

Pharmacology and Abuse Potential of Cigars

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INTRODUCTION Cigar tobacco contains the highly addictive drug nicotine in concentrations similar to those observed in cigarettes; however, since most cigars contain more tobacco, they also contain more nicotine than cigarettes. Most cigar smokers do not inhale cigar smoke, and those who do inhale far less than typical cigarette smokers (Chapter 4). The pH of the smoke from most cigars is sufficiently alkaline to enable efficient absorption of nicotine through the oral and nasal mucosa. These basic observations, along with the behavioral observation that some cigar smokers report symptoms of dependence and withdrawal similar to those of cigarette smokers, have led the American Psychiatric Association to include cigars along with cigarettes in their manual listing drug dependence and other disease states (American Psychiatric Association, 1987). This chapter will review the scientific evidence supporting the categorization of cigars as dependence-producing nicotine delivery devices.

EARLY OBSERVATIONS OF ADDICTIVE EFFECTS The history of tobacco use includes accounts of cigar smoking by native Americans dating back more than 1000 years. In fact, when the term addiction was applied to describe the enslavement of some people to their tobacco in the late 1700's, the main forms of tobacco smoking were cigar and pipe smoking (Murray et al., 1991). The cigarette, which is now the most commonly used nicotine delivery device, did not make its appearance in common use until the 1840's (McKim, 1986).

It has long been recognized that cigars contain and deliver psychoactive doses of nicotine. The concept that tobacco strain, growing conditions, and manipulation of the pH of nicotine preparations could greatly affect the amount of nicotine available from cigars was reported by Graham and Carr in 1924. In 1925, Mendenhall noted that the experiments in which a pipe or cigar was smoked were more likely to have subjects report feelings of being dizzy or sick than experiments in which subjects smoked cigarettes, presumably because the cigars and pipes delivered more nicotine than cigarettes. In 1931, Lewin reported on the psychoactive effects of cigars, noting the ceremonial use of cigars to produce a strong psychosis during which a young man can "see spirits which prophesy his future and endow him with strength, knowledge and happiness" (from *Phantastica: Narcotic and Stimulating Drugs, Their Use and Abuse* reprinted in English by E. P. Dutton and Company, 1964). Lewin concluded that the pharmacological effects of tobacco, smoked or unsmoked, were primarily due to the nicotine released from the tobacco and absorbed by the person. Other pharmacologic effects of cigar smoking, including tolerance, pleasure, and tranquilization were described by Gies et al. in 1921, who concluded that these effects contributed to the habitual use of cigars. Interestingly, Gies and colleagues (1921) listed cigars before cigarettes in the order of greatest to least degree of psychoactive and toxic potency.

Other psychological and physiological effects of cigar smoking have also been referenced in classic early psychopharmacology research. Bates reported on the cardiovascular (Bates, 1922a), as well as the cognitive and psychomotor (Bates, 1922b) effects of cigar smoking. Bates showed that smoking increased systolic and diastolic blood pressure, as well as heart rate. Mixed results of cigar smoking and cigar smoke deprivation were seen on psychomotor and cognitive performance tasks which included arithmetic and dart throwing. Dixon (1928) also reported on the cardiovascular effects of cigar smoking as well as the on the cognitive-enhancing effects of cigar smoking and the lowered cognitive performance produced by deprivation from cigars. In 1927, Dixon reported on the psychoactive and performance effects of cigar smoking and stated that “acquired tolerance to nicotine is probably the same as that of morphine” (p. 20). Thus the concept that many of the effects of cigar smoking are due to nicotine has been understood for well over 70 years.

NICOTINE DOSING CAPABILITY OF CIGARS Cigars contain and deliver a wide range of biologically-active chemicals, several of these such as nicotine, acetaldehyde, and carbon monoxide can serve to modify behavior. However, of all the chemicals known to be common across most cigar brands, nicotine is the only known dependence-producing drug present in substantial quantities. This section examines the nicotine dosing capabilities of cigars in greater detail to determine how cigars compare to products known to readily cause nicotine addiction, namely cigarettes and smokeless tobacco.

The nicotine delivery of cigars is a complex issue due to the variability in size, nicotine content, and pH of various cigar brands. Henningfield et al. (1996) examined characteristics of ten cigar brands selected from a cigar retailer in Baltimore. Table 1 summarizes the results of this study. The weight of the cigars examined ranged from 0.77 to 22 g, and the nicotine content of these products ranged from 10 to 444 mg. The pH of the tobacco in solution also varied greatly, with values ranging from 6.2 to 8.2. By contrast, cigarettes typically weigh less than 1 g and contain an average of 8.4 mg nicotine (Benowitz et al., 1983), and cigarette tobacco is generally mildly acidic with pH values ranging from 5.5 to 6 (Brunneman and Hoffmann, 1974). Additionally, in 1996, 98.2 percent of cigarettes produced in the United States had filters which prevent the direct contact of the cigarette tobacco with the lips and the buccal mucosa (United States Department of Agriculture, 1997).

The data in Table 1 indicate that cigars contain amounts of nicotine ranging (on the low end) from that equivalent to a single cigarette to (on the high end) that equivalent to an entire pack of cigarettes. With the exception of cigars that are similar in size to cigarettes, most cigars contain nicotine in quantities equivalent to several cigarettes. In addition, the higher pH of cigar tobacco and cigar smoke may result in a higher proportion of the nicotine contained in a cigar being in free unprotonated form and more available for absorption via the mouth, nose, and throat than is the case with cigarettes.

Table 1

Physical characteristics of ten cigars selected at random from a cigar retailer in Baltimore, MD, November 1995* (Reprinted from Henningfield et al., 1996)

Code	Length (mm)	Diameter (mm)	Weight (g)	Nicotine Concentration (mg/g)	Total Nicotine Content (mg)	Tobacco pH
A	68	8	0.77	14.95	16.59	6.2
B	79	8	1.12	9.00	10.08	6.6
C	124	17	9.56	17.40	166.30	6.8
D	125	12	4.20	4.70	19.74	7.6
E	138	17	12.60	8.43	106.22	7.3
F	148	12	5.78	10.74	62.07	7.2
G	149	16	10.06	7.75	77.79	8.0
H	170	17	15.37	16.35	251.30	6.7
I	198	21	22.00	22.00	444.00	7.1
J	214	20	21.29	8.90	189.50	8.2

* Nicotine content was determined by the HPLC method. Smoke pH was not assessed; however, the pH of the tobacco was determined by suspending 2 g of tobacco in 10 ml of water, mixing, then testing at fixed intervals up to 60 min.

INHALATION OF CIGAR SMOKE

The manner in which a person smokes a cigar also affects nicotine delivery. Some cigar smokers regularly inhale smoke, whereas others inhale very little (Turner et al., 1977). The pKa of nicotine is 8.02, which means that 50 percent of nicotine is in an unionized state, and this free unprotonated nicotine is present in the vapor phase of cigar smoke which contributes to the nicotine's rapid absorption through the oral mucosa (Lide, 1991). Therefore, nicotine from cigars which generate smoke with a high pH could readily be absorbed across the buccal mucosa, and smokers would not need to inhale the smoke deeply into the lung to absorb substantial amounts of nicotine. Absorption of nicotine through the buccal mucosa is highly pH dependent; absorption in the lung is less influenced by pH due to the much larger absorptive surface area of the lung. The smoke from cigarettes and those cigars which produce low-pH smoke must therefore be inhaled in order to absorb substantial amounts of nicotine. In contrast, cigar smokers with a high-pH smoke can absorb nicotine by holding the smoke in their mouth, or they can increase their absorption by inhaling. These differences in the absorption of nicotine from cigar and cigarette smoke are likely to contribute to the lower rates of inhalation among cigar smokers.

A cigar can also function much like a smokeless tobacco product such as chewing tobacco or oral snuff (i.e., "spit tobacco") and permit extraction of nicotine from the unburned tobacco so that it can be absorbed directly through the buccal mucosa and lips. This is possible for two reasons which

distinguish most cigars from most cigarettes: (1) most cigars have neither filters nor tips and are designed and used in a manner such that tobacco leaf material is in direct contact with the lips and to a lesser extent, with the tongue and gums; this contact serves to moisten the leaf and enable extraction of its nicotine; (2) most cigars are manufactured with tobacco leaf material which has been cured and/or buffered so as to produce a mildly alkaline tobacco which facilitates nicotine transfer.

Several studies have examined the absorption of nicotine from cigar smoke in human cigar smokers as well as in animals exposed to cigar smoke. Armitage and Turner (1970) examined delivery of nicotine by cigars and cigarettes through the oral mucosa in cats. The authors found that pharmacologic responses to the smoke were greater following cigar smoke exposure than following cigarette smoke exposure despite the fact that more nicotine was present in the cigarette smoke (4.4 mg versus 4.0 mg after 30 puffs of cigarette and cigar smoke, respectively). The authors interpreted these results to mean that more nicotine was absorbed from the cigar smoke due to the higher pH values in the cigar smoke (pH = 5.4 for cigarette and 8.5 for cigar smoke). Armitage and Turner (1970) also describe a separate experiment in which carotid blood levels of nicotine were measured after placing solutions of nicotine with pH values of 6, 7, and 8 in the mouths of cats. The authors found that absorption of nicotine in the first 2.5 min was 8 times higher following the pH 8 solution compared to the pH 6 solution.

Pechacek et al. (1985) examined serum thiocyanate levels, a chemical marker for inhaled tobacco smoke, in cigarette smokers, ex-cigarette-smoking cigar and pipe smokers, and never-cigarette-smoking cigar and pipe smokers. The authors found that cigarette smokers inhaled the greatest amount of tobacco smoke, followed by ex-cigarette smokers, then never-cigarette-smoking smokers of cigars and pipes. The authors suggest that most cigarette smokers inhale, whereas only some cigar smokers inhale, and that inhalation among cigar smokers is influenced by former cigarette smoking status. Serum thiocyanate levels were also related to the number of cigars smoked per day; subjects who smoked four or more cigars per day had serum thiocyanate levels comparable to cigarette smokers who smoked ten cigarettes per day. However, most of these heavy (> 4 per day) cigar smokers also tended to be ex-cigarette-smokers.

Similar results were found in a study by Turner et al. (1986) in which carboxyhemoglobin was used as the biological marker of inhaled tobacco smoke. Turner et al. found that the mean concentration of carboxyhemoglobin was 4.8 percent of the total hemoglobin among cigarette smokers, compared to 0.9 percent among never-cigarette-smoking cigar smokers and 6.8 percent former-cigarette smoking cigar smokers.

Combined data from more than 8,000 tobacco smokers, of whom more than 1,000 smoked cigars or pipes, from the Multiple Risk Factor Intervention Trial (MRFIT) confirmed significant levels of tobacco exposure (based on serum thiocyanate) and smoke inhalation (based on expired air carbon monoxide) among cigar smokers as compared to non tobacco users (Ruth and Neaton,

1991). Not surprisingly, overall levels of nicotine and smoke exposure were lower and more variable among cigar smokers than among cigarette smokers. Another analysis of data from MRFIT indicated that switching from cigarette smoking to cigar or pipe smoking resulted in decreased smoke exposure, but that levels remained significantly higher than those observed during tobacco abstinence (Ockene et al., 1987). The former cigarette smokers were also more likely to report inhaling cigar or pipe smoke into the lung than were cigar smokers who had never smoked cigarettes. The MRFIT data on cigar smoke inhalation patterns by former cigarette smokers are consistent with those reported in Chapter 2 and show that less than 15 percent of cigar smokers who never smoked cigarettes reported inhaling smoke into the lung, more than 20 percent of former cigarette smokers and approximately two-thirds of concurrent cigar and cigarette smokers reported inhaling. These data confirm that some cigar smokers who formerly or currently smoke cigarettes are likely to obtain regular doses of nicotine by inhalation of smoke directly into the lung.

RATE OF NICOTINE ABSORPTION Armitage et al. (1978) examined the absorption of nicotine from small cigars labeled with ^{14}C -nicotine. The authors found that the amount of nicotine delivered to the smoker's mouth during cigar smoking was greater than that during cigarette smoking, but the proportion retained by the subject was similar for cigars and cigarettes. Arterial nicotine concentrations were comparable for the two products, but the rise in arterial plasma nicotine levels was faster for cigarettes than for the small cigars. This difference in rates of delivery is probably due to the route of absorption since cigarette smoke is delivered largely through the lung, whereas cigar smoke is delivered through both the oral and lung routes, mostly buccal in subjects where there is little inhalation. Nicotine delivery to the brain is slower when nicotine is absorbed across the oral mucosa compared to absorption across the alveolar surfaces of the lung (Benowitz et al., 1988). In addition, absorption through the pulmonary route is more complete than through the oral route, which accounts for the fact that, whereas more nicotine was actually delivered to the mouth by the small cigars than by the cigarettes, similar amounts were actually retained.

Inhalation parameters have a dramatic affect on nicotine delivery. A study which examined the absorption of nicotine from non-inhaled cigar smoke found nicotine delivery to be slower than that observed following cigarette smoke inhalation (Russell et al., 1980). The authors studied the nicotine absorption from a single small cigar (6.2 g) and found an increase in plasma nicotine of 16.5 ng/ml after 1 hour of smoking the single cigar (Medallion Petit Corona).

Despite the acidic pH of cigarette smoke, inhalation into the lung can produce arterial nicotine concentrations as much as ten times greater than those concurrently observed in venous blood. Arterial levels achieving values of nearly 100 ng/ml have been reported with smokers smoking a single cigarette (Henningfield et al., 1993).

In summary, cigars have the capability to provide high levels of nicotine exposure, whether or not their smoke is inhaled. Furthermore, measures of physiologic response (e.g., Gies, 1921; Bates, 1922a, 1922b), as well as the toxicological consequences of cigar smoking (Chapter 3 and 4), demonstrate that humans can be exposed to high levels of nicotine through their consumption of cigars. On the other hand, the extraordinary variability in cigar nicotine content, the pH of tobacco and tobacco smoke, and inhalation patterns of cigar smokers imply that a wide range of levels of absorption, and potentially of dependence, would be expected to occur.

Drug Addiction: “Drug addiction” is the common term for the various medical and social disorders related to the compulsive ingestion of psychoactive chemicals. The term “drug addiction” is often used interchangeably with the term “drug dependence” even though the term “drug dependence” is the preferred technical term in the scientific and medical literature. In this report, the terms “addiction” and “dependence” will be used interchangeably to refer to the syndrome of drug seeking behavior that meets criteria described in Table 2.

The occurrence of an abstinence-induced withdrawal syndrome may also play a role in the development of drug dependence. A drug withdrawal syndrome reflects an adaptation of behavioral and physiologic processes such that physiologic, cognitive and behavioral functioning are impaired when the drug is no longer present. This effect of drug exposure can complicate the process of achieving and maintaining drug abstinence, and the symptoms

Table 2
1988 Surgeon General’s report criteria for drug dependence (US DHHS, 1988)

Primary Criteria:

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

Additional Criteria:

Addictive behavior often involves:

- stereotypic patterns of use
- use despite harmful effects
- relapse following abstinence
- recurrent drug cravings

Dependence-producing drugs often produce:

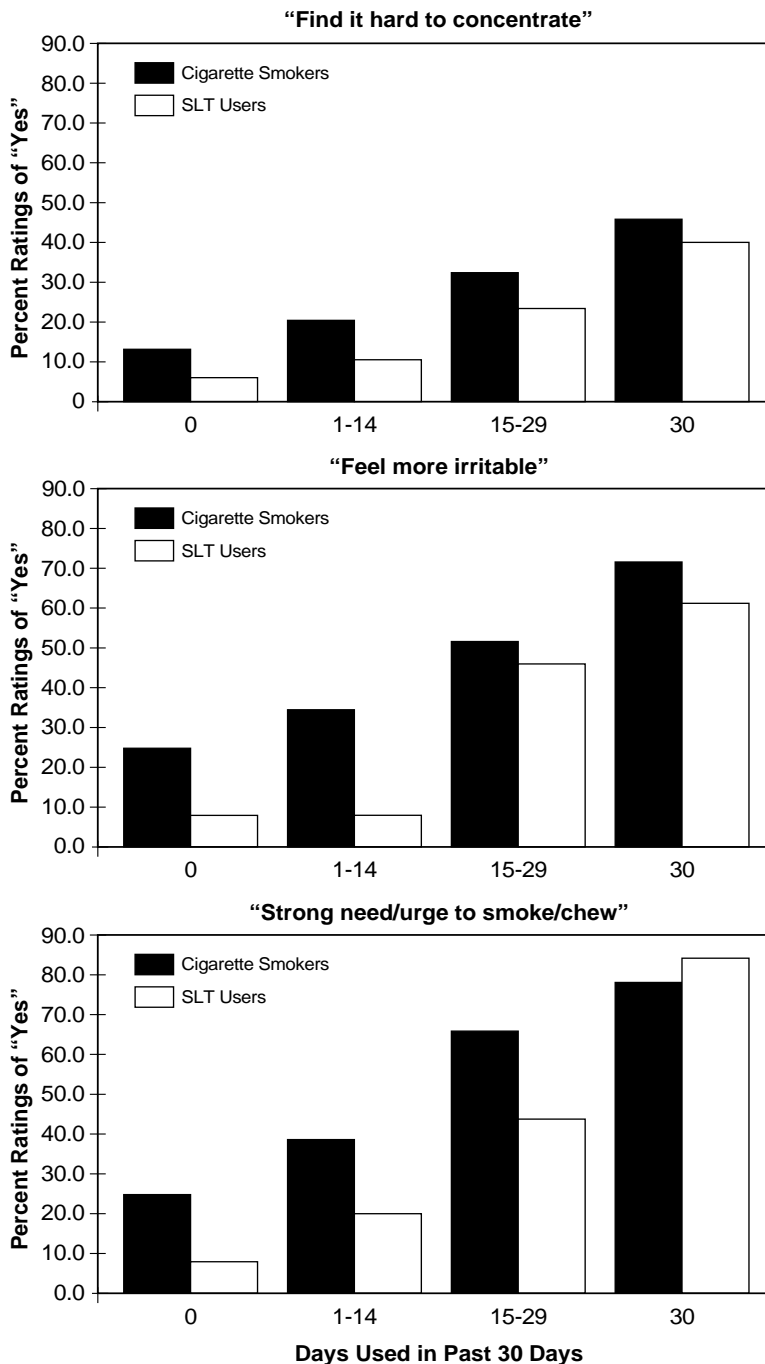
- tolerance
 - physical dependence
 - pleasant (euphoriant) effects
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can be so unpleasant as to precipitate relapse in those who do achieve abstinence (Jaffe, 1985; US DHHS, 1988). Drug addiction can be powerful even in the absence of a withdrawal syndrome, however. In fact, the majority of people monitored in surveys by the National Institute on Drug Abuse who regularly use addictive drugs (including cocaine and marijuana) report that they have not experienced withdrawal, even though many of these people feel dependent and have been unable to maintain abstinence (US DHHS, 1988).

NICOTINE Tolerance to the effects of nicotine is demonstrated by the fact that
DEPENDENCE most cigarette smokers increase their consumption of cigarettes over time. Daily use increases over several years and then stabilizes. Only 10 to 15 percent of cigarette smokers smoke fewer than five cigarettes per day (Shiffman, 1989; Giovino, 1991). Between 1/3 and 1/2 of people that try even one cigarette develop an escalating pattern of use. This rate is much higher than that seen with other addictive drugs (US DHHS, 1994). Current epidemiological data suggest that the majority of adult cigar smokers maintain patterns of intermittent use and smoke fewer cigars per day than is seen in cigarette smokers (Chapter 2).

The extensive studies of time course and symptomology of withdrawal symptoms that have been conducted in cigarette smokers have not been duplicated in cigar smokers; however, several lines of evidence suggest that it may be possible for cigar smokers to develop a similar syndrome of withdrawal. Withdrawal symptoms from cigarettes, which primarily involve lung-delivered nicotine, are generally similar in nature, but higher in magnitude when compared to withdrawal symptoms associated with smokeless tobacco use, which primarily involve buccally-absorbed nicotine (Figure 1) (Centers for Disease Control and Prevention, 1994). A pattern of increasing severity of symptom development with increasing frequency of use is present for use of both cigarettes and smokeless tobacco. Other research on withdrawal from cigars and smokeless tobacco confirms the similarities in withdrawal symptoms across nicotine delivery formulations. However, it appears that formulations which deliver nicotine very slowly (e.g., nicotine patch and smokeless tobacco), or in generally low daily doses (e.g., nicotine gum as typically used), result in weaker syndromes of abstinence-associated withdrawal. Discontinuation of smokeless tobacco results in less reliable and/or weaker syndromes of withdrawal than discontinuation of cigarette smoking (e.g., Hatsukami et al., 1987; Henningfield, et al., 1997). These observations raise the possibility that withdrawal syndromes may be associated with regular heavy cigar smoking (which typically involves less lung exposure to nicotine than cigarette smoking). However, comparisons are complicated by the extraordinarily wide variation in nicotine delivery characteristics across cigars and smoke inhalation patterns of cigar smokers along with the absence of specific data for cigar smokers.

Figure 1
Symptoms of nicotine withdrawal among adolescents and young adults by the number of days of reported use of cigarettes or smokeless tobacco within the past month. Reported withdrawal symptoms significantly increased as a function of days used (Centers for Disease Control and Prevention, 1994).



**FACTORS INFLUENCING
NICOTINE DEPENDENCE**

The level of dependence of nicotine in adults has been found to be inversely related to the age of initiation of smoking when measured by diagnostic criteria of the American Psychiatric Association (Breslau et al., 1992) or by Fagerstrom Tolerance Questionnaire Score (Henningfield, 1987). Because cigars vary so widely in their nicotine dosing characteristics, it is possible for an individual to obtain as much nicotine from one or two cigars with substantial nicotine dosing capacity as from a much larger number of smaller cigars or cigarettes. Because nicotine may be extracted directly from lip contact with the cigar tip itself, the common practice of keeping an unlit cigar in the mouth may also contribute to the total daily nicotine intake of some cigar smokers.

For many people, the process of graduation from first use to addiction is not immediate and can take months or even years (US DHHS, 1988). Initial experiences with tobacco, as with other addictive substances, are often negative, requiring social pressures and other factors to maintain exposure until the addiction develops (Haertzen et al., 1983). Over the course of many months, tolerance develops such that dysphoric subjective effects become minimal and much higher doses are needed to obtain the desired euphoric effects. At that point, mood, behavior, physiologic function, and cognition require the continued presence of nicotine to enable the person to feel normal — the person has become dependent.

With respect to cigarette smoking, 80 to 90 percent of all current cigarette smokers smoke more than five cigarettes and the vast majority of these individuals display symptoms of nicotine dependence. Some individuals who smoke fewer than six cigarettes per day appear able to smoke with a much greater degree of volition and display few symptoms of nicotine withdrawal upon cessation (Shiffman, 1989; US DHHS, 1988).

The proportion of cigar smokers showing clear signs of dependence remains unknown. Lower rates of inhalation in cigar smokers and slower absorption of nicotine through the buccal mucosa suggest that cigar smoking may have a lower potential to induce addiction to nicotine than cigarette smoking. In addition, it is plausible that persons who never had been nicotine dependent and who began smoking cigars in adulthood would be at a lower risk for developing dependence than children and adolescents who take up tobacco use. It does appear that a much higher proportion of adult cigar users compared to adult cigarette smokers are non daily users (Chapter 2).

It has long been observed that drug use that is restricted to occurring only in conjunction with social rituals may be less likely to escalate to patterns of abuse and severe dependence (e.g., Falk, 1983). These observations suggest that cigar smokers who do not begin smoking until adulthood, and who were not formerly nicotine-dependent, and who smoke only in certain settings (e.g., New Year's Eve) might be less likely to escalate their use and become dependent than someone who began smoking at a younger age.

Nicotine polacrilex gum and transdermal patch systems have low abuse liability, in part because rapid absorption is not possible from either nicotine delivery system. (Henningfield and Keenan, 1993; Henningfield and Stitzer, 1991; US DHHS, 1988). Cigar smoke may be inhaled, producing the same virtually instantaneous effects of nicotine delivery produced by cigarette smoking, or cigar smoke may be held in the nose and mouth providing a somewhat slower rate of nicotine absorption as occurs with smokeless tobacco products. Both routes of nicotine delivery are well-documented to lead to dependence and withdrawal with other forms of tobacco use (cigarettes and smokeless tobacco (US DHHS, 1986, 1988).

Henningfield and Keenan (1993) examined the pharmacokinetics of nicotine delivered by different routes of administration as well as the changes in subjective "liking" for the drugs. They found that nicotine delivered intravenously and through cigarette smoke was very rapidly absorbed and produced high scores on a question of subjective "liking" which may be indicative of the abuse liability of the drug (Jasinski et al., 1984). Nicotine delivered transdermally, however, was absorbed slowly and produced very low scores of drug liking, despite the achievement of comparable venous plasma levels. Because nicotine delivery through cigar smoke is primarily through the oral mucosa with delivery through the pulmonary route as well for those who inhale the smoke, it is likely that the delivery kinetics of nicotine may be more comparable to smokeless tobacco which had scores of subjective liking falling somewhere between those of transdermal and cigarette delivery. These observations suggest that the risk of becoming nicotine dependent might be somewhat lower in the cigar smokers as opposed to cigarette smokers.

It is likely that nicotine tolerance and physical dependence to cigars may develop among heavy regular users. However, there would be little basis to expect that substantial levels of physical dependence would be observed in people who rarely smoked on two or more consecutive days. Nicotine has a half-life of approximately 2.5 hours and therefore, smoking a single cigar or smoking with a non-daily frequency would not create a chronic exposure to nicotine. Exposure of at least a few weeks is felt to be necessary to create the degree of physical dependence that would enable substantial withdrawal symptoms to develop upon cessation of use (American Psychiatric Association, 1994). Table 3 gives DSM-IV criteria for nicotine withdrawal. The novice cigar smoker would certainly feel a number of adverse effects during smoking the first cigar, much as a first-time cigarette smoker would. These effects would include the nausea and lightheadedness associated with nicotine administration. After several cigars, however, these effects should dissipate, allowing the cigar smoker to use more of the product.

Table 3

DSM-IV criteria for nicotine withdrawal (American Psychiatric Association, 1994)

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- A. Daily use of nicotine for at least several weeks.
 - B. Abrupt cessation of nicotine use, or reduction in the amount of nicotine used, followed within 24 hours by four (or more) of the following signs:
 - (1) dysphoric or depressed mood
 - (2) insomnia
 - (3) irritability, frustration, or anger
 - (4) anxiety
 - (5) difficulty concentrating
 - (6) restlessness
 - (7) decreased heart rate
 - (8) increased appetite or weight gain
 - C. The symptoms in Criterion B cause significant distress or impairment in social, occupational, or other important areas of functioning.
 - D. The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.
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CONCLUSIONS

1. Cigars contain amounts of nicotine that vary from the amounts contained in a single cigarette to the amount contained in a pack or more of cigarettes. The amount of nicotine is usually proportional to the amount of tobacco contained in the cigar.
2. There is substantial variability in the pH of the tobacco smoke produced by cigars, but most cigars produce smoke that is more alkaline than cigarette smoke. This alkaline pH facilitates nicotine absorption across the oral mucosa and may explain why cigar smokers are less likely to inhale than cigarette smokers.
3. There is sufficient nicotine absorption among regular heavy cigar smokers to expect that nicotine dependence might develop, but studies to document the frequency or intensity of nicotine dependence have not been published.
4. The pattern of cigar use in the population (infrequent use, low number of cigars smoked per day, and lower rates of inhalation compared to cigarette smokers) suggest that cigar use which begins in adulthood may be less likely to produce dependence than cigarette smoking. However, most of the cigar smokers studied began smoking cigars as adults. The current trend of adolescent cigar use generates a concern that prior low adult rates of developing dependence may not apply to cigar use begun during adolescence.

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