rose et al., 1993.
Levin and Behm, 1990a.
Rose et al., 1985.

[118] Surgeon General's Report. 1988. Nicotine Addiction. Pages 264-265, 309.

of nicotine to assess how much nicotine they are delivering to themselves while they are smoking.[119]

B. THE IMPACT OF AFFECT (EMOTION) ON SMOKING BEHAVIOR

A number of models have been developed to distinguish psychological factors that influence smoking behavior. It must be noted, however, that most of the models were developed before much was known about the pharmacological actions of nicotine.

In 1966, Tomkins hypothesized that the psychological reasons for smoking could include habitual smoking with no affect, increasing or inducing positive affect, reducing negative affect, and maintaining addictive smoking.[120] Tomkins described these smoking behaviors as follows:

> *In habitual smoking the individual may have smoked to reduce his negative affect or to experience positive affect but he has long since ceased to do so. He may hardly be aware that he has a cigarette in his mouth.*
>
> *[P]ositive affect smoking behavior[:] Here we have distinguished two subtypes: smoking as a stimulant, to experience the positive affect of excitement, and smoking as a relaxant, to experience the positive affect of enjoyment. [It has been suggested that there is] another type of positive affect smoking - that associated with the sensorimotor aspects of smoking, i.e., what one does with one's hands and the positive affect which some smokers report about watching the smoke as it leaves their lips.*
>
> *[N]egative affect smoking behavior[:] . . . the individual smokes primarily to reduce his feelings of distress, or his fear, or his shame, or his disgust, or any combinations of these. He is trying to sedate himself rather than to stimulate or relax himself.*

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[119] Rose et al., 1993.

[120] Horn, 1968, at p. 17.

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> *[T]he addictive type of smoker[:] there is both smoking for positive affect and for the reduction of negative affect organized in such a way that there is psychological addiction. In psychological addiction to smoking behavior, first, the smoker is always aware of the fact that he is not smoking whenever this occurs . . . Second, such awareness of not smoking invariably evokes negative affect . . . Third he thinks that only a cigarette will reduce his suffering . . . Fourth, only smoking will evoke positive affect . . . Fifth, it is expected and it happens that his negative affect will increase in intensity until it is intolerable, so long as he cannot smoke . . .* [121]

In 1969, Horn modified Tomkins' model and theorized that individuals smoked to manage feelings and identified six key psychological factors: stimulation, handling-sensorimotor manipulation, pleasurable relaxation, crutch/tension reduction, craving/psychological addiction, and habit.[122]

Similar to Tomkins' model, stimulation smokers used cigarettes to energize themselves. Sensorimotor manipulation smokers enjoy the act of smoking such as holding or lighting the cigarette or watching the smoke. People who smoke for pleasurable relaxation do so to enhance their pleasurable feelings. Crutch or tension reduction smokers use smoking to calm themselves during distressing moments or situations. Those who smoke for craving or psychological addiction often crave another cigarette before they have finished the one they are currently smoking. Habitual smokers smoke without any specific need for change in affect, and smoke usually without knowing they are doing it.[123]

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[121] Horn, 1968, at p. 18.

[122] USDHEW, 1969.
Christen, 1983, at p. 97.

[123] USDHEW, 1969.
Christen, 1983, at p. 97.

Ikard et al, studied 2,094 smokers using the Horn-Waingrow scale, a self-test based on a smoking model. The study found that relatively few smokers indicated that they used cigarettes as a stimulant or that they derived any kind of sensorimotor gratification from smoking.[124] Almost all smokers indicated that smoking was pleasurable, but males were more likely to score higher as addictive or habitual smokers. Females more frequently indicated that they smoked for negative affect reduction.[125]

Christen et al, showed, using Horn's criteria, that the three most important psychological factors involved in smoking were craving, crutch/tension reduction, and pleasurable relaxation. Two-thirds of the subjects rated handling-sensorimotor manipulation as a low motivation for smoking.[126] This study showed similar results to a previous study which showed that daily cigarette consumption correlated with addictive, automatic, sedative, and stimulation smoking, but not with psychosocial or sensorimotor smoking.[127]

These early studies showed that smokers most frequently smoked for reasons (sedation, stimulation, and addiction) that are now attributed to nicotine's pharmacological effects on the brain and its ability to reinforce the positive rewards.

A recent study examined seven types of smoking motives to determine whether there were

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[124] Ikard et al., 1969, at p. 657.

[125] Ikard et al., 1969, at p. 655.

[126] Christen et al., 1983, at p. 98.

[127] Costa et al., 1980, at p. 539.

pharmacological factors involved.[128] The seven motives were automatic, sedative, addictive, stimulatory, psychosocial, indulgent, and sensorimotor manipulation. The study examined the relationship between smoking motive scores and pharmacological markers such as plasma cotinine levels, smoking rate, length of time smoking, age, and the Fagerstrom's score (that indicates the severity of nicotine dependence).

This study found no correlation between sensorimotor manipulation and smoking rate, and a negative correlation between sensorimotor manipulation and the number of years smoked, the age of the smoker, plasma cotinine levels, and the Fagerstrom's score. Positive correlations were found between addictive smoking and the smoking rate, the number of years smoked, the age of the smoker, and the Fagerstrom's score. Similar positive correlations were found with automatic smoking.[129] The results indicated that the most frequently indicated smoking motives were positively related to the pharmacologic effects of nicotine. The authors conclude that "initially, non-pharmacological rewards exert greater control over smoking; however, pharmacological rewards develop greater control."[130]

C. THE IMPACT OF PERSONALITY ON SMOKING BEHAVIOR

There is evidence that an individual's personality may play a role in determining whether or not they will become regular smokers. Studies comparing the personalities of smokers and

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[128] Tate et al., 1994, at pp. 321-330.

[129] Tate et al., 1994, at p. 327.

[130] Tate et al., 1994, at p. 322.

nonsmokers showed that smokers tend to be more extroverted, anxious, or neurotic than nonsmokers.[131] Cherry and Kiernan provided evidence that these personality differences preceded rather than followed the establishment of tobacco dependence. They reported that there was a strong correlation in the personality type of 16-year-olds and whether they will be smokers before the age of 25. Both males and females characterized as being extroverts and neurotic became regular smokers.[132]

D. THE IMPACT OF ADVERTISING ON SMOKING BEHAVIOR

Tobacco use behavior, particularly among adolescents, can be strongly influenced by advertising. Cigarette advertisements contain powerful visual images that depict smoking as an appealing activity. They include pictures of smokers engaged in parties and social activities; physically challenging activities such as skiing, mountain-climbing, and ranching; and risk-taking activities such as motorcycling and race-car driving. The advertisements convey images of independence, strength, sexual attraction, and social acceptance, self-images that are often highly desired by many adolescents.[133]

Studies have shown that young people whose image of smokers correlated with their own

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[131] Eysenck, et al., 1960, at pp. 1456-1460.
Smith, 1970, at pp. 42-61.
McRae et al., 1978, at pp. 269-273.
Haines et al., 1980, at pp. 1422.

[132] Cherry et al., 1976, pp. 123-131.

[133] Kane, 1991, at pp. 29-30.

self-image or ideal self-image were likely to report that they intended to smoke.[134] Another study found that a positive relationship between self-image and smokers' image distinguished current adolescent smokers from nonsmokers.[135]

In a 1991 unpublished study by Burton et al, a sample of 7th and 8th grade students rated the importance of particular attributes to their self-image and their ideal self-image. The greatest differences in attributes between self-image and ideal self-image occurred with "good-looking", "sexy," "tough," and "athletic." When the same students were asked how much of a particular product they would buy, those who indicated "sexy" as an ideal self-image attribute most frequently indicated that they intended to buy Camel cigarettes. The same association was noted with those that indicated "tough" as an ideal self-image attribute and the intent to buy Marlboro cigarettes.[136]

Youngsters can also be influenced by advertisements for smokeless tobacco. Prominent sports figures, particularly baseball players, have been used in advertisements to promote smokeless tobacco. "Like cigarettes, smokeless tobacco is used by "cool" personalities and athletes. Children idolize and emulate such figures."[137] "Emulating adult behavior or adopting an image of masculinity, athleticism, or toughness is very attractive to young people, especially

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[134] USDHHS, 1994a, at p. 191.

[135] USDHHS, 1994a, at p. 191.

[136] USDHHS, 1994a, at p. 192.

[137] Cocores, 1991, at p. 49.

boys."[138]

V. ESTIMATES OF NICOTINE DEPENDENCE

A. POPULATION STUDIES

Major recent studies show that at least 75% of tobacco users meet the criteria for dependence established in DSM III, DSM III-R, and ICD-10.

Summary data for five studies are included in Table 1. Details of the some of the studies are discussed below.

1. HUGHES et al. (1987)

Hughes et al sought to determine the prevalence of tobacco dependence and withdrawal using questions based on the DSM-III criteria, the Fagerstrom criteria, and their own criteria for tobacco withdrawal. The study participants included 1006 middle aged men (mean age = 51 years) in the Minneapolis-St. Paul metropolitan area. The mean number of cigarettes smoked per day was 28 and the mean number of years smoked was 33. Forty two-percent (n=423) had made at least three attempts to quit. Ninety percent (n=905) of the smokers fulfilled DSM-III criteria for tobacco dependence; 61% (n=614) had made an unsuccessful attempt to stop smoking; 21% (n=211) had experienced tobacco withdrawal symptoms; and 23% (n=231) continued to smoke despite physical illness caused by smoking. The most prevalent DSM-III criterion was unsuccessful attempts to quit.

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[138] USDHHS, 1992, at p. 11.

Among those who had quit at some time, 21% (n=184/875) fulfilled DSM-III criteria for withdrawal. The generalizability is limited since only middle-aged male smokers were included in the survey.[139]

2. WOODY et al. (1993)

The DSM-IV Substance Use field trials were conducted in 1991 and 1992 primarily at five sites (Burlington, Vt; Philadelphia, PA; Denver, CO; St. Louis, MO; and San Diego, CA). Approximately 1100 subjects were interviewed. Participants selected for the study had used alcohol, nicotine, or illegal drugs on at least six occasions. Among subjects, 65% had received substance abuse treatment. There were 645 subjects who had used tobacco six or more times. Eighty seven percent (559/645) of those who used tobacco six or more times met dependence criteria. Among those who were dependent, 78% had mild or moderate dependence. The authors conclude that tobacco use easily causes compulsive use, tolerance, and withdrawal but may be less likely to progress to severe dependence than most other substances.[140]

3. COTTLER (1993)

Using data from DSM-IV Substance Use Disorders Field Trials, Cottler et al compared criteria for diagnoses among substance users. DSM-IV Substance Use Field Trials were based on the existing DSM-III-R criteria and were conducted in 1991 and 1992 at five sites (Burlington,

[139] Hughes et al., 1987, at pp. 205-208.

[140] Woody et al., 1993, at pp. 1573-1579.

Vt; Philadelphia, PA; Denver, CO; St. Louis, MO; and San Diego, CA). With the exception of Burlington, data were obtained through personal interviews. Burlington and St. Louis, representing 37% of the sample overall, included general population subjects. The remaining 63% of the sample included patients from an inpatient treatment program (San Diego), residential polysubstance use programs (Denver and St. Louis) opiate and cocaine treatment programs (Philadelphia) and subjects in a tobacco-related physical disabilities program in Denver. Overall 887 subjects were interviewed; 41% were female and 31% were African-American. Among the 677 nicotine users who reported smoking or using tobacco daily for one month or more, 77% were labeled dependent according to DSM-III criteria and 80% according to the DSM-III-R criteria. The authors postulate that the lower rate of dependence in the DSM-III system may be attributable to DSM-III's requirement of unsuccessful attempts to quit or cut down, withdrawal symptoms, and continuing to smoke despite a physical disorder exacerbated by smoking, whereas DSM-III-R accepts any three out of nine symptoms to classify a smoker as dependent.[141]

4. HALE et al. (1993)

As part of the DSM-IV field trial site studies, Hale et al surveyed 201 residents of Burlington, Vt. and identified 46 current tobacco users. Of the 46 users, 80% met DSM-III-R criteria for drug dependence. Twenty-four percent met criteria for severe dependence, 26% for moderate dependence, and 30% for mild dependence. Eighteen percent of users did not meet the criteria for dependence. The most common criteria were persistent desire to quit/unsuccessful

[141] Cottler, 1993, at pp. 689-696.

attempts to control use (93%) and any withdrawal when stopping or cutting down (74%).[142]

5. BRESLAU et al. (1991, 1992, 1993)

Breslau et al examined the relationship between nicotine dependence and psychiatric disorders in young adults. A group of 1200 persons (21-30 years old) from an HMO in southeast Michigan was randomly selected; 1007 persons who responded were interviewed from their homes. The median age of the group was 26 years. The NIMH Diagnostic Interview Schedule (DIS) was used for the survey. The screening section on nicotine dependence inquired whether or not the respondent had ever smoked daily for a month or more. Negative responders were classified as nonsmokers. A total of 394/1007 respondents (39.1%) reported having smoked daily for a month or more in their lifetime and 292 (29%) smoked daily within the past year. Of the 394 respondents, 51% (202) respondents met criteria for the lifetime rate of nicotine dependence according to DSM-III-R criteria. Lifetime prevalence is defined as the proportion of persons in the sample who have experienced nicotine dependence up to the time of the interview. The rate of dependence in current smokers was 55%.[143] According to Breslau et al, "[t]he finding of this study on young adults, 21 to 30 years of age, might not apply to persons outside this age range . . . . [I]t could be argued that the rate of nicotine dependence in smokers would be higher among older adults than among the young adults of this sample. . ."[144]

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[142] Hale et al., 1993, abstract.

[143] Breslau et al., 1991, at p. 1070.

[144] Id. at p. 1072.

The nicotine-dependent lifetime smokers began smoking at a younger age (mean = 14.2 vs 15.3 yrs), smoked daily at an earlier age (mean = 16.6 vs. 17.8 yrs), smoked more cigarettes per day (mean = 24.8 vs. 14.3 yrs), and were more likely to have smoked during the year preceding the interview (169 vs. 123 yrs).[145]

In a separate analysis of the same data, the authors examined the occurrence of withdrawal symptoms in those who tried unsuccessfully to abstain from smoking. Sixty-one percent (241) of the 394 persons who had ever smoked daily for a month or more reported that they had tried unsuccessfully at least once to quit or cut down on smoking. Of the seven symptoms that define nicotine withdrawal in the DSM-III-R (craving for cigarettes, irritability, nervousness, trouble concentrating, restlessness, decreased heart rate, and increased appetite), five symptoms were reported by more that 50% of smokers who had tried unsuccessfully at least once to quit or cut down. The rates of withdrawal symptoms varied between 82% (craving for cigarettes) and 9.6% (decreased heart rate). Symptoms not included in DSM-III-R such as headache, drowsiness, upset stomach, tremor, and feeling depressed, were less common but not rare. The mean number of symptoms reported by smokers who had ever tried unsuccessfully to quit or cut down was 3.9. Heavy smokers (>20 cigarettes per day) reported more withdrawal symptoms than light smokers.[146]

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[145] Breslau et al., 1993b, at p. 942.

[146] Breslau et al., 1992, at pp. 464-469.

TABLE 1. STUDIES TO EVALUATE PER CENT OF TOBACCO USERS DEPENDENT ON NICOTINE

STUDY	USER *** CRITERIA	AGE	LOCATION	PER CENT DEPENDENT	CRITERIA
Hughes n = 1006	smokers (mean = 28 cig/day) n = 1006	middle-aged men	Minneapolis/St.Paul metro area	90%	DSM-III
Woody n = 1100	used tobacco >= 6 times n = 645	18-44 not specified (M/F)	5 sites-- 35% gen. pop. 65% various substance abuse programs	87%	DSM-III-R* (modified)
Cottler n = 887	used tobacco daily for >=1 month n = 677	18-44 (M/F) not specified (M/F)	5 sites-- 37% gen. pop. 63% various substance abuse programs	77% 80% 92% 86%	DSM-III DSM-III-R old ICD-10 new ICD-10
Hale n = 201	current tobacco users n = 46	not specified (M/F)	Burlington, Vt. general pop	80%	DSM-III-R
Breslau n = 1007	young adults who smoked daily for >=1 month n = 394 (lifetime) n = 292 (current)	21-30 (M/F)	random from Detroit area HMO	51% (lifetime) 55.0% (current)**	DSM-III-R

*** n = Subset of subjects who met specified criteria

** = The fraction of tobacco users addicted to nicotine will depend on the user population as well as the definition of addiction. Addiction rates tend to increase with age.

* = From DSM-IV filed trials using items similar to DSM III-R

B. RATES OF DEPENDENCE BASED ON SPECIFIC CRITERIA

In addition to published population studies on overall criteria to determine the number of dependent smokers, it may be appropriate to assess the number of dependent smokers by examining to what degree "typical" smokers meet individual DSM-III-R criteria. The weight each criterion should be given is the subject of ongoing discussion and investigation. [147]

Some of the evidence to support this reasoning is presented below. The evidence can be expanded to include additional data from published reports and data from the new drug applications for nicotine gum, patches, and spray.

DSM-III-R proposes nine criterion to identify nicotine dependence. DSM-III-R requires that at least three criteria are met to be considered dependent on nicotine.

1. Substance often taken in larger amounts or over a longer period of time than the person intended.

It appears that most smokers meet this criterion for dependence. Beginning smokers don't plan to become dependent; smokers believe they can stop when they want to. In view of the fact that about 3 out of 4 smokers say they would like to stop, it is reasonable to infer that over a period of weeks most smokers would say they smoked more than they intended to smoke.[148]

Data from the National Health Interview Survey indicate that 87.5% of current smokers smoke every day.[149]

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[147] Jaffe, 1990, at pp. 23, 29.

[148] Jaffe, 1990, at p. 23.

[149] Giovino, 1994, at p. 44.

Almost 30 years ago McKennell & Thomas demonstrated how easily people become dependent. Questions regarding the smoking experience of 984 U.K. adults were designed to trace the progression from smoking initiation through to the stage of regular smoking. Of those who smoked regularly one cigarette per day for as long as one month, about 70% go on to smoke regularly for 5 or more years. Of those who smoked more than one cigarette, 82% become regular smokers. Similar results were obtained in a study in Ireland which demonstrated that of those who had ever experimented with cigarettes 75% eventually became regular smokers (at least once a day for ≥ 6 months).[150]

Recent data in the United States and Great Britain suggest that between 33% and 50% of people who try cigarettes become regular smokers.[151]

Breslau et al examined the extent to which nicotine dependence and daily smoking might vary by age at which the first cigarette was smoked. Of the 995 respondents on whom complete data on smoking were available, 74% reported having smoked cigarettes in their lifetimes and were dependent. Of the 74% (736 respondents), about 28% smoked their first cigarette at 13 years old or younger, about 34 % started between 14 and 16 years old, and 15 % started at 17 years old or older. The overall prevalence of nicotine dependence among persons who had ever initiated smoking was 27%. [152]

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[150] Russell, 1990, at p. 295.

[151] Henningfield et al., 1995 (in press), at p. 2.
USDHHS, 1994a, at p. 67.
Giovino, 1994, slide 18.

[152] Breslau et al., 1993a, at pp. 129-137.

In unpublished data from Anthony et al., the tobacco dependence assessment survey was administered to a representative subsample (4414 persons) of the National Comorbidity Survey (NCS) population (8098 persons). Using survey data (1990 and 1992) obtained from an expanded version of the Composite International Diagnostic Interview (CIDI), Anthony et al estimated the prevalence of DSM-III-R dependence on tobacco, alcohol, controlled substances, and inhalants among non-institutionalized Americans age 15 to 54 years old. The authors also studied the transition from drug use to drug dependence. Based on the survey data about Americans 15-54 years old, an estimated 31.9% of persons who had smoked tobacco at least one time had developed tobacco dependence. They did not report the prevalence of dependence among current smokers.[153]

Adolescent smokers in the United States are highly likely to become adult smokers. Among high school seniors from the Monitoring the Future Project (1976-1986) almost half of the daily smokers reported that they would either probably or definitely not be smoking 5 years after graduation. In a follow-up study conducted 5 to 6 years after graduation, 20% of the daily smokers had quit smoking, 13% had cut down, 26% were smoking at the same level, and 40% reported smoking more cigarettes than they had in high school.[154]

With respect to smokeless tobacco, a 1992 Monitoring the Future Project (MTFP) survey gathered data on the frequency of smokeless tobacco use among approximately 2600 high school seniors. Users were classified according to the number of days they used smokeless tobacco over

[153] Anthony et al., 1994 (unpublished), at p. 15.

[154] Elders et al., 1994, at p. 544.

a period of 30 days. Thirty-eight percent reported that they had used smokeless tobacco at least once every day.[155]

Glover et al reviewed studies from the 1980's on smokeless tobacco. They found that 13% of third-grade males and approximately 22% of fifth-grade males in the state of Oklahoma were regular users of smokeless tobacco. These percentages increased to approximately 22%, 33%, and 39% among the seventh-, ninth-, and eleventh-grade boys, respectively.[156] Lichtenstein, Severson, and co-workers reported two studies of prevalence rates of smokeless tobacco use among junior and senior high school students in Oregon. Approximately 9% of seventh-grade boys, 19% of ninth-grade boys, and 23% of tenth grade boys were found to use smokeless tobacco on a daily basis. Eight surveys conducted in Canada, Nebraska, Oregon, Georgia, and Colorado (1981-1983) indicated that about 8 to 10% of the young males (ages 5-19) were regular users of smokeless tobacco.[157]

Two studies have shown that smokeless tobacco users initiating use at an earlier age report greater intake per day compared with those initiating use at a later age. Another study found that a greater percentage of older smokeless tobacco users purchased brands higher in nicotine content compared with younger users.[158]

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[155] USDHHS, 1994, at p. 97

[156] Glover et al., 1988, at p. 287.

[157] Glover et al., 1988, at pp. 287, 288.

[158] Hatsukami et al., 1991, at p. 561.

2. Persistent desire or one or more unsuccessful efforts to cut down or control substance use.

Surveys have found that most smokers report they would like to stop smoking. Many, despite multiple attempts at quitting, have been unable to stop smoking. The following are some data that indicate the difficulty some smokers have in quitting.

a. Adults and Tobacco Use

There are approximately 46 million cigarette smokers in the United States, at least 15 million of whom try to quit smoking each year.[159]

Using data from the 1985 NIDA National Household Survey on Drug Abuse, among all tobacco users who had used cigarettes at least once, more than half (54.2%) had tried to cut down. Of users who were currently smoking a pack or more per day, 84.3% had tried to cut down.[160]

In a study of 394 young adults who had ever smoked daily for a month or more, 241 (61.2%) reported that they had tried unsuccessfully at least once to quit or cut down on smoking.[161]

As part of the DSM-IV field trial site studies, Hale et al surveyed 201 residents of Burlington, Vt. Among current tobacco users (n= 46), the most common dependence criterion

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[159] Giovino, 1994, slide 17.
Henningfield et al. 1995 (in press), at p. 2.

[160] Henningfield et al., 1990, at pp. 280, 281.

[161] Breslau et al., 1992, at p. 465.

was persistent desire to quit/unsuccessful attempts to control use (93%).[162]

In a 1987 study of 1006 middle aged men in the Minneapolis-St.Paul metropolitan area, 42% of users (n=423) had tried to quit at least three times.[163]

Results from a 1987 Gallup Poll indicate that three-fourths of all smokers (77%) say they would like to quit smoking.[164]

Data from the 1991 and 1992 National Household Survey on Drug Abuse indicate that 34 million people tried to cut down on their use of cigarettes during that time period but more than 75% reported that they could not cut down.[165]

Based on data from the 1991-1992 National Household Survey on Drug Abuse, 80% of 25+ year old smokers who smoke between 16 and 25 cigarettes per day stated they were unable to cut down on their use of cigarettes. Among the 12-24 year olds smoking 16-25 cigarettes per day, 90% were unable to cut down.[166]

Novotny et al reported on the prevalence of smokeless tobacco use for adults 21 years and older in the Adult Use of Tobacco Surveys, conducted between 1964-1986. Among current users, 39.1% had attempted to quit, and, of these, 46.7% reported experiencing difficulty in doing

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[162] Hale et al., 1993, at p. 181.

[163] Hughes et al., 1987, at p. 206.

[164] Gallup, 1987.

[165] Giovino, 1994, at p. 47.

[166] Giovino, 1994, slide 22.

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Glover conducted two pilot "quit smokeless tobacco clinics" adapting the American Cancer Society's Fresh-Start smoking cessation program for 41 male subjects aged 18-22. Only one of the participants was able to go for more than four hours during waking hours without the use of smokeless tobacco.[168]

b. Data on Youth and Tobacco Use:

The Teenage Attitudes and Preference Survey (TAPS) examined reasons for smoking in 10-22 year olds. Among smokers who smoked more than 16 cigarettes per day, 80 percent reported they smoked because "it's really hard to quit" and 74% of daily users said "it's hard to quit."[169] Among smokeless tobacco users (ages 10-22) who used tobacco 3 or more times per day, nearly 60% reported they used because "it's really hard to quit" and 74% of daily users said "it's hard to quit."[170]

Results from a 1992 Gallup survey of teenagers aged 12-17 who smoked found that two out of three would like to give up smoking but have not, and half have already made serious attempts to quit but have failed.[171]

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[167] Novotny et al., 1989, at p. 27.

[168] Glover, 1986, at p. 207

[169] Giovino, 1994, at p. 49 and slide 21.

[170] USDHHS, 1994b, at p. 747.

[171] Gallup, 1992, at pp. 7, 16.

In the 1986-1989 TAPS, 12 through 18 year olds who regularly used smokeless tobacco were asked to report the number of times they had tried to quit. Thirty-three percent of males and 72 percent of females had made one attempt to quit, 27% of males and 14% of females had tried quitting 2 or 3 times, and 21% of males and no females had tried to quit four or more times.[172]

c. Data from New Drug Applications:

Estimates based on several data sources indicate that about 1 of 40 smokers quit permanently every year. Among people who have quit for one year, 33% will relapse. Data taken from New Drug Applications (NDA's) for approved smoking cessation products also provide insight into the difficulties smokers have in quitting. Trials supporting the NDA's represent data collected primarily on middle-aged male and female smokers in the U.S. who smoke at least a pack of cigarettes a day and who are highly motivated to quit. Even among these highly motivated smokers, quitting is difficult. Data from the NDA's are described in detail in the section Smoking Cessation Experience.

3. A great deal of time spent in activities necessary to get the substance, take the substance, or recover from its effects.

With the exception of chain smokers, this criterion is not commonly used in diagnosing tobacco dependence. However, it may become more important in the future as

[172] USDHHS, 1994a, at p. 101.

the number of smoking-restricted environments and no-smoking work-sites increase.[173]

4. Frequent intoxication or withdrawal symptoms when expected to fulfil major role obligations at work, school or home.

Role impairment attributable to tobacco dependence is minimal.[174] Withdrawal, however, can interfere with optimal workplace performance.[175]

5. Important social, occupational or recreational activities given up or reduced because of substance use.

"As long as society remains permissive and tolerant of tobacco uses and smoking, those smokers who can tolerate a period of abstinence of a few hours should continue to find little interference with daily life."[176]

6. Continued substance use despite knowledge of having a persistent or recurrent social, psychological or physical problem that is caused or exacerbated by the use of the substance.

Most smokers know that tobacco smoking has been linked to a wide range of medical disorders, yet they keep smoking.[177]

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[173] Jaffe, 1990, at p. 27.

[174] Jaffe, 1990, at p. 27.

[175] Heishman et al., 1994, at pp. 345-395.

[176] Jaffe, 1990, at p. 27.

[177] Jaffe, 1990, at pp. 28-29.

Approximately fifty percent of smokers who survived a heart attack resume smoking.[178] Of patients smoking at the time of diagnosis or surgery for lung cancer, more than half resume smoking.[179] Forty percent of persons who are smokers at the time of laryngectomy resumed smoking after surgery. [180]

From the 1993 Gallup Poll: [181]

- Sixty five percent of smokers believe that smoking has already affected their health.
- Seventy-eight percent of smokers believe that it is very likely or likely that they will have serious health problems from smoking if they continue to smoke.
- Seventy-seven percent of smokers believe that they could avoid or decrease serious health problems from smoking if they quit.
- Ninety percent of smokers felt that smoking was harmful to their health.

Cigarette smoking is responsible for one of every five deaths in the United States. More than 400,000 cigarette smokers die each year because of their tobacco intake.[182]

Novotny et al reported on the prevalence of smokeless tobacco use for adults 21 and older in the Adult Use of Tobacco Surveys, 1964-1986. Among current users, 77.4% believe that smokeless tobacco use is a health hazard.[183]

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[178] Burling et al., 1984.

[179] Davison G. and Duffy M., 1982.

[180] Himbury and West, 1985

[181] Gallup, 1993.

[182] Henningfield, 1995 (in press), at p. 2.

[183] Novotny et al., 1989, at p. 27.

Ary et al found that over 33% of current male adolescent smokeless tobacco users in their survey reported unsuccessful attempts to quit despite the finding that 92% of these users believed that their smokeless tobacco use posed a health risk.[184]

7. Marked tolerance: need for markedly increased amounts of the substance (i.e. at least a 50% increase in intake to achieve intoxication or desired effect or markedly diminishing effect with continues use of the same amount).

Based on data from the 1991-1992 Household Survey on Drug Abuse, 12% of smokers 25 years or older who smoke between 16 and 25 cigarettes per day reported feeling the need for more cigarettes to get the same effect. Twenty percent of 12-24 year olds smoking 16-25 cigarettes per day reported feeling the need for an increased number of cigarettes over time to get the desired effects.[185]

8. Characteristic withdrawal symptoms.

The tobacco withdrawal syndrome is characterized by irritability, anxiety, inability to concentrate, changes in the EEG and cardiovascular function, decreases in psychomotor performance, and weight gain.[186] Studies have shown the following:

- Of the 394 persons who had ever smoked daily for a month or more, 241 (61.2%) reported that they had tried unsuccessfully at least once to quit or cut down on smoking.

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[184] Ary et al., 1989b, at pp. 456, 462.

[185] Giovino, 1994, at p. 52 and slide 24.

[186] Shiffman et al., 1979, at p. 178.

- Of the seven symptoms that define nicotine withdrawal in the DSM-III-R (craving for cigarettes, irritability, nervousness, trouble concentrating, restlessness, decreased heart rate, increased appetite), five symptoms were reported by more than 50% of smokers who had tried unsuccessfully at least once to quit or cut down. The rates of withdrawal symptoms varied between 82% (craving for cigarettes) and 9.6% (decreased heart rate).[187]

Hughes et al examined withdrawal data from a clinical trial of nicotine gum. A total of 315 smokers who met DSM-III criteria for tobacco dependence were recruited. The symptoms of tobacco withdrawal based on rating of withdrawal among the 105 subjects who received placebo gum included hunger in 67% of subjects. Self-reported anger, anxiety, difficulty concentrating, impatience, and restlessness occurred in 52% to 59% of subjects. Self reported craving, drowsiness, insomnia, physical symptoms, and stomach ache occurred in 28% to 40% of subjects. Sixty-eight percent of subjects reported at least four criteria and would have been diagnosed as having nicotine withdrawal according to DSM-III-R.[188]

Based on data from the 1991-1992 National Household Survey on Drug Abuse, 35% of smokers 25 years or older who smoke between 16 and 25 cigarettes per day reported experiencing withdrawal symptoms. Withdrawal symptoms were experienced by 44% of 12-24 year olds smoking 16-25 cigarettes per day.[189]

In the TAPS II study, of smokers aged 10-22 years old who smoked more than 16

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[187] Breslau et al., 1992, at pp. 465-466.

[188] Hughes et al., 1991, at pp. 52-55.

[189] Giovino, 1994, at p. 51 and slide 23.

cigarettes per day, 83% reported cravings, 78% reported irritability, 69% reported restlessness, 55% reported difficulty concentrating, 51% reported hunger, 30% reported feeling sad or blue, and 83% reported one or more withdrawal symptoms with previous attempts to quit. Of those who smoked daily, 80% reported cravings, 74% reported irritability, 62% reported restlessness, 50% reported hunger, 47% reported difficulty concentrating, 25% reported feeling sad or blue, and 82% reported one or more withdrawal symptoms with previous attempts to quit.[190]

A study by Hatsukami et al. to determine the effects of abstinence from smokeless tobacco (n = 20) showed significant increases during abstinence in craving, difficulty concentrating, restlessness, excessive hunger, eating, reaction time, variability of reaction time, and total withdrawal scores.[191]

In a study of regular users, Keenan et al. sought prospectively to determine the effects of 24 hours of smokeless tobacco deprivation on reaction time and attentiveness. The study population consisted of 50 males, 40 regular Copenhagen chewers and 10 non-chewers. A regular user was defined as someone who used smokeless tobacco daily and chews a minimum of 1.5 containers per week. The signs of smokeless tobacco withdrawal included increases in self-rated cravings and withdrawal symptoms checklist score, and a decrease in heart rate. Results indicated behavioral, subjective, and physiological changes are associated with smokeless tobacco deprivation in chronic regular users.[192]

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[190] Giovino, 1994, slides 27-33.

[191] Hatsukami et al., 1992, at pp. 60, 64.

[192] Keenan et al., 1989, at pp. 126-129.

TAPS II (ages 10-22 years) examined indicators of addiction in persons who tried to quit tobacco use. Of smokeless tobacco users who used 3 or more times per day, 70.1% reported cravings, 56.0% reported irritability, 44.9% reported restlessness, 41.8% reported hunger, 36.6% reported difficulty concentrating, 10.4% reported feeling sad or blue, and 78.4% reported one or more withdrawal symptoms with previous attempts to quit.[193] The relationship of these indicators was also looked at with respect to the number of days per month that tobacco was used. Of those who used daily, 85.4% reported cravings, 62.9% reported irritability, 55.2% reported restlessness, 41.1% reported difficulty concentrating, 38.9% reported hunger, 9.0% reported feeling sad or blue, and 93.3% reported one or more withdrawal symptoms with previous attempts to quit.[194]

[193] USDHHS, 1994 draft, table 2.

[194] USDHHS, 1994b, at p. 748.

VI. SMOKING CESSATION EXPERIENCE FROM THE NDA SUBMISSIONS

The following studies provided information that has been presented to the FDA in support of new drug applications (NDA's) for products to treat nicotine addiction.[195] The data are significant and strongly support the scientific findings regarding the abuse and addiction to nicotine and tobacco products. Nicotine, either as a pure substance, or as delivered from tobacco, induces a dependency syndrome that has an associated withdrawal symptom complex. If nicotine is provided to patients who complain of withdrawal symptoms when attempting to stop smoking, they experience a diminution of withdrawal symptoms and are more successful in smoking cessation. This evidence, from double-blind, placebo-controlled, trials, provides substantial evidence that nicotine is effective in relieving tobacco withdrawal symptoms and promoting a lasting abstinence from cigarettes.

Nicotine is the most prevalent alkaloid in tobacco and is the major alkaloid in tobacco products. Nicotine users develop tolerance to both its toxic and rewarding properties, and cessation of nicotine use is associated with a withdrawal symptom complex that can be quantified. Nicotine replacement in 14-24 mg/day doses relieves withdrawal symptoms, (even when a placebo with the taste and flavor of nicotine is provided), and patients have reported becoming cross-dependent on nicotine delivered from pharmaceuticals. These findings leave little room for doubt

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[195] NDA 18612 (Nicorette gum 2 mg)
NDA 20066 (Nicorette gum 4 mg)
NDA 19983 (ProStep Transdermal Patch)
NDA 20150 (Nicotrol Transdermal Delivery System)
NDA 20076 (Habitrol Transdermal Delivery System)
NDA 20165 (Nicoderm Transdermal Delivery System)
NDA 20385 (Nicotine Nasal Spray)

that nicotine from tobacco products is producing a dependency syndrome in regular users.

A. NICOTINE POLACRILEX

1. Nicorette Gum (2 mg)

Nicotine Polacrilex (Nicorette gum, 2 mg), the first nicotine replacement product approved, is the subject of considerable international literature regarding its use. The NDA was approved on the basis of two pivotal studies, one done in the U.S. at Indiana University and one done in the United Kingdom. The U.S. (Christen) study compared active gum against placebo, while the UK study (Russell) compared the active gum against an unbuffered gum that provided the taste and flavor of 1 mg of nicotine but with a pH too low to allow effective absorption of the nicotine.

In the Christen study, the subjects were selected on the basis of their desire to quit smoking, and were considered to be typical smokers with an average of 15-17 years smoking experience. Patients were considered successful if they remained abstinent for four consecutive weeks or more (validated by carbon monoxide (CO) measurements at weekly counseling) at the six week time point. In this motivated group , Nicorette was statistically significantly more effective than the placebo: 36 of 95 Nicorette users (38%) and 11 of 96 placebo users (12%) had successfully quit by six weeks.

In the Russell study, volunteers seeking to stop smoking were randomized to receive either 2 mg buffered (absorbed) Nicorette or 1 mg unbuffered placebos (non-absorbed). In this study, which included weekly counseling, Nicorette was again statistically significantly more

effective than the placebo: 28 of the 58 Nicorette users (48%) met the one-month abstinence rate, while only 14 of 58 (24%) unbuffered gum users did so.

There were a number of other studies in the NDA, but only these two met the standards for adequate and well controlled trials. In one study conducted by Fagerstrom, which classified smokers by the degree of dependence on nicotine (wake to smoke, smoke upon arising, avoid places where one cannot smoke, etc.), highly dependent smokers showed a much greater efficacy difference between Nicorette and placebo than did smokers with lesser degrees of dependence.

2. Nicorette Gum (4 mg)

Nicorette gum (4 mg) is a product line extension of 2 mg Nicorette. Two adequate and well controlled studies were reported in support of Nicorette efficacy, one by Tonnesen, and one by Merrell Dow (multi-center).

The Tonnesen study was done in Denmark and selected patients on the basis of their smoking more than 10 cigarettes a day, being more than 16 years old, and wanting to quit. Dependence was assessed via the Horn-Russell scale, and about 2/3 were classified as low dependence (less than 19 of 27 questions positive) and 1/3 as high dependence (more than 19 of 27 questions positive). This study had physician-led weekly small group counseling, CO confirmation, and allowed one "slip" of one or two cigarettes on one occasion without classifying the patient as a failure.

The high dependency patients were randomized to 4 or 2 mg Nicorette, and the low dependency to 2 mg or placebo. The data for all 173 patients was reported as a two-way table

(High v. Low Nicorette dose and High v. Low nicotine dependence). The results were as follows:

Successful (one month abstinent) Patients

	High Dose	Low Dose	Placebo
High Dependence	22 of 27 (81%)	18 of 33 (54)	
Low Dependence		44 of 60 (73)	22 of 53 (41)

The large Merrell Dow study was a standard double-blind, parallel-group study using placebo, 2 mg, and 4 mg gum. Patients were selected on the basis of a Fagerstrom score greater than 7 (physically dependent), age 25-60 years old, and having a desire to quit smoking. Weekly counseling with CO monitoring was required. Of the 563 enrolled patients, 56/184 were successful with placebo (30%), 62/190 with 2 mg (32%), and 75/189 (39%) with 4 mg. When only the 289 patients who actually chewed the gum (compliance subgroups) were examined, the success rates were 30/92 (32%), 33/104 (31%), & 52/93 (55%) for placebo, 2 mg, and 4 mg, respectively.

Patients in this study rated their craving for a cigarette on a 0-4 point scale, and the mean craving for a cigarette for the diary data was 3.32 for placebo, 3.15 for 2 mg and 2.60 for 4 mg. All patients showed a decline in craving over the first week of cessation.

B. TRANSDERMAL PATCHES

1. ProStep Transdermal patch (11 or 22 mg/day systems)

The ProStep transdermal system is available in 11 and 22 mg/day doses. Four efficacy studies were done in support of the application.

Study 88-01 was an 80 subject, randomized, double-blind trial of six weeks of wearing the 22 mg system against placebo in 25-60 year old, male and female, pack-a-day smokers with a group mean Fagerstrom score of 7 (half classified dependent, half not). In this study, the quit rate for weeks 3-6 was 20% for ProStep and 13% for placebo. The long term (14 week) quit rate off patch was 13% for ProStep and 8% for placebo, a statistically significant result.

Study 88-02 was a larger (263 evaluable subjects) study of six weeks of a 22 mg ProStep or placebo patch in a mixed group of smokers with an average age of 40, Fagerstrom score of 7, 22 years of smoking, and one and one-half pack a day usage. Individual counseling was provided at follow-up visits. Early quit rates were 15% for ProStep and 11% for placebo, a statistically significant result. Long-term success rates off patch (12 months) and off placebo were 6% and 8%, respectively.

Study 90-01 was a 235 patient study of eight weeks of ProStep and placebo in a population with an average age of 43 years old, a Fagerstrom rating of 7, 20-25 years of smoking, who smoked 1-1.5 packs a day. Counseling was individual, and the success rate was 33% for ProStep and 15% for placebo (abstinence weeks 3-6). With abrupt discontinuation of the patch, abstinence rates were 27% and 10% at week 8 1/2, 23% and 10% at week 12, and 20% and 8% at week 26.

Study 90-03 was a 260 patient study of six weeks of ProStep or placebo in a population

nearly identical to study 90-01. The efficacy results for the period when the patients were wearing the patches (week 3-6) was 24% for ProStep and 15% for placebo. After the patients had stopped wearing the patches, the efficacy was 18% v. 13 % (week 8.5), and 3-7% at week 26.

2. Nicotrol Nicotine Transdermal Delivery System
(5, 10, or 15 mg/day delivered over 16 hours with an 8 hour "trough")

Nicotrol was approved on the basis of two large multi-center efficacy studies against placebo. In each case, treatment consisted of daily application of active (15 mg) or placebo patch for 12 weeks, followed by 4-6 weeks of weaning with lower doses. Counseling was limited to a brief intervention by the physician and self-help materials. Successful abstinence was defined as 30 days without smoking with no slips and CO verification of abstinence.

In study 1 (Tonnesen), the population of 289 subjects was about 70% female, aged about 45, had a 20-30 years smoking history, smoked about a pack a day, and had a mean Fagerstrom score of 7 and a Horn-Russell of 16. About 39% had tried to quit on at least one prior occasion. This sponsor provided cross-sectional quit rates at multiple time points, and showed a significant reduction in craving for weeks 1, 2, 3, and 6:

Nicotrol Quit Rate Study 1 (16-18 weeks of treatment)

	Week 6	Week 12	Week 26	Week 52
Nicotrol	35%	30%	19%	12%

Placebo	7%	5%	3%	3%

In study 7 (Sachs), the design was similar, but all patients had 12 weeks of the 15 mg system, 3 weeks of the 10 mg system, and 3 weeks of the 5 mg system in forced weaning approach. The population of 215 subjects was about 60% female, 40-50 years old, had smoked for 25-30 years, smoked 25-30 cigarettes a day, and had a Fagerstrom score of 7 with 4-6 previous tries at quitting. This study examined craving for a cigarette in both treatment groups and found nicotine replacement significantly reduced craving.

Nicotrol Quit Rate Study 7 (18 weeks of treatment)

	Week 6	Week 12	Week 18	Week 26	Week 52
Nicotrol	61%	45%	41%	35%	25%
Placebo	35%	26%	16%	12%	9%

3. Habitrol, Nicotine Transdermal Delivery System
(7, 14, or 23 mg/day delivered over 24 hours)

Habitrol is another multi-dose transdermal system that was studied in two conventional studies and in one "medical model" study where the counseling was provided by a medical practitioner in a brief intervention.

Study 06 was a titration, parallel group study of Habitrol v. placebo. Subjects using more than 25 cigarettes a day were started on the high dose 23 mg system, those individuals using

fewer cigarettes were placed on the 14 mg system. All subjects could increase their patch size during a 3-week titration period, used a constant patch size during a 4-week maintenance period, then had a 3-week weaning period. The study population was similar to those studied elsewhere: 40-50 years old, 55% female, 25-30 years of smoking, had Fagerstrom scores of 7-8, and had 5-6 previous quit attempts.

The quit rates were significantly higher for Habitrol than for placebo in this study (CO validated continuous abstinence), as shown below, with a reduced craving for cigarettes in the treatment group over placebo at all time points:

Habitrol Quit Rate Study 06 (10 weeks of treatment)

	Week 3	Week 4	Week 6	Week 8	Week 10
Habitrol	89%	50%	40%	35%	34%
Placebo	84%	33%	26%	18%	18%

Study 07 was a 243 patient, four-center, randomized, placebo-controlled trial similar to 06. The population was 60% female, about 40 years old, had Fagerstrom scores of 7-8, 20-25 years of smoking, smoked 2- 2 1/2 packs of cigarettes a day, and reported multiple prior quit attempts.

The quit rates for Habitrol and placebo in this study (CO validated continuous abstinence) were as shown. In this study, craving was significantly reduced only during the maintenance phase:

Habitrol Quit Rate Study 07 (10 weeks of treatment)

	Week 3	Week 4	Week 6	Week 8	Week 10
Habitrol	79%	50%	34%	28%	24%
Placebo	78%	31%	23%	21%	20%

Study 08 was a 276 patient, five-center, randomized, double-blind, out-patient, parallel-group trial similar to 06. The population was 67% female, about 40 years old, Fagerstrom score of 7-8, 20-25 years of smoking, 2- 2 1/2 packs of cigarettes a day, and reported 3 or more prior quit attempts. This study used the brief medical intervention model along with self-help materials.

The quit rates for Habitrol were significantly greater than for placebo at 4 weeks in this study (CO validated continuous abstinence), as shown. Craving was reduced at all patch-wearing time points.

Habitrol Quit Rate Study 08 (10 weeks of treatment)

	Week 3	Week 4	Week 6	Week 8	Week 10
Habitrol	87%	26%	18%	16%	13%
Placebo	80%	16%	13%	13%	11%

4. Nicoderm, Nicotine Transdermal Delivery System
(7, 14, or 21 mg/day delivered over 24 hours)

Nicoderm was studied in two conventional pivotal studies and in one "high-risk" study in

patients with known coronary artery disease. Both of the pivotal studies used the conventional parallel-group, randomized, double-blind design; patients were randomized to six weeks of treatment with active drug or placebo. All patients were then entered in a follow-up study phase which examined weaning from the transdermal system and relapse.

Study 010 enrolled patients 21-65 years of age who were smoking one or more packs a day and who desired to quit. For the 487 subjects (121 subjects in each of the 21 mg/14 mg/7 mg groups and 124 in the placebo group) in the study, 59% were women, the average age was 40-45 years of age, the average Fagerstrom score was 6-8, subjects had smoked for 20-25 years, smoked 1.5 packs per day, and had an average of four prior quit attempts. Group behavioral support (Quit & Win program) was provided weekly, and outcome was indicated by diary and CO verification. 403 patients completed week 6 and were eligible for continuation. 256 patients entered the continuation study and 156 patients completed week 24 of the study.

Outcome for the six weeks of parallel group treatment was dose related and carried on into the follow-on period:

Nicoderm Quit Rate Study 010 (6 weeks of treatment)

Treatment	Week 2	Week 6	Week 12	Week 24
Nicoderm 21 mg	96%	71%	50%	33%
Nicoderm 14 mg	93%	54%	31%	22%
Nicoderm 7 mg	86%	48%	31%	23%
Placebo	88%	33%	23%	18%

Craving for a cigarette was reduced over placebo.

Study 011 was similar in design, but the 7 mg dose was used only for weaning. In this study, the population was 60% female, had a mean age of 43 years, a mean Fagerstrom of 7, 25 year history of smoking one and one-half packs per day, and 4-5 prior quit attempts. There were 390 evaluable patients (128/133/129) randomized to 21 mg, 14 mg and 0 mg, respectively.

Outcome for the six weeks of parallel group treatment demonstrated significant efficacy, which carried on into the follow-on period:

Nicoderm Quit Rate Study 011 (6 weeks of treatment)

Treatment	Week 2	Week 6	Week 12	Week 24
Nicoderm 21 mg	89%	51%	29%	20%
Nicoderm 14 mg	89%	44%	23%	14%
Placebo	84%	21%	9%	7%

Craving for a cigarette was reduced over placebo.

Study 005 was a special study in a mostly male (80%) patient population with known coronary artery disease. The average age was 50-60 years, Fagerstrom scores of 8-9, 38 years smoking history, an average of one and one-half packs per day, and 5-6 prior quit attempts. This population was selected as a population classified as highly motivated to quit (known coronary artery disease, smoking greater than a pack a day, Fagerstrom score greater than 7) and was

selected as a high-risk, highly dependent population. Patients were selected, started on a 14 mg system, and titrated to an individualized dose (7 or 21 mg) after one week. Outcome was by self-report validated by CO. There were 77 evaluable patients on Nicoderm and 78 on placebo in this study.

The outcome (cross-sectional quit rate) was as follows:

Nicoderm Quit Rate Study 005 (5 weeks of treatment)

Treatment	Week 1	Week 5	Week 8
Nicoderm	100%	36%	26%
Placebo	99%	22%	13%

Withdrawal scores were collected and trended higher for placebo patients. These results were not significant.

A major outcome of the study was the relative frequency of angina or other adverse cardiac events. No significant difference was seen between the groups in the frequency of cardiac events, and the overall count of such events fell to about half of the baseline frequency over the five weeks of the study.

C. NICOTINE NASAL SPRAY (NNS) 0.5 MG/APPLICATION SELF-TITRATED SPRAY

Nicotine Nasal Spray is a pending new drug application for a self-administered product consisting of a solution of nicotine in water that is sprayed intranasally and absorbed in the nasal mucosa. Of all the currently marketed products, it most closely approximates a cigarette in terms of speed and intensity of nicotine absorption.

Three pivotal studies have been conducted by Schneider, Russell, and Hjalmarson, respectively. All three studies included a nearly equal number of men and women, mean age about 40, who were smoking 1 to 1 1/2 packs a day, and who were seeking to quit smoking. In all cases, the patients self-administered the product ad lib. (as cigarettes), titrated themselves to an

individualized dose, and used the product for up to six to twelve months. Counseling was provided in all cases, including family-centered interventions in some studies.

Schneider studied 128 NNS patients and 127 placebo patients. Russell studied 116 NNS and 111 placebo patients, and Hjalmarson studied 125 NNS and 123 placebo patients. The results of the studies are shown below using the 4 week CO validated abstinence criteria. In these studies, the patients were not cut off from the nicotine replacement products at 6-12 weeks as in earlier trials:

Success As Defined By 4 Week Abstinence From Cigarettes

Treatment	Russell	Schneider	Hjalmarson
NNS Spray	49%	58%	53%
Placebo	21%	32%	27%

The cross-sectional (continuous) abstinence rates were as follows:

	Week 8	Week 13	Week 26	Week 52
NNS Russell	49%	41%	32%	26%
NNS Hjalmarson	53%	41%	35%	27%
NNS Schneider	58%	46%	32%	24%
PLC Russell	21%	17%	12%	10%
PLC Hjalmarson	27%	20%	15%	15%
PLC Schneider	32%	20%	14%	9%

Of concern with this product was evidence of both abuse (continued use against medical advice), tolerance development (use at doses above those initially prescribed), and dependence (patients engaging in compulsive use of the spray). The application was discussed at the August 1, 1994, meeting of the Drug Abuse Advisory Committee. The committee members decided that the product had some addictive properties, but presented a lower risk of abuse than cigarettes.

D. PATIENT SELECTION AND GENERALIZABILITY

The smoking cessation studies performed by pharmaceutical firms were conducted in such a way as to have very similar structures and to allow fairly direct comparisons across the products. Studies may be compared as to patients selected for study, treatment outcomes, and an overall discussion of the outcome of attempts to quit smoking.

All of the studies selected adult patients who wished to quit smoking, who were usually attracted by advertisements or referrals from clinical, workplace, or community settings. The specific selection criteria usually included a minimum and maximum age, a minimum level of cigarette use, sometimes a prior failed quit attempt, and some measure of nicotine dependence.

Patient Characteristics

Study Name	Size	% Female	% Male	Mean Age	SD	Fager-strom Score	SD	Years of Smoking mean	SD	Cigarettes Per Day mean	SD	Prior Quit Attempts
Christen	191	NR	NR	NR	NR	6	NR	NR	NR	NR	NR	NR
Russell	116	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Tonnesen	173	NR	NR	45	10	NR	NR	26	14	25	7	3
Merrell-Dow	289	50	50	40	8	8.5	1	22	8	25	10	4
88-01	80	55	45	37	8	7.4	2	19	8	25	6	NR
88-02	263	58	42	40	9	7.0	2	22	9	31	12	NR
90-01	235	52	48	43	11	7	2	24	10	28	9	4.5
90-03	260	63	37	41	9	6.9	2	24	9	28	11	NR
Tonnesen	289	72	28	45	14	7.1	2	26	12	21	7	NR
Sachs	215	59	41	47	10	6.7	2	29	10	27	9	5
Study 06	273	55	45	46	11	7.8	1	28	10	28	10	5
Study 07	243	60	40	42	10	7.5	1	23	10	27	11	NR
Study 08	276	67	33	42	10	7.6	1	23	10	28	9	3
Study 010	487	60	40	42	10	7.1	2	23	9	31	10	4
Study 011	390	61	39	43	10	7.1	2	25	10	30	10	4
Study 005	155	21	79	56	7	8	1	38	9	32	10	6
Hjalmarson	248	56	34	45	11	7.2	2	27	10	21	6	NR
Schneider	255	64	36	40	10	6.2	2	22	8	29	10	NR
Russell	227	64	36	40	10	NR	NR	22	10	26	10	NR
Total	4712	57	42	43	10	7	2	25	10	27	9	4

The composition of the population studied was fairly constant across all studies, and can be compared both to the general US Population, the US smoking population and to the population of individuals who quit smoking without medical intervention (data courtesy of Hughes, Giovino, Klevins and Fiore, in press).

Smoking Cessation Populations

	US Pop Age (18-65)	Current Smokers	Self-Quitters	Treatment Seekers	NDA DATA
Age	42	42	37	39	43
% Female	51	47	65	53	57
Cigarettes/Day	NR	21	19	28	27

The data suggest that the population studied in the trials is representative of the general experience of the population of current smokers.

Outcome of Treatment

The following table, drawn from the studies submitted in NDA's, presents the abstinence rates for each study at one month (3-5 weeks), two months (5-10 weeks), six months (20-28 weeks) and 12 months (50-56 weeks):

Nicotine Replacement Groups
Percentage Successful by Trial Criteria

NDA Source	Study Name	Size	Months One	Two	Four	Six	Twelve
Nicorette	Christen	191		38			
Nicorette	Russell	116		48			
Nicorette	Tonnesen	173		70			
Nicorette	Merrell-Dow	289		55			
Prostep	88-01	80		20	13		
Prostep	88-02	263		15			6
Prostep	90-01	235		33	23	20	
Prostep	90-03	260		24	18	3	
Nicotrol	Tonnesen	289	35	35	30	19	12
Nicotrol	Sachs	215	61	45	41	35	25
Habitrol	Study 06	273	50	35	34		
Habitrol	Study 07	243	50	28	24		
Habitrol	Study 08	276	26	16	13		
Nicoderm	Study 010	487	57		37	26	
Nicoderm	Study 011	390	47		26	17	
Nicoderm	Study 005	155	36	26			
N N Spray	Hjalmarson	248		53	41	35	27
N N Spray	Schneider	255		58	46	32	24
N N Spray	Russell	227		49	41	35	26
	Mean		49	38	30	25	20
	SEM*		4.7	4.0	3.2	3.9	3.9

Double-Blind Placebo Groups
Percentage Successful by Trial Criteria

NDA Source	Study Name	Size	Months One	Two	Four	Six	Twelve
Nicorette	Christen	191		12			
Nicorette	Russell	116		24			
Nicorette	Tonnesen	173		41			
Nicorette	Merrell-Dow	289		32			
Prostep	88-01	80		13	8		
Prostep	88-02	263		11			8
Prostep	90-01	235		15	10	8	
Prostep	90-03	260		15	13	7	
Nicotrol	Tonnesen	289	7	7	5	3	3
Nicotrol	Sachs	215	35	26	16	12	9
Habitrol	Study 06	273	33	18	18		
Habitrol	Study 07	243	31	21	20		
Habitrol	Study 08	276	16	13	13		
Nicoderm	Study 010	487	33		23	18	
Nicoderm	Study 011	390	21		9	7	
Nicoderm	Study 005	155	22	13			
N N Spray	Hjalmarson	248		27	20	15	15
N N Spray	Schneider	255		32	20	14	9
N N Spray	Russell	227		21	17	12	10
	Mean		25	20	15	11	9
	SEM*		3.5	2.3	1.6	1.7	1.7

* = standard error of the mean

Plotting the data :

There appears to be a pattern in the data, such that the quit rate in the nicotine group is about twice the quit rate in the placebo group. Plotting the quit rates for each time point in each study in this fashion (placebo on x-axis, nicotine on y-axis):

Discussion

The consistency of the NDA data shows the difficulty of smoking cessation, even for committed adults who decide to seek medical help in quitting. The data also reveal the widespread importance of nicotine's central nervous system effects in smoking by illustrating the efficacy of nicotine delivery systems (including "tasteless" transdermal systems) in helping people reduce or quit smoking--at least while using smoking cessation products. For this population of male and female, pack-a-day, typical smokers aged 20-50, nicotine replacement products reliably improved their ability both to stop smoking and to remain abstinent from cigarettes. Smokers using products that delivered about 14-24 mg/day of nicotine had an initial quit rate of about 50%, twice that of placebo patients (25%). This two-fold difference held throughout a full year of follow-up and was associated with reductions in craving, withdrawal symptoms, and the desire to smoke in those studies that measured subjective symptoms.

Even with the best of medical treatment and good nicotine replacement therapy, only half of the patients studied are able to stop smoking for even one week, and the long-term failure rate of over 80%, even in motivated patients, suggests that this is a tenacious addiction. The treatment experience with cigarette addiction demonstrates that those who try to stop smoking, even with the best available help, are much more likely to fail than to succeed on any given attempt. Based on the data available to the agency, the natural outcome of cigarette use is addiction within a short time period, initiation of cessation attempts within a few years, and a cycle of multiple quit attempts that extends over many years. Most patients who make a serious

attempt to quit will, even with good therapy, have to make 4-6 serious attempts to become abstinent (5-15% will remain successfully abstinent after each attempt).

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