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▲ 11.5 Cannabis-Related Disorders

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HISTORY

Cannabis preparations are obtained from the plant *Cannabis sativa*. The cannabis plant has been used by humans in China, India, and the Middle East for approximately 8,000 years for its fiber and as a medicinal agent. Cannabis was introduced to Europeans in the 19th century via Napoleon's troops returning from Egypt and to Britain for medical use by a surgeon who had served in India. Cannabis was mostly used in Europe for fiber and to a lesser extent for therapeutic purposes. There was some recreational use in the Parisian bohemian demimonde in the late 19th century.

Recreational cannabis use was introduced to the United States in the 1930s from Mexico and spread via jazz musicians to cities in the northeastern United States. Its use was banned in the United States in 1938 and in most other countries by international drug control treaties in 1961. It was used in bohemian circles in the United States in the 1940s and 1950s before gradually being disseminated to the wider U.S. youth population in the late 1960s and through the 1970s and 1980s. Its use was disseminated via movies, media, and popular culture to many other developed countries in the 1970s and 1980s.

Cannabis use is still illegal in most developed societies, but it has become a common feature of youth culture, with a declining age of first use among more recent birth cohorts. Cannabis is the most widely used illicit drug worldwide (with approximately 150 million users or 3.7 percent of the world's population 15 years of age and older). It is the fourth most commonly used psychoactive drug in the United States after caffeine, alcohol, and nicotine.

CANNABIS PREPARATIONS

The cannabis plant occurs in male and female forms. The female plant contains the highest concentrations of more than 60 cannabinoids, substances that are unique to the plant. The one that is primarily responsible for the psychoactive effects that are sought by cannabis users is Δ_9-tetrahydrocannabinol (THC). THC is found in a resin that covers the flowering tops and upper leaves of the female plant. Most of the other cannabinoids are either inactive or only weakly active, although they may interact with THC.

The most common cannabis preparations are marijuana, hashish, and hash oil. Marijuana is prepared from the dried flowering tops and leaves of the plant. Its potency depends on the growing conditions, the genetic characteristics of the plant, the ratio of THC to other cannabinoids, and the part of the plant that is used. The flowering tops have the highest THC concentration, with much lower concentrations in the leaves, stems, and seeds. Varieties of cannabis cultivated for hemp fiber usually contain very low levels of THC. Cannabis plants may be grown to maximize their THC production by the "sinsemilla" method, in which only female plants are grown together.

The concentration of THC in marijuana may range from 0.5 to 5.0 percent, whereas the sinsemilla variety may contain 7 to 14 percent THC. The potency of marijuana preparations being sold in the United States has probably increased during the past several decades, although it has not increased 30-fold, as has been claimed in the popular media. Hashish, or hash, consists of dried cannabis resin. It may be light brown to almost black and may contain between 2 and 8 percent THC. Hash oil is obtained by extracting THC from hashish (or marijuana) in oil. Its color may range from clear to pale yellow–green through brown to black. The concentration of the THC in hash oil is between 15 and 20 percent.

METHODS OF USE

Cannabis is typically smoked as marijuana in a hand-rolled cigarette or "joint," which may include tobacco to assist burning. A water pipe, or "bong," is an increasingly popular way of using all cannabis preparations. Hashish may be mixed with tobacco and smoked as a joint or smoked in a pipe with or without tobacco. Because hash oil is extremely potent, a few drops may be applied to a cigarette or a joint or to the mixture in a pipe or the oil can be heated and the vapors inhaled. Whatever preparation or method of smoking is used, smokers typically inhale deeply and hold their breath to ensure maximum absorption of THC by the lungs.

The oral route of administration may also be used. Hashish may be cooked in foods and eaten. In experimental research, THC dissolved in sesame oil is swallowed in gelatin capsules. In India, cannabis may be consumed in the form of "bhang," a tea brewed from the leaves and stems of the plant. Cannabis does not lend itself to injection because THC does not dissolve in water. All but a handful of cannabis users in developed societies smoke cannabis. The chemistry and pharmacology of cannabis dictate that it be smoked. Given the preponderance of smoking as the route of administration, the reader should assume that, unless otherwise stated, cannabis is smoked.

Comparative Nosology

There is a distinction between the use and problematic use of cannabis. The existence of a dependence syndrome, and the nature of problematic cannabis use, has been an area of relatively recent research and a matter of some debate. The most recent editions of the two major diagnostic classification systems, tenth revision of the *International Statistical Classification of Diseases and Related Health Problems* (ICD-10) and the revised fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR), have both included categories (*harmful use* and *abuse*, respectively) that attempt to encapsulate problematic use that does not satisfy criteria for dependence but which is causing the user harm. Both classification systems have a definition of cannabis *dependence*, which is characterized by marked distress resulting by a recurring cluster of problems related to cannabis use that reflect impaired control over cannabis use despite the harms such use may be causing.

Research has suggested that ICD-10 and DSM-IV-TR classification systems agree extremely well in their identification of cases of cannabis dependence. However, each of the diagnostic systems differs slightly in their criteria for harmful use/abuse, and this is reflected in poorer agreement between the two systems on the classification of cases with respect to this diagnosis.

Epidemiology of Cannabis Use

In the United States, two major surveys of illicit drug use have been undertaken since the early 1970s. The Monitoring The Future project has surveyed

Table 11.5–1
Prevalence of Cannabis Use per 100 per Year According to the U.S. National Household Survey on Drug Abuse (2000)

Age (Yrs)	Lifetime Use	Past 12 Mos Use	Past Mo Use
12–17	18.3	13.4	7.2
18–25	45.7	23.7	13.6
26+	34.4	5.0	3.0
Total	34.2	8.3	4.8

Table 11.5–3
Prevalence of Cannabis Use per 100 per Year in the 2001 U.S. Monitoring the Future Survey

Age	Lifetime Use	Past 12 Mos Use	Past Mo Use	Past Mo Daily Use
8th grade (12 yrs)	20.4	15.4	9.2	1.3
10th grade (14 yrs)	40.1	32.7	19.8	4.5
12th grade (18 yrs)	49.0	37.0	22.4	5.8
College	51.2	34.0	20.0	4.6
19–28 yrs	55.1	27.9	16.1	4.2

nationwide samples of high school seniors, college students, and young adults annually since 1975. The National Household Survey on Drug Abuse (sponsored by the National Institute on Drug Abuse [NIDA]) has surveyed household samples of adults throughout the United States since 1972.

NIDA has surveyed approximately 9,000 people 12 years of age and older in randomly selected households throughout the United States every 2 to 3 years since 1972. The survey has been conducted annually since 1991 with a sample of more than 30,000 participants.

In 2000, 34 percent of the U.S. national sample reported that they had used cannabis, 8 percent had used in the past year, and 5 percent were current users (Table 11.5–1). Lifetime use increased from 18 percent among those aged 12 to 17 years to 46 percent among those aged 26 to 34 years before declining to 34 percent among those older than the age of 35 years. Rates of discontinuation of use were high: More than two-thirds of men and three-fourths of women who had used cannabis at some time in their lives had not used it in the last year. Monthly cannabis use was more common among men (19 percent) than women (13 percent) and most common among those aged 18 to 25 years (14 percent) (Table 11.5–1).

The NIDA household survey series from 1974 to 2000 (Table 11.5–2) shows that rates of past-month cannabis use increased throughout the 1970s, peaked in 1979, and declined steadily throughout the 1980s to reach their lowest level in 1992 before increasing again in 1995.

In the Monitoring the Future project, the prevalence of cannabis use has been estimated among secondary school students, college students, and young adults (Table 11.5–3). Since 1975, approximately 15,000 high school seniors have been surveyed. The samples of college students and young adults who are surveyed each year represent a sample of those who were originally surveyed as high school seniors (approximately 14 percent) and have been followed up every 2 years. Since 1991, national samples of eighth- and tenth-grade students have also been annually surveyed.

In the 2000 survey, lifetime cannabis use increased with each older age group, but use in the past year reached a plateau in the 18- (last year of high school) to 28-year age group. Daily use peaked at 18 years of age, with 6 percent of high school seniors and 4.2 percent of 19- to 28-year-olds reporting daily cannabis use. This is much lower than the 11 percent of high school seniors in the peak year of 1978 who reported such use.

In 1982, 21 percent of the 12th graders reported that they had smoked cannabis daily for 1 month or more. This decreased to 8 percent by 1992. Daily use has been consistently higher among males than females and among those not planning to attend college. More than one-half of those who were daily users by 18 years of age began this pattern of heavy use by 16 years of age.

There have been long waves of consumption in cannabis use among American adolescents since 1975. Among 18-year-olds, lifetime prevalence peaked at 65 percent in 1980, then fell by nearly one-half by the early 1990s. Use in the past year peaked at 51 percent in 1979 and fell to 22 percent by 1992. The rate of discontinuing use also decreased (Table 11.5–4), with few of those who had used cannabis ten or more times ceasing use by 18 years of age. Most of those who ceased cannabis use had not had a great deal of experience with cannabis. The time trends in cannabis use were different from those of other drugs, suggesting that the changes in cannabis use reflected factors specific to that drug. Whereas most users of other illicit drugs also had used cannabis, trends in the use of other illicit drugs were independent of the cannabis-use trends.

After more than a decade of decreasing rates of cannabis use among American secondary students, the 1992 and 1993 surveys showed that cannabis use began to increase sharply among eighth, tenth, and 12th graders and, to a lesser extent, among college students and young adults. There was an increasing initiation rate and a higher rate of continued use. Lloyd Johnston and colleagues have argued that changes in beliefs about the risks of cannabis use were responsible for the reduction in use between 1979 and 1991 and for

Table 11.5–2
Trends in Past Month Cannabis Use (U.S. National Household Survey on Drug Abuse 1974 to 2000)

Age (Yrs)	1974	1976	1977	1979	1985	1988	1990	1992	1995	1996	1999	2000
12–17	12.0	12.3	16.6	16.3	13.2	8.1	7.1	5.3	10.9	9.0	7.2	7.2
18–25	25.2	25.0	27.4	38.0	25.3	17.9	15.0	13.1	14.2	15.6	14.2	13.6
26+	2.0	3.5	3.3	—	—	—	—	—	—	—	2.8	3.0
26–34	—	—	—	20.8	23.1	14.7	10.9	11.4	8.3	8.4	—	—
35+	—	—	—	2.8	3.9	2.3	3.1	2.5	2.8	2.9	—	—

Note: Numbers are per 100 per year.

Table 11.5–4
Trends in Cannabis Use among Those in Year 12 (U.S. Monitoring the Future Study 1999)

Year	Lifetime Use	Past 12 Mos Use	Discontinuation Rate among Those Who Had Used Cannabis	
			Ever	10+ Times
1975	47	40	15	4
1980	60	49	19	5
1985	54	41	25	8
1990	41	27	34	12
1992	33	22	33	11
1993	45	36	20	8

Note: Numbers are per 100 per year.

the increase in use since 1992. They reported a strong negative correlation over time between the rates of cannabis use and the perceived risk of using cannabis and peer disapproval of use. Between 1979 and 1992, a marked increase in perceived risk and a smaller increase in personal disapproval of use preceded a large decrease in rates of use. Johnston et al. attributed the sharp upturn in cannabis use after 1992 to a preceding decline in perceived risk.

Only a small proportion of cannabis users use the drug for several years or more. The daily or near-daily use pattern over a period of years is the pattern with the greatest risk of experiencing adverse health and psychological consequences. Daily cannabis users are more likely to be male and less well educated; they are also more likely to regularly use alcohol and to have experimented with a variety of other illicit drugs, including amphetamine and other psychostimulants, hallucinogens, sedatives, and opioids.

Correlates of Cannabis Use

Age First use of cannabis typically begins in the teens, and the heaviest rates of use occur in the early 20s. Rates of cannabis use remain relatively high during the early 20s but decline thereafter. The majority of young adults who experiment with cannabis have done so by 18 years of age and rates of use decline steadily from the mid 20s into the early 30s.

Gender Rates of cannabis use in the lifetime, the past year, and the past week are consistently higher among men than women. Daily use and long-term daily use are much more common among men.

Income A positive relationship has been found between income in adolescence and early adult life and cannabis use, with those earning more money more likely to report cannabis use. In the United States, daily cannabis use is positively correlated with income and hours worked on a paid job.

Socioeconomic Status The relationship between cannabis use and socioeconomic status (SES) is weak. Higher rates of cannabis use are sometimes found among lower SES individuals, but in the past two decades, there has been no relationship between parents' education and cannabis use among 12th-grade students in the United States, with the exception that the group with lowest parental education had slightly lower cannabis use than the others. That difference may be better explained by differences in income during adolescence rather than by social class.

Ethnicity Information on the relationship between ethnicity and cannabis use is limited. Ethnic differences in one country may not generalize to others, and small sample sizes often make ethnic comparisons unreliable. Even in the very large Monitoring the Future survey, samples from several years have to be combined to make reliable comparisons between the three largest ethnic groups. These show that black students have lower rates of use in all grades than white or Hispanic students. Hispanics, on the other hand, tend to have the highest rates of use in the early grades, before the rates of school drop-out increase.

Availability In general, the more freely available a drug is, the higher its use in the population. This hypothesis has been broadly supported in the case of alcohol consumption, in which the larger the number of licensed outlets and the longer the hours of trading, the higher the levels of community alcohol consumption and alcohol-related problems. There is very little evidence to rigorously test this hypothesis in the case of cannabis use. Self-reports from surveys on how easy it is to obtain cannabis have shown very little change over long periods during which rates of cannabis use have increased and decreased in the United States.

Pharmacology of Cannabinoids

Laboratory research on animals and humans has demonstrated that the primary psychoactive constituent in cannabis is THC and its metabolites. THC acts on specific receptors or molecules in the brain and immune system. These receptors are found in areas of the brain that underlie the psychoactive and other effects of cannabis use. Two "endogenous," or naturally occurring, molecules have been discovered in the brain and body that bind to the cannabinoid receptor and mimic the action of THC.

A typical joint of between 0.5 and 1.0 g of cannabis plant contains between 5 and 150 mg of THC. Twenty to 70 percent of the THC is found in the smoke that reaches the lungs; the rest is burnt and lost in side-stream smoke. Only 5 to 24 percent of THC in the joint reaches the bloodstream when cannabis is smoked. Two to 3 mg of THC produces a brief high in an occasional user, and a single joint may provide enough THC for two or three such individuals. A heavy cannabis smoker may use five or more joints per day, whereas heavy users in Jamaica, for example, may consume up to 420 mg of THC per day.

Different methods of using cannabis lead to differing absorption, metabolism, and excretion of THC. When smoked, THC is absorbed from the lungs into the bloodstream within minutes. It is first metabolized in the lungs and then in the liver. The metabolite 9-carboxy-THC is detected in blood within minutes of smoking. Peak blood levels of THC are usually reached within 10 minutes of smoking and decrease to approximately 5 to 10 percent of their initial level within 1 hour. This rapid decline reflects the rapid conversion of THC to its metabolites and the distribution of THC to fatty tissues, including the brain.

When swallowed, THC takes 1 to 3 hours to enter the bloodstream, delaying the onset of psychoactive effects. Another metabolite, 11-hydroxy-THC, which is 20 percent more potent than THC, is found in high concentrations after being swallowed.

THC and its metabolites are highly fat soluble, so they may remain in the fatty tissues of the body for long periods. THC and its metabolites accumulate in the body because of their slow rate of clearance. They may be detected in the blood for several days and traces may persist for several weeks. THC may be stored in body fat for more than 28 days.

It has been claimed that the medical literature underestimates the adverse health effects of cannabis because it is based on research

conducted on less potent forms of cannabis than have become available in the past decade. The evidence suggests that the average potency of cannabis has increased but not to the extent often claimed. Changes in patterns of cannabis use, with earlier age of first use and more regular use of more potent forms of cannabis, have probably been more important in increasing average dose of THC than any increase in the THC content of cannabis plants.

DIAGNOSTIC AND CLINICAL FEATURES

Cannabis Dependence For much of the 1960s and 1970s, cannabis was not regarded as a drug of dependence because it did not seem to produce tolerance or a withdrawal syndrome such as that seen in alcohol and opioid dependence. Views changed in the late 1970s and early 1980s with the adoption of a broader conception of drug dependence. This new conception reduced the emphasis on tolerance and withdrawal and placed more emphasis on the compulsion to use, a narrowing of the drug-using repertoire, rapid reinstatement of dependence after abstinence, and the high salience of drug use in the user's life.

Drug Dependence in DSM-IV-TR "The essential feature of Substance Dependence is a cluster of cognitive, behavioral and physiologic symptoms indicating that the individual continues use of the substance despite significant substance-related problems." A diagnosis of substance dependence is made if *three or more* of the following criteria occur at any time in the same 12-month period:

- Tolerance, as defined by either of the following:
  - Need for markedly increased amounts of the substance to achieve intoxication or desired effect
  - Markedly diminished effect with continued use or the same amount of the substance
- Withdrawal, as manifested by either of the following:
  - The characteristic withdrawal syndrome for the substance
  - The same (or closely related) substance is taken to relieve or avoid withdrawal symptoms
- The substance is often taken in larger amounts or over a longer period than was intended.
- There is a persistent desire or unsuccessful efforts to cut down or control substance use.
- A great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors, driving long distances), use the substance (e.g., chain smoking), or recover from its effects.
- Important social, occupational, or recreational activities are given up or reduced because of substance use.
- The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.

DSM-IV-TR *substance abuse* is defined as:

- A. A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring within a 12-month period:
  - Recurrent substance use resulting in failure to fulfill major role obligations at work, school, or home
  - Recurrent substance use in situations in which it is physically hazardous (e.g., driving while intoxicated)
  - Recurrent substance-related legal problems
  - Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance
- B. The symptoms have not met criteria for substance dependence.

The Epidemiological Catchment Area (ECA) study estimated that 4.4 percent of the U.S. population had a diagnosis of cannabis abuse or dependence according to DSM-III criteria. One-third of those with lifetime cannabis abuse or dependence (38 percent) reported problems with cannabis use in the last year. Men had a higher risk of cannabis dependence than women, with the highest risk among 18- to 29-year-olds.

The most common symptoms reported by those who were cannabis dependent were requiring larger amounts (21 percent), having psychological (21 percent) or social (17 percent) problems attributed to cannabis, and inability to reduce use (8 percent). Few reported health problems (5 percent) or withdrawal sickness (3 percent). Surveys using similar methods to the ECA have produced similar estimates of the rate of cannabis dependence in Canada and New Zealand.

The National Comorbidity Survey (NCS) conducted in the United States between 1990 and 1992 found that 4.2 percent of adults met DSM-III-R criteria for cannabis dependence at some time in their lives. The proportion of people who had ever used cannabis who met criteria for cannabis dependence was 9 percent.

Risk of Cannabis Dependence People who use cannabis daily over weeks to months are most likely to become dependent. Approximately one in three daily cannabis users meet DSM-III criteria for dependence. The risk of dependence among less frequent users of cannabis is lower. In the ECA study, 17 percent of those who used cannabis more than five times met DSM-III criteria for dependence at some time in their lives. In the National Comorbidity Study, the proportion of people who had ever used alcohol, amphetamines, cannabis, cocaine, heroin, nicotine, and sedatives who met DSM-III-R criteria for dependence on each drug at some time in their lives was 32 percent for nicotine, 23 percent for heroin, 15 percent for alcohol and cocaine, and 9 percent for cannabis.

These estimates suggest the following rules of thumb about the risks of cannabis dependence. For those who have ever used cannabis, the risks of developing dependence are probably of the order of one chance in ten. Among those who use the drug more than a few times, the risk of developing dependence is from one in five to one in three. As a rule, the more often cannabis has been used and the longer it has been used, the higher the risk of dependence.

The following factors also predict a higher risk of regular involvement with cannabis: poor academic achievement, deviant behavior in childhood and adolescence, nonconformity and rebelliousness, personal distress and maladjustment, poor parental relationships, earlier use, and a parental history of drug and alcohol problems.

Clinical Populations Cannabis-dependent people seek help with cannabis-related problems in Australia, the United States, and Europe. In Australia, the proportion of cases in which cannabis was the *main* drug problem increased from 4 percent in 1990 to 7 percent in 1995. Between 1994 and 1998, cannabis was the primary drug of abuse for between 11 and 26 percent of clients of treatment agencies in the United States. Cannabis was the primary drug problem for between 2 and 16 percent of clients attending treatment agencies in the European Union in 1998.

A Swedish treatment program reported that its clients typically complained of unsuccessful attempts to stop or moderate use and frequent (often daily) intoxication despite having adverse effects connected with their cannabis use. These included sleeplessness, depression, impaired concentration and memory, and blunting of emotions.

Common symptoms among people seeking help to cease cannabis use include an inability to stop using (93 percent), feeling bad

about using cannabis (87 percent), procrastinating (86 percent), loss of self-confidence (76 percent), memory loss (67 percent), and withdrawal symptoms (51 percent). Similar experiences have been reported among users in recent U.S. and Australian studies of interventions for problem cannabis use. In the Australian study, among 180 long-term cannabis users seeking help, the most common symptoms were withdrawal and use to relieve withdrawal.

Cannabis Intoxication The main reason why most young people use cannabis is to experience a "high": mild euphoria; relaxation and perceptual alterations, including time distortion; and the intensification of ordinary experiences such as eating, watching films, listening to music, and engaging in sex. When used in a social setting, the "high" may be accompanied by infectious laughter, talkativeness, and increased sociability. Cognitive changes include impaired short-term memory and attention. These make it easy for the user to become lost in pleasant reverie and difficult to sustain goal-directed mental activity. Motor skills, reaction time, motor coordination, and many forms of skilled psychomotor activity are impaired while the user is intoxicated.

Cannabis Intoxication Delirium Psychotic symptoms, such as delusions and hallucinations, are very rare experiences that may occur at very high doses of THC and perhaps in susceptible individuals at lower doses.

High doses of THC have been reported to produce visual and auditory hallucinations, delusional ideas, and thought disorder in normal volunteers. In traditional cannabis-using cultures, such as India, a "cannabis psychosis" has been reported in which the symptoms are preceded by heavy cannabis use and remit after abstinence.

The existence of a cannabis psychosis in Western cultures is still a matter of debate. In its favor are case series of cannabis psychoses and a small number of controlled studies that report characteristic differences between the symptoms of cannabis psychoses and those of psychoses in individuals who were not using cannabis at the time of hospital admission. Critics of the hypothesis emphasize the fallibility of clinical judgments about etiology, the poorly specified criteria used in diagnosing these psychoses, the dearth of controlled studies, and the striking variations in the clinical features assigned to cannabis psychoses.

Cannabis and Schizophrenia There is clinical and epidemiological evidence of an association between schizophrenia and cannabis use that suggests that cannabis use can precipitate schizophrenia or exacerbate its symptoms. But this is not the only explanation of the association: People with schizophrenia may use cannabis as a form of self-medication, or there may be other variables that explain both, such as cannabis use being a marker of other psychotogenic drug use or of vulnerability to schizophrenia.

There is good clinical and epidemiological evidence that cannabis use exacerbates the symptoms of schizophrenia in affected individuals. This includes the findings of a number of prospective studies that have controlled for confounding variables. It is also a biologically plausible relationship. Psychotic disorders involve disturbances in the dopamine neurotransmitter systems because drugs that increase dopamine release produce psychotic symptoms when given in large doses, and neuroleptic drugs that reduce psychotic symptoms also reduce dopamine levels. Cannabinoids, such as THC, increase dopamine release.

There is good prospective evidence from a Swedish conscript study that cannabis use precipitates schizophrenia in people who are vulnerable because of a personal or family history of schizophrenia. This hypothesis is consistent with the stress-diathesis model of schizophrenia in which the likelihood of developing schizophrenia is the product of stress acting on a genetic "diathesis" to develop schizophrenia. The Swedish findings have recently been confirmed in a further follow-up of the original cohort and in four other prospective studies in Israel, The Netherlands, and New Zealand. All of these studies have been able to better control for the most plausible alternative explanations of the relationship between cannabis use and schizophrenia than the original Swedish study. These studies provide strong support for the hypothesis that cannabis use, especially early-onset use, can precipitate schizophrenia in susceptible individuals.

Although it is likely, there is very little direct evidence that genetic vulnerability increases the risk that cannabis users develop psychosis. In one British study, people with a history of heavy cannabis use who developed a psychosis were ten times more likely to have a family history of schizophrenia than people with a psychosis who had not used cannabis. It is difficult to identify a genetic diathesis in the majority of cases of schizophrenia because 81 percent of people with schizophrenia do not have a first-degree relative with the disorder, and 63 percent do not have an affected first- or second-degree relative.

It seems likely that cannabis use can precipitate schizophrenia in vulnerable cases, but it is more contentious whether cannabis use can cause schizophrenia that would not otherwise have occurred. One cannot rule this possibility out, but it is unlikely to account for more than a minority of cases. Most of the 274 Swedish conscripts who developed schizophrenia had not used cannabis, and, at most, 7 percent of cases of schizophrenia could be attributed to cannabis use. Moreover, the *treated* incidence of schizophrenia, and particularly of early-onset acute cases, has declined (or remained stable) during the 1970s and 1980s when cannabis use increased among young adults in Australia and North America. Although there are complications in interpreting such trends, a large reduction in treated incidence has been observed in a number of countries, although cannabis use has increased.

Cannabis-Induced Anxiety Disorder Some users report unpleasant experiences after using cannabis. These include anxiety, panic, a fear of going mad, and depression. These are often reported by users who are unfamiliar with the effects of cannabis and by some patients given THC for therapeutic reasons. More experienced users may report these effects after swallowing cannabis because its effects may be more pronounced and of longer duration than they usually experience after smoking.

The most immediate effect of smoking cannabis is an increasing heart rate by 20 to 50 percent within a few minutes to one-quarter of an hour of smoking cannabis. Changes in blood pressure also occur. These depend on posture: Blood pressure is increased while the person is sitting and decreases while they are standing. A sudden change from lying down to standing up may produce postural hypotension and a feeling of "light-headedness" and faintness that is often the earliest indication of intoxication in naïve users. In healthy young users, these cardiovascular effects are unlikely to be of any clinical significance. They may amplify anxiety if the cannabis-induced palpitations and feeling faint are misinterpreted as symptoms of serious misadventure.

Withdrawal and Tolerance Tolerance to many of the behavioral and physiological effects of THC has been demonstrated in humans and animals. The precise mechanisms are unknown, but they probably involve changes in cannabinoid receptor function.

Early case reports of cannabis withdrawal symptoms in humans have been supported by abstinence symptoms in laboratory studies. Studies in clinical and nonclinical samples of long-term cannabis users have reported withdrawal symptoms such as anxiety, insomnia, appetite disturbance, and depression.

Regular cannabis users who are abruptly withdrawn from cannabis after 2 weeks on high doses of oral THC have complained within 6 hours of "inner unrest," and after 12 hours, they reported "irritability, insomnia, and restlessness," which were also observed by staff. These symptoms were correlated with THC dose and frequency of use and were reduced after using cannabis. Similar symptoms have been reported during the first week of abstinence in subjects who had received 210 mg of smoked cannabis a day for 4 weeks. Recent laboratory studies have reported withdrawal symptoms at much lower doses of THC given orally and by smoking. The most common symptoms were anxiety, depression, and irritability.

A controlled prospective study has been done on withdrawal symptoms among chronic cannabis users who were assessed daily on various withdrawal symptoms while in a hospital ward for 28 days. Their ratings of mood, anxiety, depression, and irritability were compared with those of two control groups of abstinent former heavy cannabis users and nonusers of cannabis. During the course of the 28 days, the chronic cannabis users showed decreases in mood and appetite; increases in irritability, anxiety, physical tension, and physical symptoms; and increased scores on the Hamilton Depression and Anxiety scales. These appeared within 24 hours and were most marked in the first 10 days, although the increase in irritability and physical tension persisted throughout the 28-day observation period.

Research using the cannabinoid antagonist SR 141716A (which immediately reverses the effects of THC) has shown that a withdrawal syndrome can be produced in rats, mice, and dogs that have been maintained on THC. The antagonist produces compressed and accentuated symptoms that are much more dramatic than the milder and more prolonged symptoms that occur under usual conditions of human use. The relatively long half-life and complex metabolism of cannabis may also result in a less intense withdrawal syndrome than drugs such as opiates.

Cannabis Disorders Not Otherwise Specified

Amotivational Syndrome The evidence that chronic heavy cannabis use produces an amotivational syndrome consists largely of case studies. Controlled field and laboratory studies have not found evidence for such a syndrome, although their value is limited by the small sample sizes and limited sociodemographical characteristics of participants of the field studies, the short periods of drug use, and the youth, good health, and minimal demands made of the volunteers in the laboratory studies. If there is such a syndrome, it is a relatively rare occurrence even among heavy, chronic cannabis users. The phenomenon may be better explained as the result of chronic intoxication in dependent cannabis users.

Cognitive Impairment The fact that cannabis use acutely impairs cognitive functioning has raised the reasonable concern that chronic use may produce cognitive impairment. The available evidence, however, suggests that the long-term heavy use of cannabis does not produce any severe or grossly debilitating impairment of cognitive function. There is no evidence, for example, that it produces anything comparable to the cognitive impairments found in chronic heavy alcohol drinkers; if it did, research to date should have detected it.

There is more recent clinical and experimental evidence, however, that the long-term use of cannabis may produce more subtle forms of cognitive impairment in the higher cognitive functions of memory, attention, and organization and in the integration of complex information. This evidence suggests that the longer the period of heavy cannabis use, the more pronounced the cognitive impairment. Nonetheless, because the impairments in performance are subtle, it remains to be determined how significant they are for everyday functioning. It also remains to be investigated whether these impairments can be reversed after an extended period of abstinence from cannabis.

A suspicion that chronic heavy cannabis use may cause gross structural brain damage was raised by a single poorly controlled study using an outmoded method of investigation, which reported that cannabis users had enlarged cerebral ventricles. Since then, a number of better-controlled studies using more sophisticated methods of investigation have consistently failed to demonstrate evidence of structural change in the brains of heavy, long-term cannabis users. These negative results are consistent with the evidence that any cognitive effects of chronic cannabis use are subtle and unlikely to manifest as gross structural changes in the brain.

Effects on Adolescent Development Cross-sectional and longitudinal studies of adolescents in the 1970s and 1980s indicate that chronic heavy cannabis use may adversely affect adolescent development in a number of ways. Interpretation of this evidence is complicated by the fact that many of the indicators of adverse development that have been attributed to cannabis use precede its use and make it more likely that a young person will use cannabis. These include minor delinquency, poor educational performance, nonconformity, and poor adjustment.

Among American adolescents in the 1970s and 1980s, the typical sequence of initiation into drug use was that the use of alcohol and tobacco preceded the use of cannabis, which, in turn, preceded the use of hallucinogens, amphetamines, and the later use of heroin and cocaine. Generally, the earlier the age of first use and the greater the involvement with any drug in the sequence, the more likely a young person was to use the next drug in the sequence.

The explanation of cannabis' role in this sequence remains contested. The evidence for the hypothesis that cannabis use has a pharmacological effect that increases the risk of using later drugs in the sequence is, at present, not compelling. More plausible hypotheses are that the sequence of drug involvement reflects a combination of the early recruitment into cannabis use of nonconforming and deviant adolescents who are likely to use alcohol, tobacco, and illicit drugs; a genetic vulnerability to become dependent on a range of substances; and socialization of cannabis users within an illicit drug–using subculture that increases the exposure, opportunity, and encouragement to use other illicit drugs. Recent prospective studies that have controlled for many of these factors have failed to eliminate the apparent "gateway effect" of cannabis.

In cross-sectional surveys of young people, cannabis use is associated with the inability to complete a high school education and with job instability in young adulthood. The complication is that those who are most likely to use cannabis have lower academic aspirations and poorer school performance *before* using cannabis than those who do not. When these differences are taken into account, the relationship between cannabis use and educational and occupational performance is much more modest. Even so, the adverse effects of cannabis and other drug use on educational performance are important because they further impair poor performance, and level of education affects choice of occupation, level of income, choice of mate, and quality of life.

There is also suggestive evidence that heavy cannabis use has adverse effects on family formation, mental health, and involvement

in drug-related (but not other types of) crime. In the case of each of these outcomes, the apparently strong associations revealed in cross-sectional data are much more modest in longitudinal studies that control for associations between cannabis use and other variables that predict these adverse outcomes.

Flashbacks There are a small number of case reports of cannabis "flashbacks"—that is, experiencing symptoms of cannabis intoxication days or weeks after the individual last used cannabis. Because of their rarity and the fact that many affected individuals have also used other drugs, it is difficult to draw any conclusions about the relationship between these symptoms and cannabis use. It is often difficult to decide whether these are rare events that are coincidental with cannabis use; the effects of other drugs that are often taken together with cannabis; rare consequences of cannabis use that only occur at doses that are much higher than those used recreationally or that require unusual forms of personal vulnerability; or the results of interactions between the cannabis and other drugs.

ADVERSE EFFECTS OF CANNABIS USE

Psychomotor Effects and Driving Cannabis intoxication impairs a wide range of cognitive and behavioral functions that are involved in driving an automobile or operating machinery. The effects are generally larger, more consistent, and more persistent in tasks that require sustained attention. Recreational doses of THC produce similar performance impairments in laboratory tests and standardized driving courses to blood alcohol concentrations of between 0.07 and 0.10 percent.

It has been difficult to estimate how these impairments affect the risk of being involved in motor vehicle accidents. Studies of the effect of cannabis on driving performance on the road have found only modest impairments because cannabis-intoxicated drivers drive more slowly and take fewer risks than alcohol-intoxicated drinkers. Cannabis users seem to be more aware of their psychomotor impairment than alcohol users.

Cannabinoids are found in between 4 and 37 percent of blood samples of accident victims, but these findings are difficult to evaluate for the following reasons. First, it has been difficult to decide whether people with cannabinoids are overrepresented among accident victims because it is not known how often cannabinoids are found in the blood of people who are *not* involved in accidents. Second, cannabinoids in blood indicate recent use, but they do not necessarily mean that the driver was intoxicated at the time of the accident. Third, many drivers with cannabinoids in their blood also have high blood alcohol levels, making it difficult to separate the effects of cannabis on accident risk from those of alcohol. Laboratory studies have suggested, however, that the separate effects of alcohol and cannabis on psychomotor impairment and driving performance are approximately additive.

There is recent evidence from controlled epidemiological studies that cannabis users are two times more likely to be involved in motor vehicle or other accidents than nonusers. This evidence is not yet as strong as comparable evidence for alcohol use, for which there are more case-controlled studies showing that people intoxicated by alcohol are overrepresented among accident victims. Cannabis users who also use alcohol are even more highly overrepresented among the victims of motor vehicle accidents.

Cardiovascular System A few minutes to one-quarter of an hour after cannabis is smoked or swallowed, THC increases heart rate by 20 to 50 percent. This may last for up to 3 hours. Blood pressure is increased while the person is sitting and decreases on standing. In healthy young users, these cardiovascular effects are unlikely to be of any clinical significance because tolerance develops to the effects of THC, and young, healthy hearts are only mildly stressed. These effects may pose more of a risk to patients with heart disease.

The acute toxicity of cannabis, and cannabinoids generally, is very low. There are no cases of fatal cannabis poisoning in the human medical literature. Animal studies indicate that the dose of THC required to produce 50 percent mortality in rodents is extremely high in comparison with other pharmaceutical and recreational drugs. The lethal dose also increases as one moves up the phylogenetic tree, suggesting that the lethal dose in humans could not be achieved by smoking or swallowing cannabis.

The changes that cannabis causes in heart rate and blood pressure are unlikely to harm healthy young adults, but they may be less benign in patients with hypertension, cerebrovascular disease, and coronary atherosclerosis in whom cannabis smoking may pose a threat because it increases the work of the heart. The seriousness of these effects will be determined as the cohort of chronic cannabis users of the late 1960s enters the age of maximum risk for atherosclerosis in the heart, brain, and peripheral blood vessels. A recent study of the relationship between cannabis use and myocardial infarction suggests that the acute cardiovascular effects of cannabis may be life-threatening in middle-aged adults with heart disease.

Respiratory System Regular cannabis smoking impairs the functioning of the large airways and causes symptoms of chronic bronchitis such as coughing, sputum, and wheezing. Given that tobacco and cannabis smoke contain similar carcinogenic substances and that tobacco smoke has adverse effects on the respiratory system, it is likely that chronic cannabis use also increases the risks of respiratory cancer. There is evidence that chronic cannabis smoking produces histopathological changes in lung tissues of the type that precede the development of lung cancer. Concern about the possibility of cancers caused by chronic cannabis smoking has been raised by case reports of cancers of the aerodigestive tract in young adults with a history of heavy cannabis use. A recent case-controlled study has provided the first suggestion of an increased risk of aerodigestive tract cancers among cannabis smokers.

Cellular Effects and Cancers There is weak evidence that THC can alter cell metabolism and deoxyribonucleic acid (DNA) synthesis in the test tube. There is stronger evidence that cannabis *smoke* produces mutations in cells in the test tube and in live animals and, hence, is a potential cause of cancer. Cannabis smoke contains many of the same carcinogenic substances as cigarette smoke. If cannabis smoking causes cancer, it is most likely to be cancers of the lung and upper aerodigestive tract, which are maximally exposed to cannabis smoke.

Aerodigestive tract cancers have been reported among young adults who have been daily cannabis users, and a case-controlled study has found an association between cannabis smoking and head and neck cancer. A prospective cohort study of 64,000 adults did not find an increased incidence of head and neck or respiratory cancers, but it found increased rates of prostate cancer. The relative youth of the participants and their low rates of regular cannabis use may have reduced the ability of this research to detect an increase in respiratory cancers. Further studies are needed to clarify the issue.

There is much weaker evidence for an increased risk of cancers among children born to women who smoked cannabis during pregnancy. Three studies of very different types of cancer have reported an association with maternal cannabis use. None of these was a

planned study of the role of cannabis use in these cancers, so replication of their results is required. There have not been any increases in the rates of these cancers that parallel increased rates of cannabis use over the past three decades.

Immunological Effects Cannabinoids impair cell-mediated and humoral immunity in rodents and reduce resistance to infection by bacteria and viruses in animals. Cannabinoid receptors are expressed in cells of the immune system in animals and humans, although the significance of this for immune function is unclear. Cannabis smoke also impairs the functioning of alveolar macrophages, the first line of the body's immune defense system in the lungs. The clinical relevance of these findings is uncertain because the doses required to produce these effects have been very high, and extrapolation to the doses used by humans is complicated by the fact that tolerance may develop to these effects.

The limited experimental and clinical evidence in humans suggests that the adverse effects seen in animals are not replicated in humans. There is no conclusive evidence that cannabinoids impair immune system function in humans, as measured by T lymphocytes, B lymphocytes or macrophages, or immunoglobulin levels. There is suggestive evidence that THC impairs T-lymphocyte responses to mitogens and allogenic lymphocytes.

The clinical and biological significance of these possible effects in chronic cannabis users is uncertain. There is no epidemiological evidence of increased rates of disease among chronic heavy cannabis users, and several large prospective studies of human immunodeficiency virus (HIV)–positive homosexual men have found that cannabis use does *not* increase the risk of progression to acquired immune deficiency syndrome (AIDS).

Reproductive Effects Chronic administration of THC disrupts male and female reproductive systems in animals, reducing testosterone secretion and sperm production, motility, and viability in males and disrupting the ovulatory cycle in females. It is uncertain whether cannabis use has these effects in humans because of the inconsistency in the limited literature on human males and the lack of research in the case of human females. There is uncertainty about the clinical significance of these effects in normal healthy young adults.

It is likely that cannabis use during pregnancy impairs fetal development, leading to smaller birth weight, perhaps as a consequence of shorter gestation and probably by the same mechanism as cigarette smoking. There is no clear evidence that cannabis use during pregnancy increases the risk of birth defects as a result of exposure of the fetus to cannabis in the uterus.

There is some evidence that infants exposed to cannabis in the uterus may show transient behavioral and developmental effects during the first few months after birth. These effects are small in comparison to those caused by tobacco use during pregnancy and have not been observed in all studies. The evidence for this consequence of cannabis use is still weak.

LABORATORY EXAMINATION

It is possible to detect cannabinoids in head hair, pubic hair, urine, sweat, saliva, and blood. Given the nature of cannabinoids and the fact that they are stored in the fat cells of the body, cannabis remains in the body for an extended period, compared with other drugs. In some cases, it may remain in urine for up to 11 weeks after use. Detection of cannabinoids is possible in hair, and some research has suggested that higher concentrations of cannabinoids may be found in pubic hair, compared with head hair. Cannabinoids may be detected in saliva and sweat, but the concentrations of cannabinoids in these fluids tend to be lower compared with urine, and in some cases, cannabinoids may not be detected using these fluids.

Cannabinoid levels in the blood vary among individuals and depend on the dose received and the individual's history of cannabis use. Blood levels of THC may range between 0 and 500 ng/mL depending on the potency of the cannabis and the time since smoking. The detection of THC in blood more than 10 to 15 ng/mL is evidence of recent use, although it is difficult to be precise about how recent. A more precise estimate of time since last use is provided by the ratio of THC to 9-carboxy-THC. Similar blood concentrations of THC and this metabolite indicate that cannabis has been used in the past 20 to 40 minutes and so suggest a high probability of intoxication, although this is less clear in regular users.

Cannabis intoxication impairs skills required to drive a motor vehicle, so it is desirable to have a measure of cannabis intoxication similar to the breath test for alcohol intoxication. The major obstacle is the lack of a simple relationship between blood levels of THC (and its metabolites) and degree of psychomotor impairment.

With repeated frequent dosing of cannabis, THC accumulates in fatty tissues in the human body, where it may remain for considerable periods. The health significance of this storage is unclear. The storage of cannabinoids *would* be serious cause for concern if THC were a highly toxic substance that remained physiologically active while stored in body fat. THC is not a highly toxic substance, and it is inactive while stored in fat. Stored cannabinoids could conceivably be released into blood, producing a "flashback," although this is likely to occur very rarely, if at all.

TREATMENT

Cannabis Dependence Until recently, little research had been done on the type of assistance that should be given to cannabis users who seek help to stop using cannabis. Although many users may succeed in quitting without professional help, those who are unable to stop on their own need to be assisted. It is not clear what type of treatment should be provided for dependent cannabis users who have repeatedly failed to stop using cannabis and seek help.

There have been a small number of randomized controlled trials comparing group-based relapse prevention and social support in subjects who answered advertisements for help to stop using cannabis. The earliest study reported that, at 1 month after treatment, only 30 percent of their patients were still abstinent, and by the end of 1 year, only 17 percent remained abstinent.

Later studies have compared group relapse prevention intervention, individualized advice, and motivational interviewing adapted from Miller's Drinker's Check-Up with a delayed treatment condition in which participants did not receive any treatment for 4 months. At the 4-month follow-up, all three groups had reduced their cannabis use, but the two treatment groups showed the largest reduction and did not differ from each another. In the treatment groups, 37 percent were abstinent, compared with only 9 percent in the delayed treatment group. The amount of cannabis use also declined by 70 percent in the treatment groups and by 30 percent in the delayed treatment groups. Abstinence rates decreased over time, but the two treatments did not differ at 7, 13, and 16 months after treatment. Twenty-two percent of participants were abstinent throughout the 16-month study, and their abstinence was corroborated by partners and family members.

A more recent study has compared motivational enhancement to quit, motivational enhancement plus behavioral coping skills, and

motivational enhancement and behavioral treatment plus incentives (vouchers for retail items) to remain abstinent. The last group had a longer period of continuous abstinence than the other two groups, which did not differ from each other. By 14 weeks' posttreatment, however, fewer than 10 percent of participants had been continuously abstinent from cannabis.

A recent Australian study has reported a comparison of a six-session cognitive-behavioral intervention with a single-session cognitive-behavioral treatment and a delayed treatment control group that was offered treatment for 4 months. Only 6.5 percent of all subjects (N = 11) were continuously abstinent during the 8-month follow-up period, and all of these were in the treatment groups. There were greater reductions in cannabis-related problems and in dependence symptoms in the two treatment groups.

To date, rates of continuous abstinence from cannabis have been low in the behavioral and cognitive treatments tested, although there have been substantial reductions in rates of cannabis use and self-reported problems related to use. Nonetheless, much more research is needed before sensible advice can be given about the best ways to achieve abstinence from cannabis. In the absence of better evidence of treatment effectiveness, people offering treatment for cannabis dependence should avoid replicating experience in the treatment of alcohol dependence in which inpatient treatment has been widely adopted in the absence of any evidence that it is more effective than outpatient forms of treatment.

There is increasing interest in the use of antidepressants to treat dependent cannabis use because of the high rates of depression reported on presentation for treatment and after cessation. Small studies have been conducted to examine the effectiveness of such a treatment, but no large randomized controlled studies have been conducted to date. This is likely to be an area of increasing research interest in the future.

Cannabis Intoxication The adverse acute effects of cannabis (such as anxiety symptoms) can be prevented by preparing users about the cardiovascular effects they may experience. If these symptoms develop, they can usually be managed by reassurance and support.

Therapeutic Effects of Cannabinoids When cannabinoids and cannabis are advocated for medical uses, it is primarily to relieve symptoms rather than to cure underlying diseases. The conditions for which cannabis is most commonly advocated are for symptomatic relief of nausea and vomiting caused by cancer chemotherapy, appetite loss in AIDS, and muscle spasticity and chronic pain in neurological disorders.

Analgesia Animal studies and the biology of cannabinoid receptors suggest that cannabinoids may be useful analgesics with mild to moderate efficacy. The few controlled studies in humans have suggested that THC and other cannabinoids have modest analgesic effects on acute postoperative and chronic pain (compared with placebo) that are equivalent to 60 mg of codeine. Because patients often report adverse psychotropic effects, their use for these purposes is likely to be limited. The development of synthetic cannabinoids with fewer psychotropic effects seems a more promising way ahead than the use of THC or cannabis products.

Nausea and Vomiting Most research on the antiemetic effects of cannabis or cannabinoids in patients receiving cancer chemotherapy was done in the 1980s using THC, nabilone, and levonantradol. Many of these studies were small in size and not well controlled. These studies showed *some* antiemetic efficacy in comparison with the antiemetic agents then available (namely, prochlorperazine [Compazine]). Clinical interest in cannabinoids decreased with the use of selective serotonin type 3 receptor agonists, such as ondansetron (Zofran), which have dramatically reduced nausea and vomiting. These provide complete control over nausea induced by cisplatin in 75 percent of cases and up to 90 percent for less emetogenic chemotherapy, whereas THC provides control in only one-third of patients. The difference in efficacy is apparent in an experimental comparison of the effects of smoked marijuana and ondansetron on nausea induced by syrup of ipecac. Marijuana had a self-reported antiemetic effect and very slightly reduced the frequency of vomiting, whereas ondansetron prevented all vomiting. Cannabinoids have a modest antiemetic effect that is offset by a high rate of adverse effects such as hypotension, dizziness, and dysphoric effects.

Wasting Syndrome and Appetite Stimulation in HIV/AIDS THC has been shown to stimulate appetite and assist weight gain in AIDS patients in short-term trials. It has been registered for medical use for this purpose in the United States. Some patients do not like dronabinol (Marinol) because of its psychoactive side effects, the difficulty of titrating the dose, the delayed onset of effects, and the prolonged duration of the effects. There are anecdotal reports that smoked cannabis is also effective in the treatment of HIV/AIDS-associated anorexia and weight loss, but there have not been any controlled studies. A clinical trial is under way in California that examines the use of smoked cannabis in HIV-infected patients to see if they are vulnerable to immunosuppressive effects of cannabis and to infectious organisms found in cannabis.

Muscle Spasticity *Muscle spasticity* is the increased resistance to passive stretch of muscles and increased deep tendon muscles. Involuntary contractions may occur that can be painful and debilitating. Approximately 90 percent of multiple sclerosis (MS) patients eventually develop muscle spasticity, as do a substantial proportion of patients with spinal cord injuries. A survey of MS patients suggested that cannabis reduced muscle spasticity, but a recent clinical trial has failed to find evidence of benefit.

Movement Disorders Movement disorders are caused by abnormalities in areas of the brain that are connected to areas of the cortex that control motor functions. They result in abnormal skeletal muscle movements in the face, limbs, and trunk. The disorders most often mentioned as candidates for medical cannabis use are dystonia, Huntington's disease, Parkinson's disease, and Tourette's syndrome. There is limited evidence that cannabis is useful for treating any of these movement disorders. The health risks of the regular cannabis smoking that is required in people already with these health conditions provide a major limitation on its use in these disorders.

Epilepsy There are case reports suggesting that cannabis can control epileptic seizures and one observational study that suggests that cannabis use was protective against seizures, but it has major limitations. Most of the anticonvulsant properties of cannabinoids appear to be attributable to cannabidiol (CBD) rather than to THC. Because CBD, which has no psychoactive effects, is not a controlled substance, there are no obstacles to its clinical use if its safety and efficacy are demonstrated in controlled trials.

Glaucoma Elevated intraocular pressure is a chronic condition that produces blindness if untreated. Intraocular pressure must be con-

trolled continuously to reduce the risk of blindness. Cannabis and THC taken orally or intravenously (IV) reduce intraocular pressure by 25 percent, but the effect lasts only 3 to 4 hours. The high doses of THC that are required to produce these effects produce side effects that preclude the lifelong use of cannabis or cannabinoids to treat glaucoma. Water-soluble cannabinoids that may be topically applied and that have no psychoactive effects may be a better prospect.

THC and other cannabinoids have not been widely used therapeutically or investigated in clinical trials. This is because, in the United States, clinical research on cannabinoids has been discouraged by regulation and the fact that THC, the most therapeutically effective cannabinoid, is the one that produces the psychoactive effects sought by recreational users. THC is also a naturally occurring substance that cannot be patented, which means that companies are unlikely to conduct research into its medical uses. The discovery of a cannabinoid receptor and the cannabinoid-like substance anandamide may encourage more basic research into the therapeutic uses of natural and synthetic cannabinoids.

SUGGESTED CROSS-REFERENCES

An overview of substance-related disorders, including substance abuse and dependence, appears in Section 11.1. Schizophrenia is discussed in Sections 12.1 and 12.2, drug-induced psychotic disorders are discussed in Section 12.16g, and substance-induced anxiety disorders are discussed in Section 14.8.

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▲ 11.6 Cocaine-Related Disorders

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Few public health issues attracted as much media attention in the United States during the 1980s and early 1990s as the problems resulting from the use of cocaine and "crack." Although the intranasal use of cocaine hydrochloride in the early 1980s was associated with high-income, "jet-set" users, smokable "crack" cocaine has become an endemic drug problem in the inner cities across the United States. Epidemiological evidence has documented that the peak of this epidemic has passed in the United States, but available data indicate that rates of cocaine use are increasing in a number of European countries.

There is a wealth of new information on the neurobiology of cocaine and cocaine dependence, treatment research efforts have