NICOTINE ADDICTION AND SMOKING CESSATION

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INTRODUCTION

There is no doubt that smoking has been and remains a major health problem in the United States. This statement seems obvious today, but the concern is only recent. During the first half of the twentieth century, smoking rates increased dramatically. The ability to mass produce cigarettes, advertising, and the link of tobacco use to the entertainment industry and athletic performance all contributed to this rise in the use of tobacco. Reports of the significant medical effects of smoking tobacco appeared in the medical literature in the 1950's; probably because of social pressures and the general public's acceptance of smoking, the medical profession as a whole did not denounce the use of tobacco until recently. However, the 1964 Surgeon General's Report on Smoking and Health[1] officially pronounced smoking as a causative agent in the development of lung cancer and a contributing factor for the development of other diseases. Since that time there has been escalating interest by medical and lay groups regarding this issue. This has resulted in an increase in criticism of the tobacco industry's practices and profits by the medical profession and groups of the general population. The recent allegation of a cigarette manufacturer increasing the nicotine content of certain products is such an example. This review will summarize the magnitude of the problem of cigarette and tobacco use, review the pathophysiology of nicotine addiction, and summarize current concepts in treatment strategies.

1. SMOKING IS A MAJOR HEALTH PROBLEM IN THE UNITED STATES

Tobacco use is the leading cause of preventable death in this country, directly accounting for approximately 400,000 deaths per year[2]. Many diseases have been linked to tobacco use, and these will not be discussed in detail in this review. Some of diseases associated with tobacco use can be found in Table I. Cigarette smoke generates thousands of different compounds, but the precise toxic compounds causing many of the diseases are not known. Carbon monoxide, nicotine, and carcinogenic polynuclear aromatic hydrocarbons are some of the identified compounds that may cause smoking related disease. The exact pathophysiologic mechanisms that account for the adverse health effects of cigarette smoking are extremely complex because of the

large number of compounds in cigarette smoke. These substances, combined with other environmental and genetic factors, make a precise identification of the disease related substances difficult.

TABLE I
DISEASE LINKED TO TOBACCO USE

CANCER	RESPIRATORY	VASCULAR DISEASE	OTHER
Lung	COPD	CAD	HTN
Urinary Bladder	Spontaneous Pneumothorax	Cerebrovascular disease	Osteoporosis
Larynx	Chronic Laryngitis	Peripheral Vascular Disease	Alzheimer's
Mouth & Gum	Bronchitis	Aortic Aneurysm	PUD
Cervix	Otitis Media	Arterial Thrombosis	Periodontal Disease
Esophagus	Asthma		
Pancreas	Bacterial & Tuberculous Pneumonia		
Kidney	Mesothelioma		
Stomach	Oral Leukoplakia		
Pharynx			
Liver			
Breast			
Brain			

The association of lung cancer and smoking has been well documented and was the first health problem directly related to smoking. In 1964, Surgeon General's Report[1] concluded that cigarette smoking had a direct link to lung cancer in men. The risk for individual smokers, however, varies and depends upon the amount and techniques of smoking, with deeper inhalations and earlier age of onset of smoking increasing the risk of developing lung cancer. The incidence of lung cancer may be decreased by smoking low tar cigarettes since the carcinogenic compounds are found mostly in smoke. The incidence of lung cancer in women has been increasing over the last several years due to an increased prevalence of smoking among this group.

The pulmonary effects of smoking are well known. Cigarette smoking causes structural and functional changes in the airways that predisposes patients to the development of obstructive lung disease. In addition, other lung diseases have been reported to be associated with smoking. These include pneumothorax, chronic laryngitis, acute bronchitis, asthma, various types of pneumonia, and oral leukoplakia. Smoking combined with other environmental exposure can produce serious health hazards with the smoke and environment agent combining for a synergistic increase in disease, *e.g.*, COPD in smoking coal miners and lung cancer in smoking asbestos workers.

Malignancies other than lung cancer have also been linked to the use of cigarettes, although the relationship is not as strong. Smoking has been identified as a contributing causative factor for the various cancers listed in Table I.

The cardiovascular effects of smoking are well known. Cigarette smokers have approximately a 70% greater death rate due to coronary disease than non-smokers and approximately 40% of deaths from coronary artery disease are attributable to cigarette use. Carbon monoxide, hypoxia, increased free fatty acids, increased levels of LDL and VLDL cholesterol, and hypercoagulation probably contribute to this increased risk.

Women are not spared the ravages of cigarette smoking. It is well known that smoking increases the risk for myocardial infarction, stroke and thromboembolic disease in women. There is also an increased risk for placenta previa, abruptio placentae, premature birth, spontaneous abortions, fetal and neonatal death, premature labor, preeclampsia, SIDS, and growth retardation. The more a woman smokes, the more likely the above complications will occur. Certainly, women who smoke should be counseled against tobacco use at any time, but this is especially true during pregnancy and if the woman takes estrogen.

The medical significance of smoking is not evenly spread over the population. For example, 90% of alcoholics in the United States smoke, compared with about 30% of the population in general. These high smoking rates and the synergistic pathologic effects of smoke and alcohol make the alcoholic patient much more likely to develop tobacco related diseases than non-alcoholic patients. This is especially true of cancer of the mouth, pharynx, larynx, esophagus and lung. It has been estimated that a heavy smoker and drinker has 38 times the likelihood of developing oropharyngeal cancer than a non-smoking, light drinker (Table II[3]).

TABLE II

RISK OF ORAL CANCER

BEHAVIOR	RISK RATIO
Heavy Alcohol	5.8
Heavy Smokers	7.4
Heavy Smoking and Drinking	37.7

The reasons that persons who drink alcohol are more likely to use tobacco are not fully understood. Underlying addictive personalities, a tendency for increased socialization and

exposure to other smoking adults, the presence of oral tendencies in alcohol drinkers, and the biologic interaction of nicotine and alcohol all contribute to the high rate of tobacco use in drinkers. Also, the smoking rates in other drug users is very high, especially among cocaine and heroine users where rates of 80-90% are seen[4].

The magnitude of the 400,000 deaths per year that can be attributed directly to the use of tobacco becomes more apparent if one compares the number of deaths due to chronic tobacco use to that of other drugs. Such a comparison is illustrated in Table III.

Table III

DRUG/SUBSTANCE	DEATHS PER YEAR (in thousands)
Tobacco	350-400
Alcohol	125-150
Alcohol plus other drugs	4
Heroin	4
Cocaine	2
Marijuana	0.75

Smokers, in general, have a 30-80% higher death rate when compared to non-smokers. 25% of fire-related deaths, 30-40% of coronary artery disease deaths, 80-85% of lung cancer deaths and 80-90% of deaths from chronic obstructive pulmonary disease (COPD) are directly related to smoking. Estimates indicate that smokers who die prematurely lose an average of 20 years of life because of smoking and 25% of long-time smokers will die directly because of their smoking habits.

The chronic health effects of environmental smoke have become a topic of major interest during the last decade. Estimates from the Environmental Protection Agency indicate that "passive smoking" may account for as many as 50,000 deaths annually in the United States, including 3,000 from lung cancer, 35,000 from coronary artery disease, and 10,000 from other kinds of cancer. Although the exact number of deaths will continue to be debated, there is little doubt that environmental smoke contributes to a significant number of deaths yearly in this country.

The magnitude of tobacco consumption and the costs of smoking-related problems in the United States are staggering. Each year over 2000 cigarettes are consumed for each person in

the United States. It has been estimated that the direct health care costs of smoking-related diseases account for more than $16 billion per year. The indirect costs of smoking, *i.e.* missed days of work, lost productivity, etc., cost the American economy more than $37 billion per year[5].

Tragically, the children of this country are a significant part of the group that uses tobacco products in this country. It has been estimated that 3 million American children under the age of 18 years consume approximately 947 million packs of cigarettes and 26 million containers of smokeless tobacco per year. This use accounts for approximately $1.26 billion in total sales and $221 million in profits for the tobacco industry. Before we become too indignant, though, we must realize that the population in general benefits from the sale of tobacco to minors in that approximately $152 million in federal taxes and $173 million in state taxes are collected each year from the sale of cigarettes to children under the age of 18[6]. The average age of first use of cigarettes among child smokers is about 13 years. It has been well-documented that minors can easily purchase cigarettes in almost every part of the country, although the sale of tobacco to minors is specifically prohibited in most states.

Smoking among older Americans has been identified as an important target for smoking cessation research. Because of the aging process, this group tends to manifest many of the associated diseases affected by or caused by smoking. Many of the benefits of smoking cessation, such as a reduction in cancer incidence and the manifestations of coronary artery disease occur within the first 5 or 10 years of stopping smoking[7]. Consequently, short term benefits from smoking cessation will be magnified in this group of patients. However, the smoking habits of older Americans have not been studied in detail. A study by Orleans *et al*[8], from the Fox Chase Cancer Center has revealed some important considerations in this older population. In this study, 289 smokers ages 50-74 took part in a survey to examine smoking habits and patterns of this group. Several patterns could be seen in the data and are summarized as follows:

1) More than half of married smokers' spouses also smoked.
2) Half reported smoking related symptoms.
3) Only 42% reported that some medical advice to quit smoking had been received in past year (75% reported at least one health care visit in past year).
4) Mean age of starting smoking was 19.6 years.
5) Mean number of years smoked was 44.6
6) Smokers tended to want to stop smoking but felt unable to do so.
7) More than 75% had seriously attempted to quit smoking, 40% within the past year.
8) Barriers to quitting smoking included fear of failure, craving of cigarettes, nervousness, irritability and trouble concentrating.

The news, however, is not all grim. Since the early 1970's, there has been a decrease in the prevalence of smoking in the United States from 40% of adults in 1965 to approximately

26% of adults in 1990[9]. This decrease is partially due to social pressures and the increasing lack of acceptability of public smoking in this country as well as increased education of the public regarding the hazards of smoking. However, the decrease has not been equally shared among all groups[10]. As illustrated in Table IV[2] the decrease in smoking has been less among women and African-Americans. In addition, the decline in smoking prevalence among blue collar workers and the less educated has been less than the general population.

TABLE IV

POPULATION	1965 % WHO SMOKE	1986 % WHO SMOKE
Adult Male	51	29.5
Adult Females	33	23.8
Caucasian Males	51	32
African-American Males	60	41
Caucasian Females	35	28
African-American Females	33	32

The news regarding smoking by children is grim. While adult smoking has decreased, adolescent smoking rates remain steady with approximately 3,000 new smokers per day. This statistic is particularly alarming since it accounts for 85-90% of new smokers in the United States. Studies have shown that role models, especially parents, peers, sports figures and entertainment figures have a significant influence on whether or not a child begins smoking[11].

The Youth Risk Behavior Survey[12] has shed additional light on the problem of child smokers. In this study, the smoking habits and attitudes were examined from 11,248 responders from the U.S. in grades 9-12. This study revealed that 72% of students have experimented with smoking and 32% smoke currently. As can be seen, students who are older and white and those with low academic performance (Table V) are more likely to smoke as well as those who do not participate in sports (Table VI). Students who began smoking before age 12 were more likely to continue and smoke more than others (Table VII).

TABLE V
SMOKING PATTERNS BY SELECTED CHARACTERISTICS*
(Prevalence Smoking Patterns, %[±95%CI])†

CHARACTERISTIC	REGULAR LIGHT	REGULAR HEAVY
Age‡		
13	7 (3)	2 (2)
14	10 (3)	6 (3)
15	10 (1)	7 (2)
16	11 (2)	9 (2)
17	11 (2)	14 (4)
≥18	10 (2)	16 (4)
Race/ethnicity§		
White	12 (2)	13 (3)
Latino	11 (1)	5 (1)
African American	4 (1)	1 (1)
Sex‖		
Female	12 (2)	9 (2)
Male	9 (1)	11 (4)
Academic performance¶		
Excellent	8 (1)	6 (2)
Average	12 (2)	12 (3)
Below Average	19 (5)	27 (9)
No. of Sports#		
None	11 (2)	14 (3)
1	10 (2)	7 (3)
2	8 (3)	6 (3)
≥3	7 (3)	4 (2)
Overall	10 (1)	10 (3)

* Data obtained from 1990 Youth Risk Behavior Survey
† Percentages across rows may exceed 100 because of rounding. CI indicates confidence interval
‡ We excluded 27 students who had unknown information about age or amount smokes or were younger than 12 years of age (11,221 remained)
§ We excluded 737 students who had unknown information about race/ethnicity or amount smokes or who described themselves as Asian, Pacific Islander, Native American, Alaska Native, or other (10,511 remained)
‖ We excluded 21 students who had unknown information about sex or amount smoked (11,227 remained)
¶ We excluded 142 students who had unknown information about amount smokes or academic performance (11,106 remained)
# We excluded 77 students who had unknown information about amount smokes or participation in interscholastic sports (11,171 remained)

TABLE VI

PREVALENCE OF REGULAR AND HEAVY SMOKING BY PARTICIPATION IN INTERSCHOLASTIC SPORTS*

No. of Sports	Regular Smoking Among Students† Prevalence‡	Heavy Smoking Among Current Smokers Prevalence‡
None	25	40
1	18	26
2	14	25
≥3	11	21

* Data obtained from 1990 Youth Risk Behavior Survey.
† We excluded 187 students who had missing information about age, race/ethnicity, sex, academic performance or sports participation (11,061 remained)
‡ Trend in decreasing prevalence is statistically significant ($P < .0001$; Cochran-Mantel-Haenszel test for trend).

TABLE VII

PREVALENCE OF REGULAR AND HEAVY SMOKING AMONG HIGH SCHOOL STUDENTS BY AGE AT SMOKING INITIATION*

Age, y	Regular Smoking Among Ever Smokers† Prevalence	Heavy Smoking Among Current Smokers Prevalence
> 12	34	29
≥12	39	42

* Data obtained from 1990 Youth Risk Behavior Survey
† We excluded 75 ever smokers who had missing information about age, race/ethnicity, sex or academic performance (5,963 remained)

The use of snuff and other smokeless tobacco has continued to be a risk for health problems in the United States. These forms of tobacco have been used more in the past than today, but young users of tobacco many times find them more socially acceptable. The long-term use of these products is associated with an increased risk of oral cancer and nicotine addiction. In 1991 it was estimated that over 5 million U.S. adults were current users of smokeless tobacco with the highest prevalence being among men aged 18-24 years. The prevalence of its use was also highest among American Indians/Alaska natives and whites and among residents in the rural areas of the Southern United States[13].

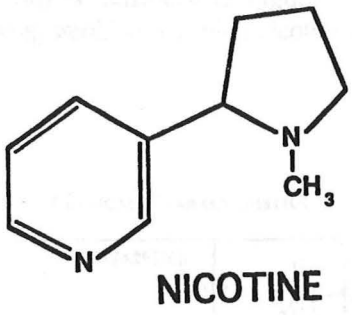
These data are important in that the tobacco industry has targeted young males as a focus for advertising and have linked the use of these products to athletic ability and virility. The chronic effects of smokeless tobacco use needs continued study because there is some evidence that nicotine by this route may play a contributory role in the development of coronary artery disease, peripheral vascular disease, peptic ulcer disease and hypertension. The advertising of tobacco related-products has been a source of considerable controversy over the last few years. The arguments are probably not pertinent to this discussion, but center mostly around the motive of the tobacco industry with such advertising. These marketing strategies have targeted certain groups, *e.g.* young men with their use of smokeless tobacco and have probably been quite effective in persuading some to take up tobacco use. The ethics of such advertising will not be discussed here, but it is complicated involving business and marketing strategies and personal freedom.

Since the 1988 Surgeon General's Report, most authorities have accepted the fact that chronic cigarette use is due, in large part, to nicotine addiction. Estimates are that 70-90% of smokers would like to stop smoking. This is evidenced by the fact that 17 million smokers attempt to quit each year. Unfortunately, only approximately 1.3 million persons are successful, making this a significant problem to the health care industry.

2. NICOTINE IS ADDICTING AND IS A PRIMARY REASON MANY PERSONS SMOKE

There is little doubt now that nicotine addiction is the primary reason that many patients develop a cigarette smoking habit. This fact was emphasized by the Surgeon General's Report on the Health Consequences of Smoking in 1988[2] in which the addiction to nicotine was compared to cocaine and heroin. Recent allegations by the press regarding a cigarette producer's attempt to add supplemental nicotine to certain cigarettes to lure smokers has increase the public attention to the idea that addiction to this substance is one of the reinforcing components in cigarette smoking. However, others have argued that nicotine is no more of an addiction risk than caffeine and that its use is more of an habituation than addiction.

Nicotine (Figure 1) is a tertiary amine that is soluble in water and lipids depending on Ph. In its pure form, nicotine is a clear, volatile, alkaline liquid that turns brown on exposure to air. Most cigarettes contain approximately 8 mg. of nicotine and deliver 0.1-1.9 mg. to the smoker depending on many variables involving the cigarette itself and the method of smoking. Nicotine is carried in smoke in droplets of "tar" that also contain carcinogenic polycyclic aromatic hydrocarbons.



NICOTINE

Figure 1. Chemical Structure of Nicotine

The absorption of nicotine is pH dependent. It is a weak base with a pKa of 8.0. At physiologic pH, about a third of the drug is not ionized and readily crosses lipid membranes. Many cured tobaccos produce a smoke that is acidic, and in this environment most of the nicotine is ionized and does not readily cross lipid membranes. Consequently, very little nicotine is absorbed in the mouth and upper airways in this situation. In the lung, the smoke pH rapidly increases and absorption is good since more of the drug is in a lipid soluble form. Many nicotine preparations, such as therapeutic gum, snuff and chewing tobacco, are buffered to an alkaline pH which greatly increases the amount of lipid soluble drug and enhances absorption in the oral cavity. If the pH of the mouth is decreased with coffee or other beverages, the oral absorption of the nicotine can be greatly reduced. Smoke from some air-cured tobacco used in pipes and cigars is also alkaline increasing oral mucosal absorption considerably.

Several types of tobacco exist that vary in chemical composition and other factors that influence their popularity as a source of nicotine. Flue-cured tobacco (bright leaf, Virginia) is the major component of American blend cigarettes. It has a high sugar to nitrogen ratio, which produces an acidic smoke when it burns. Light air-cured tobacco includes Burley tobacco and Maryland tobacco. Burley tobacco has a large cellular structure to its leaf making it ideal for absorbing casings such as sugars and is very popular for chewing tobaccos. Maryland tobacco has a relatively low nicotine content but its fluffiness reduces the chance that the cigarette will self-extinguish. Consequently, it is used in many blends today. Dark tobaccos have a low sugar content and consequently produce alkaline smoke making it ideal for use in cigars and pipe tobacco blends, as well as chewing blends. Oriental tobaccos are air-cured and fermented and have a moderate sugar content. They are used in American blends primarily for their aroma.

Nicotine that is inhaled in the form of cigarette smoke into the lungs is rapidly absorbed into the systemic circulation from the alveolar spaces because of the tremendous blood flow and

surface area of the lungs. This is illustrated in Figure 2 where the blood concentrations of nicotine are compared following smoking, chewing nicotine gum, chewing tobacco, and dipping snuff[14].

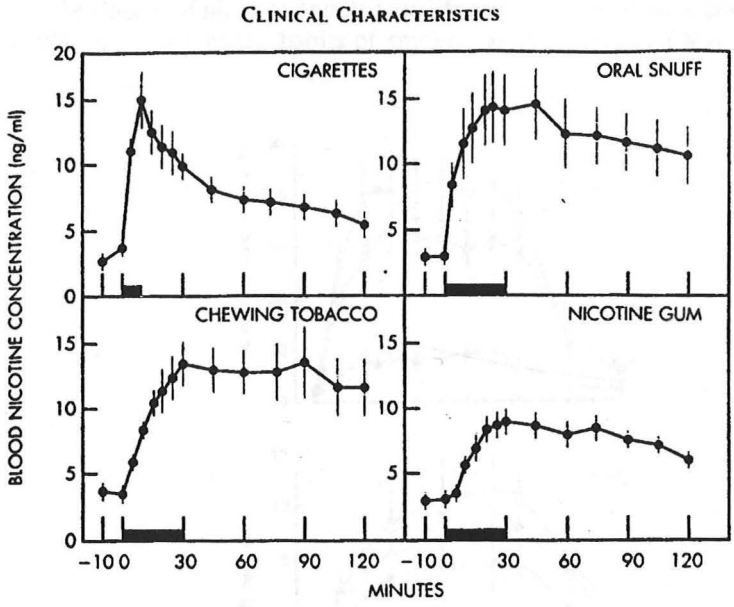


Figure 2. Concentrations of Blood Nicotine from Various Sources

After absorption in the lungs, blood concentrations of nicotine rise very quickly. This is in contrast to the rise in blood nicotine levels seen with the use of nicotine gum or smokeless tobacco which is gradual. Nicotine that is swallowed is absorbed poorly in the acidic gastric environment but is efficiently absorbed in the small intestines. The biologic availability is approximately 30% since 70% of the drug is metabolized during the first pass through the liver. Nicotine is concentrated in tissues with brain:blood concentrations being approximately 3 to 1.

The rapid absorption of nicotine into the systemic circulation allows a large concentration of the drug to be delivered to the brain in a short period of time. This rapid transfer to the brain is very important for rapid behavioral reinforcement from smoking and for the smoker to feel that there is significant control over the response of smoking by varying smoking techniques. Oral absorption being much less rapid provides less individual control over the pharmacologic

effects. Consequently, the drug is probably less addicting when used by the oral route. The half-life of nicotine is about 120 minutes due to metabolism by the liver to cotinine (cytochrome p450-dependent) and nicotine oxide. A smaller amount of nicotine is metabolized in the lung and kidney. Cotinine has a long half-life (18-20 hours) making it a useful index of nicotine intake when monitoring patients. Urinary excretion of nicotine is also pH dependent with increased clearance in acidic urine.

The dosing of nicotine and its half-life are very important in producing the desired effects and explaining many of the habits of smokers as illustrated in Figure 3[15].

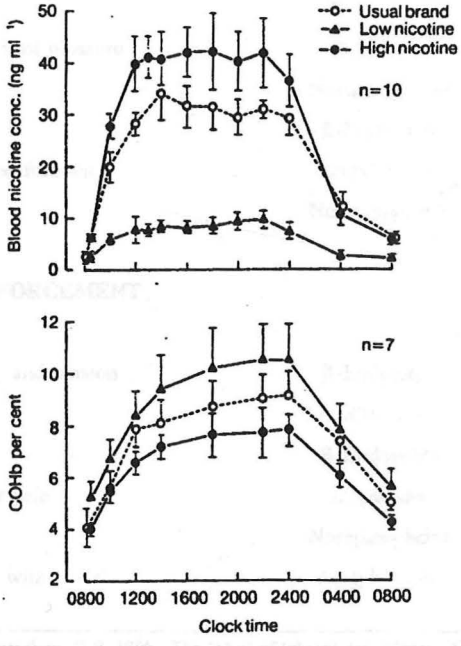


Figure 3. Blood Nicotine Concentrations Smoking Various Cigarettes.

Daytime blood levels of nicotine level off at approximately 35 ng/ml after several hours of smoking during the day. After overnight abstinence, morning levels are about 5 ng/ml. This lower level and the subsequent greater relative change in blood levels with each cigarette may account for the reported heightened effects with the first cigarette of the day and the craving for a smoke that occurs on awakening.

Nicotine acts primarily on nicotinic receptors in the nervous system as well as other areas of the body. In the central nervous system nicotine receptors are a heterogeneous group

composed of *alpha* and *beta* subunits. Stimulation of these receptors by nicotine result in a variety of neuroendocrine responses summarized in Table VIII[16].

TABLE VIII

REINFORCEMENT CONSEQUENCES AND PUTATIVE NEUROREGULATORY MECHANISMS*

POSITIVE REINFORCEMENT	ASSOCIATED WITH INCREASE IN:
Pleasure/enhancement of pleasure	Dopamine
	Norepinephrine
	β-Endorphin
Facilitation of task performance	Acetylcholine
	Norepinephrine
NEGATIVE REINFORCEMENT	
Reduction of anxiety and tension	β-Endorphin
Antinociception	Acetylcholine
	β-Endorphin
Avoidance of weight gain	Dopamine
	Norepinephrine
Relief from nicotine withdrawal	Acetylcholine

*Reprinted by permission from: Pomerleau, O.F. 1986. The "why" of tobacco dependence: Underlying reinforcing mechanisms in nicotine self-administration. in: Ockene, J.K. (Ed.) *The Pharmacologic Treatment of Tobacco Dependence: Proceedings of the World Congress. November 4-5, 1985.* Cambridge, Massachusetts: Institute for the Study of Smoking Behavior and Policy.

Release of these neurotransmitters is important for the behavior reinforcing effects of nicotine. As is noted, the release of dopamine and norepinephrine by nicotine has been associated with euphoria and anorexia while the release of beta-endorphin may be associated with the effects of smoking on anxiety and tension.

The pharmacologic effects of nicotine are summarized in the following table from Benowitz[17].

TABLE IX
HUMAN PHARMACOLOGY OF NICOTINE

Primary Effects	Withdrawal
Pleasure	Irritability, restlessness
Arousal, enhanced vigilance	Drowsiness
Improved task performance	Difficulty concentrating: impaired task performance
Relief of anxiety	Anxiety
Reduced hunger	Hunger
Body weight reduction	Weight gain
	Sleep disturbance
	Cravings or strong urge for nicotine
EEG desynchronization	Decreased catecholamine excretion
Increased circulating levels of catecholamines, vasopressin, growth hormone, ACTH, cortisol, prolactin, beta-endorphin	
Increased metabolic rate	
Lipolysis, increased free fatty acids	
Heart rate acceleration	Heart rate slowing
Cutaneous and coronary vasoconstriction	
Increased cardiac output	
Increased blood pressure	
Skeletal muscle relaxation	

The complex physiologic changes seen with nicotine administration are due in part to the fact that it has both stimulant and depressant effects. In general the stimulant effects occur at lower doses and the depressant effects result from higher or more prolonged dosing. In the central nervous system, nicotine in moderate doses stimulates activity producing tremors and sometimes seizures. Higher doses result in central nervous system depression with apnea due to central paralysis and muscular weakness. In the cardiovascular system, nicotine produces a variable rise in heart rate and blood pressure due to stimulation of the sympathetic nervous system and adrenal medulla.

The addiction liability of nicotine has been the subject of some debate. The twentieth report of the Surgeon General of the United States reviewed this topic in detail in 1988 and came to the following conclusions:

1) Tobacco is addicting.
2) Nicotine is the drug in tobacco that is addicting.
3) The pharmacologic and behavioral processes that determine tobacco addiction are similar to those that determine addiction to other drugs such as heroin and cocaine.

Although the last comment probably is the most controversial, there has been some debate

over the addiction potential of nicotine. The arguments for and against this have been summarized nicely by Collins[18]. As noted above, nicotine is clearly the substance most sought by smokers in cigarettes, and the evidence for this is fairly solid. Smokers who use low yield cigarettes smoke more cigarettes per day than those who smoke cigarettes higher in nicotine. In addition, smokers of low nicotine cigarettes use techniques that increase the amount of nicotine obtained from each cigarette. Further evidence for nicotine being the addictive drug in cigarettes is shown by the fact that treatment with a nicotine receptor inhibitor such as mecamylamine results in the smoker taking an increased number of cigarettes, presumably to increase the pharmacologic effect of the nicotine which is being blocked.

The fact that debate exists over the addiction potential of cigarettes is interesting given the behavior of tobacco users. If one examines the American Psychiatric Association (DSM-IIIR) diagnostic criteria for psychoactive substance dependence, there is little doubt that nicotine fulfills most if not all of the criteria. The diagnostic criteria for substance dependence are given in the Table X[19].

TABLE X
AMERICAN PSYCHIATRIC ASSOCIATION (DSM-IIIR)
DIAGNOSTIC CRITERIA FOR PSYCHOACTIVE SUBSTANCE DEPENDENCE

A.	At least three of the following phenomena are necessary:	
	1.	Substance often taken in larger amounts or over a longer period than the person intended.
	2.	Persistent desire or one or more unsuccessful efforts to cut down or control substance abuse.
	3.	A great deal of time spent in activities necessary to get the substance (*e.g.*, theft), taking the substance (*e.g.*, chain smoking), or recovering from its effects.
	4.	Frequent intoxication or withdrawal symptoms when expected to fulfill major role obligations at work, school or home (*e.g.*, does not go to work because hung over, goes to school or work "high", takes care of his or her children while intoxicated), or when substance use is physically hazardous (*e.g.*, drives when intoxicated).
	5.	Important social, occupational, or recreational activities given up or reduced because of substance abuse.
	6.	Continued substance use despite knowledge of having a persistent or recurrent social, psychological, or physical problem caused or exacerbated by the use of the substance (*e.g.*, keeps using heroin despite family arguments about it, suffers cocaine-induced depression, or makes an ulcer worse by drinking).
	7.	Marked tolerance; need for markedly increased amounts of the substance (*i.e.*, at least 50% increase) to achieve intoxication or desired effect, or markedly diminished effect with continued use of the same amount.
		NOTE: The following items may not apply to cannabis, hallucinogens, or phencyclidine (PCP):
	8.	Characteristic withdrawal symptoms (see specific withdrawal syndromes under Psychoactive Substance-Induced Organic Mental Disorders).
	9.	Substance often taken to relieve or avoid withdrawal symptoms.
B.	Some symptoms of the disturbance have persisted for at least 1 month or have occurred repeatedly over a longer period of time.	

As noted above, cigarette smokers fulfill at least three if not all of the criteria. The scientific proof of nicotine's addictive potential has been more difficult to prove. There is evidence that genetic factors predispose some persons to tobacco and nicotine use. This is illustrated in a study by Fisher reviewed by Gurling, et al[20], where the smoking behavior of identical twins and found that the concordance for smoking behavior was greater in a population of identical twins when compared to dizygotic twins. He argued that this evidence indicated that genetic factors were influencing the behavior. In addition, several environmental factors certainly influence smoking. Social pressure to smoke affected adults greatly in the past; today, this pressure is greater in situations involving young groups. Smokers tend to increase their use of tobacco during stressful situations, and the consumption of alcohol greatly increases the likelihood of smoking. Also, rats that are exposed to stress self-inject nicotine more than in the non-stressed state. These examples illustrate the significant impact environmental has on smoking habits.

However, there are several lines of evidence to indicate that nicotine by itself is addicting. Self-administration studies have shown that animals and humans both will press a lever to obtain an intravenous nicotine reward. It is interesting to note that patients who have a history of substance abuse have problems discriminating the effects of intravenous nicotine from cocaine. The dosing of nicotine, however, may be critical and environmental factors may play a role. Other methodologies investigating the use of nicotine in animals using conditioned preference and drug discrimination studies have also shown that nicotine is addicting. Whatever the arguments, most studies have shown that nicotine has a reinforcing effect on users.

The issue of tolerance to nicotine use is important when studying the behavior patterns of chronic smokers. There is no doubt that tolerance develops very quickly with nicotine use. Most are familiar with the initial effects of smoking which include nausea, vomiting, headache, dysphoria and dizziness. These symptoms of toxicity rapidly decrease even though increasing amounts of nicotine are taken. The mechanism of nicotine tolerance has been studied in animals and in humans and is probably due to an increased number of brain nicotinic receptors. Rapid tolerance or tachyphylaxis to the action of nicotine develops in many smokers. This is illustrated by the fact that smokers report that the first cigarette of the day is the most pleasurable and that the effects of nicotine through the day markedly decreases. This rapid tolerance obviously develops with the first few doses, making chronic tolerance to the effects of nicotine more difficult to explain.

The physiologic effects of nicotine in the brain and their relationship to addiction have only recently been significantly studied. Some postulate that the addiction to nicotine is mediated through the pleasurable effects of dopamine released in the mesolimbic system. Infusion of nicotine into the nucleus accumbens by a microdialysis probe results in an increase of extra-cellular dopamine, and the release is related to the dose of nicotine used. This action can be blocked by mecamylamine infused systemically indicating that nicotinic receptors in this area mediate the process. The role of this system in the addiction process, however, is unknown.

Another hypothesis regarding the effects of nicotine has to do with its effect on

corticotropin (ACTH). Many years ago, Haggard and Greenberg[21] noted an increase in blood glucose in patients after smoking cigarettes. Subsequently, nicotine was identified as the component of cigarettes that mediated this response and that plasma cortisol also increased. More recent studies of this mechanism indicate that nicotine probably increases plasma cortisol levels by increasing ACTH via increased CRH[22] action secondary to the stimulation of nicotine receptors in the paraventricular nucleus of the hypothalamus. It has also been shown that the mediation is not due to stimulation of peripheral nicotinic receptors.

The degree of the addictive potential of nicotine, however, is still being debated. Robinson & Pritchard[23] summarize an opposing view of the addictive potential of tobacco and concluded that it is more like the role of caffeine in coffee than the role of cocaine in coca leaf. Their argument is clouded by the fact that they represent R. J. Reynolds Tobacco Company. Most scientists[24] as well as the population in general have accepted the fact that nicotine is addictive. The importance of the nicotine dependence in smoking behavior will continue to be debated. While this debate is important, one should not overlook the social pressures that cause many young persons to start smoking. It has been estimated that over 90% of teenagers who smoke three or four cigarettes will be influenced to continue smoking as a regular habit[25]. Prevention strategies must influence the experimentation with cigarettes as well as treating nicotine addiction after it has already developed.

3. TREATMENT METHODS ARE AVAILABLE FOR PATIENTS WHO WANT TO STOP SMOKING

Because of the known health hazards of smoking, physicians should obviously counsel all patients who smoke that they should quit. Approximately 70% of patients who smoke want to quit: so encouragement, many times, is all that is required to initiate a conversation with a patient regarding methods of smoking cessation. The first step in this process is a thorough evaluation of the patient with respect to smoking history and complications.

The history of patients who smoke should include a thorough evaluation of previous and current smoking habits and possible smoking complications. This evaluation should include a detailed family history of smoking related diseases such as cancer of the lung, larynx, bladder, cervix, esophagus, mouth, gum, and pancreas; coronary artery disease; hypertension; stroke; peripheral vascular disease or emphysema. The age of onset of smoking and the amount and type of tobacco consumed through the patient's smoking life is very important. The type of cigarettes smoked is important from a historical perspective but may be irrelevant from a complication standpoint since the amount of tar and nicotine inhaled in low-tar and low-nicotine cigarettes may be the same as with other cigarettes because of alterations in smoking habits and techniques by those who use these cigarettes[26]. The presence of a morning cough and mucus production may help in predicting the onset of certain complications[27]. A thorough history of occupational exposure is also important for the identification of synergistic compounds. Finally,

the Fagerstrom Dependency Score[28,29] may help identify patients with more severe nicotine addiction who will have greater difficulty with smoking cessation (Table XI).

TABLE XI

ITEMS AND SCORING FOR FAGERSTROM TEST FOR NICOTINE DEPENDENCE (FTND)

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

Positive answers to questions 1, 3, and 4 correlate with high blood levels of nicotine and cotinine. A Fagerstrom addiction score above 5 points is considered high.

The physical examination should concentrate on the detection of complications of chronic smoking and include a search for hypertension, tobacco stained fingers, expiratory wheezes or increased exhalation time, cardiac arrhythmias, tobacco odor and the signs and symptoms of other complications of cigarette smoking discussed above.

Laboratory evaluation of smokers should include spirometry. Although many of the chronic effects of cigarette smoking are irreversible, their detection can be a tremendous help in evaluating and treating smoking patients. Spirometry does identify smokers who are at risk for myocardial infarction, lung cancer, stroke and COPD[30]. The Framingham Heart Study found that a reduced vital capacity is a predictor of premature morbidity and mortality from myocardial infarction[31]. With respect to spirometry, all that is really needed is an evaluation of the forced expiratory volume in one second ($FEV_{1.0}$) and the forced vital capacity (FVC). If some degree of obstruction is detected, improvements that may follow smoking cessation may reinforce treatment[32]). Exhaled carbon monoxide and serum, urine, or salivary cotinine determination can be used to determine compliance of smoking cessation and also can be used as a motivating factor in the person trying to stop smoking[33,34]. A resting electrocardiogram and a total cholesterol should also be obtained, searching for other risk factors for coronary artery disease.

After the evaluation is completed, the physician should initiate a serious discussion regarding the physician's and patient's role in the treatment process. This discussion should include serious evaluation of the risks of smoking and emphasize that smoking cessation is a very complicated process. This simple counseling has resulted in yearly cessation rates as high as 5%, whereas no advice results in rates of less than 1%. It is important that the patient realize that relapse is part of the smoking cessation process and that the physician will be available to advise and counsel the patient whenever necessary.

TREATMENT OF SMOKING AND NICOTINE ADDICTION

Only recently has the medical field become seriously interested in helping patients stop smoking. Consequently, most smokers who have quit in the past have done so on their own. The process of smoking cessation is very complex. Smokers vary in their desire to quit, their addiction to nicotine, and their psychological reasons for smoking, physicians must offer a wide range of cessation options tailored to the individual needs of the patient. Most patients who want to quit would rather do so on their own without much supervision, but this method is the most likely to fail. Patients can quit smoking on their own but rarely remain tobacco free for a significant period of time. Success rates at 12 months of 20-30% should be considered successful since without supervision the success rate is less than 5%. While a 20% success rate may not sound that good, one must remember the absolute number of smokers is very large. Consequently, a small percentage of this number translates into tremendous savings to the health care system per year.

The process of smoking cessation involves 5 distinct phases: 1) Precontemplation; 2) Contemplation; 3) Action; 4) Maintenance and, 5) Relapse. These phases must be understood if a behavioral and pharmacologic intervention is planned.

During the precontemplation phase, the patient is not actively thinking about withdrawing from smoking. Intervention during this phase should include a calm discussion of the medical consequences of smoking. Many times, aggressive attempts to convince the patient to stop smoking during this phase by a health care professional or a family member will result in denial and hostility.

The contemplative stage is a time when the patient is thinking about or is receptive to the notion of stopping smoking. Discussions with the smoker about nicotine withdrawal during this time can be very productive.

The action stage is when the patient actually attempts to quit smoking. It is helpful if the patient will set a quit date during a relatively stress-free time period, i.e., not during a holiday or other stressful times.

During the maintenance phase, the nonsmoker is trying to refrain from smoking use.

The relapse is perhaps the most important part of the smoking cessation process. One must understand that addiction to nicotine and smoking is chronic and relapsing. Consequently, the patient must realize that relapse is not an automatic indication of failure of the smoking cessation process. Each year 17 million smokers quit their habit, but only about 1.3 million succeed[35]. From a medical standpoint, relapse should be expected, anticipated and accepted as a part of the recovery process in some smokers.

Whenever smoking patients are seen for any reason in a physician's office, smoking cessation should be discussed. Smoking cessation treatment should be attempted only after the patient has decided that it is time to stop smoking. Many times a quit date can be negotiated with the patient. After treatment is started, patients probably should be seen every 2 weeks during the acute phase of nicotine withdrawal.

Behavioral treatment is an essential part of the smoking cessation process. As noted above, a great deal of counseling and advice is necessary before the actual treatment can begin. Most studies have found that pharmacologic treatment without behavior modification results in only short term benefits in smoking rates. This accounts for the fact that most acute interventions in smokers have long term abstinence rates that depend more on behavioral changes than on acute interventions. Long term benefit must come from changing the cues for smoking or treating the psychological pathology that results in smoking. Nicotine has strong stress and anxiety relieving properties making it attractive psychologically to those who suffer from these disorders. In addition, depressed patients often feel better when taking nicotine because the smoker is able to regulate affect with the drug. In these situations, long term treatment of the underlying stress, anxiety, and/or depression is essential if long term success with smoking cessation is to be expected. Often this can be accomplished with relaxation meditation, and other methods to relieve stress. A detailed description of different behavioral treatment modalities can be found in reference 36.

Nicotine replacement has been the most effective drug therapy in nicotine addiction. This is not surprising given the role of nicotine in the smoking addiction process. Nicotine replacement has been useful in the treatment of nicotine addiction especially when used in the setting of behavioral modification[37]. When used alone, it is better than placebo in obtaining short-term abstinence rates. However, its effect diminishes with increasing time. With behavioral treatment and counseling, nicotine replacement does improve abstinence rates when compared to placebo even after several months as illustrated in Figure 4[38].

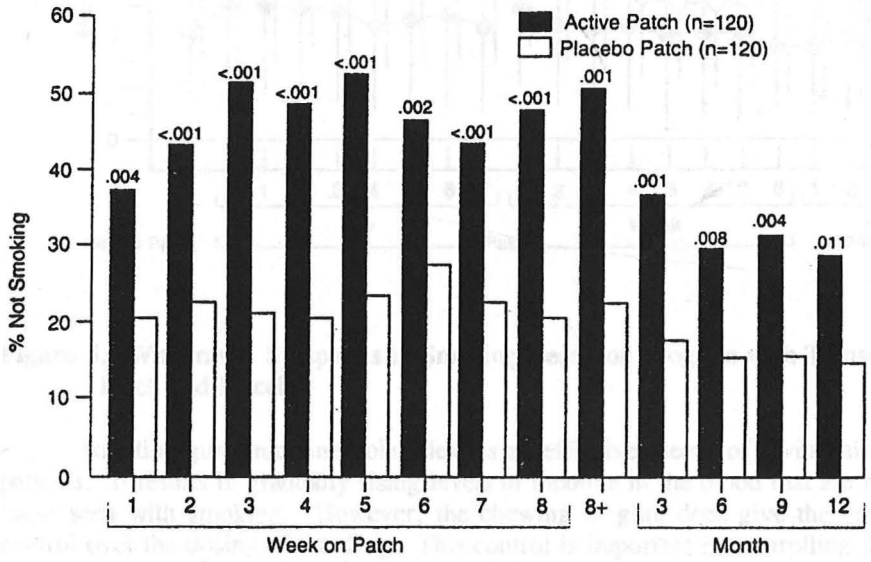


Figure 4. Smoking Cessation Success Rates Using Transdermal Nicotine Patch and Placebo.

Only a small percentage of patients use nicotine replacement gum according to established guidelines if given at the patient's request without any educational training. When used properly, nicotine replacement is effective in preventing the symptoms of nicotine withdrawal as illustrated in Figure 5.

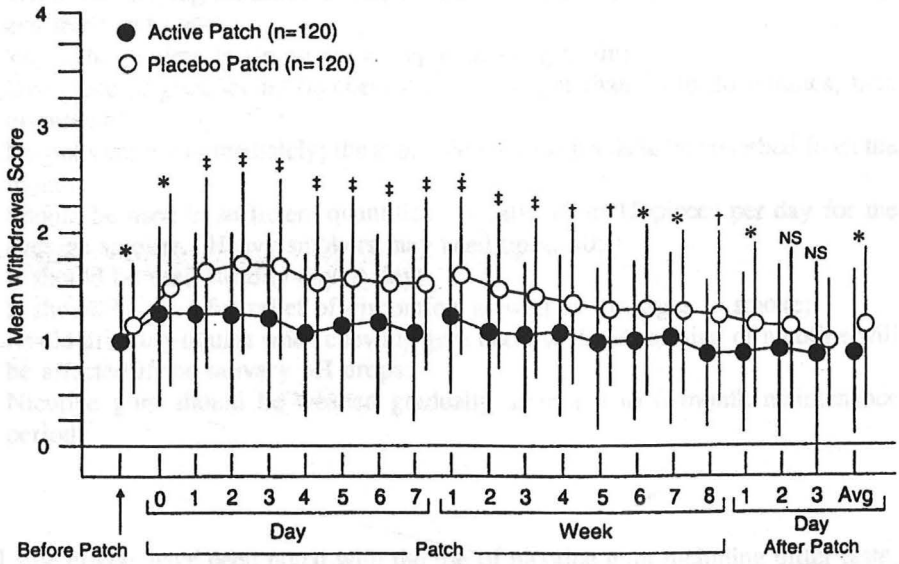


Figure 5. Withdrawal Symptoms in Smoking Cessation Program with Transdermal Nicotine Patch and Placebo.

Nicotine gum (nicotine polacrilex) is an effective means of giving nicotine to addicted patients. It results in gradually rising levels of nicotine in the blood that are much slower than those seen with smoking. However, the chewing of gum does give the user some sense of control over the dosing of the drug. This control is important in controlling the urge to smoke noted by many patients. Peak blood levels occur 15-30 minutes from starting the gum. The absence of a sustained method of releasing nicotine allows for nicotine withdrawal at night that is similar to that seen with cigarette smoking. Patients who use nicotine gum tend to use the same amount of nicotine during a 24 hour period as when they smoke. Used alone, it is not as addicting as cigarettes because of its gradual absorption from the oral mucosa leading to a slower rise in serum concentration and less reinforcing effects on the brain. Used as directed, nicotine gum suppresses most nicotine withdrawal symptoms, especially anger, anxiety and impatience. It also suppresses hunger and craving to a lesser extent. Nicotine gum is available in the United States in a 2 mg dose. The patient is instructed to chew the gum whenever the urge to smoke occurs. Instructions for using nicotine gum should include the following adapted from Sees[39]:

1) It should be chewed slowly and intermittently;
2) It takes approximately 15 chews to release the nicotine from the polacrilex; at that time a tingling sensation will be felt in the mouth;

3) When the tingling sensation starts, the gum should be placed between the cheek and teeth and gums;
4) When the tingling is almost gone, begin chewing again;
5) One piece of gum should be chewed for no longer than 20 to 30 minutes, then discarded;
6) Do not swallow immediately; the available nicotine needs to be absorbed from the mouth;
7) Should be used in sufficient quantities - usually 10 to 15 pieces per day for the average smoker. Heavy smokers may need up to 30;
8) It should be used steadily day to day;
9) It should be used for relief of discomfort as well as for urges to smoke;
10) Avoid drinking liquids when chewing gum because the absorption of nicotine will be affected if the salivary pH drops;
11) Nicotine gum should be weaned gradually after a 3 to 6 month maintenance period.

Several side effects have been noted with the use of nicotine gum including bitter taste, jaw fatigue, gastrointestinal distress, and the risk of continued nicotine addiction. Contraindications to nicotine treatment are as follows:

EXCLUSION CRITERIA FOR NICOTINE GUM

History of Myocardial Infarction
Peripheral Vascular Disease
Significant cardiac arrhythmias
Hypertension
Vasospastic Disease
Active Peptic Ulcer Disease
Active Esophagitis
Oral or Pharyngeal Inflammation
Pheochromocytoma
Hyperthyroidism
Insulin-dependent Diabetes Mellitus
Pregnancy
Breast Feeding
Active TMJ Disease
Extensive Dental Work

Over the last couple of years, nicotine patches for transdermal nicotine replacement have

become a popular means of treating nicotine withdrawal. Given by the continuous transdermal route, nicotine has somewhat different physiologic action from smoking or oral administration and has fewer side effects. The gradual onset of physiologic effects and the lack of transient increases in blood nicotine levels controlled by the user make it less reinforcing and addicting than smoking. However, the maintenance of a constant lower blood level of nicotine (10-15 ng/ml) in the blood blocks nicotine withdrawal symptoms. Available preparations include Habitrol, Nicoderm, ProStep and Nicotrol. Trials have shown that these preparations are effective in smoking cessation for at least 6 months[40]. The ease with which a transdermal preparation may be applied and the fact that it only has to be taken once a day results in increased compliance[41]. Nicoderm and Habitrol come in 7 mg., 14 mg., and 21 mg. sizes. The 21 mg. size should be used for patients who smoke a pack or greater per day. The patch should be placed on the upper trunk or arm in a hairless area which gives a nicotine level of about 1/2 that seen by cigarette smoking. It is recommended that one use the 21 mg. patch for 6 weeks, the 14 mg. patch for 2 weeks and the 7 mg. patch for 2 weeks. ProStep is available in 22 and 11 mg. patches, Nicotrol comes in 15 mg., 10 mg., and 5 mg. packages providing nicotine release over about 16 hours. This allows overnight withdrawal of nicotine not seen with the 24 hour preparations. Contraindications to the use of nicotine patches are the same as for nicotine gum except for oral lesions.

Nasal and inhaled nicotine preparations are available experimentally. They more closely resemble actual nicotine intake and allow for direct substitution for smoking. Unfortunately, this advantage is also the primary disadvantage for their use. The rapid rise in blood levels and brain concentrations make these preparations as addicting as smoking. They probably will be the most useful as adjunctive therapy in patients taking a longer acting, slower onset nicotine preparation.

No good studies have indicated one patch to be superior to another. All seem to provide better than placebo smoking cessation rates over short-term periods.

Side effects of the patch include skin irritation and itching which can be treated by removing the patch or by the use of topical corticosteroids. Patients should be warned not to smoke while using the patch since very high levels of nicotine can occur in these situations and possibly lead to symptoms and side effects of acute nicotine intoxication. The patch may be supplemented with nicotine gum during times of intense nicotine craving.

Clonidine has been used for several years with limited success in treating symptoms of nicotine withdrawal[42]. It is a centrally acting *alpha*$_2$-receptor agonist that is useful in the treatment of the symptoms of alcohol and narcotic withdrawal. Although it is not approved by the Food and Drug Administration for the treatment of tobacco abuse, it seems to block the symptoms of nicotine withdrawal and diminish cigarette craving. Controlled studies have revealed conflicting data regarding the difference from placebo of this drug in its ability to accomplish better smoking cessation rates long-term[43]. However, it probably is helpful in the short term control of symptoms during smoking cessation. The transdermal form of clonidine also may provide fewer side effects and improve patient compliance due to its gradual onset of action and long duration of effect. In summary, clonidine should be used as an adjunct to

nicotine replacement and as part of a comprehensive nicotine withdrawal program. It should not be used as first-line therapy in most patients.

Mecamylamine hydrochloride, a nicotine antagonist, may prove to be beneficial in the future by directly blocking the effects of nicotine. However anticholinergic and hypotensive side effects have limited its use.

Silver acetate has been formulated into several products in the form of gum and lozenges. It causes an unpleasant taste in the mouth when exposed to smoke. Prolonged use of these products can result in silver poisoning (argyria).

Lobeline is a partial nicotine receptor antagonist found in some over-the-counter preparations. Studies have found it to be no more effective than placebo.

ACTH was first used in 1985 when it was given to 10 patients by Bourne[44]. Although this study was not well controlled, 10 patients who were given this drug abstained from smoking for 7 months. This postulated that the success rate was due to the block of the nicotine-mediated increase in cortisone and glucose that he felt caused the smoking "lift".

Buspirone, doxepin, fluoxetine, and other antianxiety/antidepressant medications may be used in patients with evidence of significant anxiety or depression. However, these drugs should not be used generally as first-line therapy before nicotine replacement.

Acupuncture has been used in the treatment of smoking cessation with variable results. Probably it is most effective to those that expect the treatment to be successful. Some groups have found in large studies that acupuncture can be as effective as nicotine chewing gum in the short-term treatment of smoking, but probably it is no better than any treatment to reduce relapse. In summary, acupuncture seems to decrease symptoms of nicotine withdrawal in patients who believe before the treatment that it will work. It's effectiveness in patients who do not feel it will be effective has not been proven. There is no significant evidence that it decreases long-term relapse rates. It may be useful in conjunction with other treatment modalities. Theoretically acupuncture may affect nicotine withdrawal symptoms by increasing ACTH release[45].

Hypnosis has also been used to treat nicotine withdrawal. It seems to be effective in some patients[46] but it's long-term success rates have not been studied well enough to recommend its use.

In summary, the treatment of nicotine withdrawal and addiction is a complex process. Pharmacologic treatments are generally effective in controlling nicotine withdrawal symptoms and give good short-term cessation rates. Benowitz has proposed a stepped-care approach to the problem of nicotine addiction that is outlined in Figure 6[17]. Initial therapy should consist of nonpharmacologic therapy. Those who fail step 1 should receive nicotine replacement therapy with a slow release preparation. The most addicted or resistant patients should receive more

intense nicotine replacement with a short-acting nicotine preparation if available and other adjunctive pharmacologic measures. As noted above, all patients should have extensive counseling and training in behavior modification techniques if one desires long term success in smoking cessation.

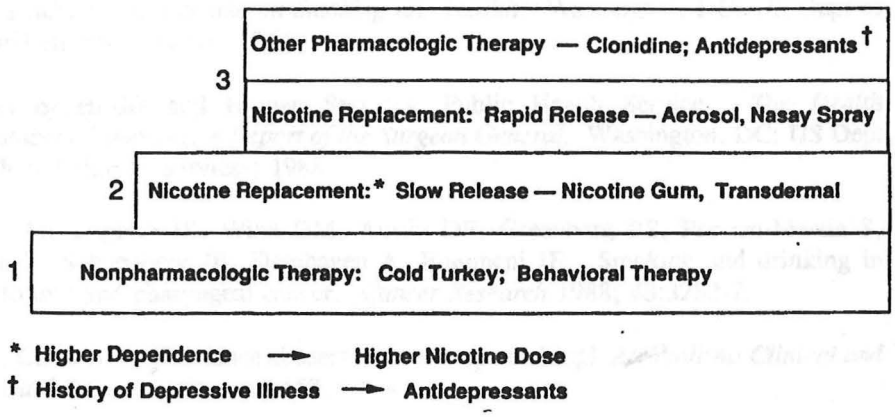


Figure 6. Stepped-care Approach to Smoking Cessation

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