MARIJUANA AND SUBSTANCE USE DISORDER, Part 1:
a historical perspective and DSM-5 overview

Introduction

Marijuana is the most widely used illicit drug in the Western world and the third most commonly used recreational drug after alcohol and tobacco. According to the World Health Organization, it also is the illicit substance most widely cultivated, trafficked, and used.

Although the long-term clinical outcome of marijuana use disorder may be less severe than other commonly used substances, it is by no means a "safe" drug. Sustained marijuana use can have negative impacts on the brain as well as the body. Studies have indicated a link between regular marijuana use and schizophrenia as well as a demonstrated relationship between marijuana use and a higher incidence of lung cancer. Although there are no pharmacological treatments available with a proven impact on marijuana use disorder, there are several types of behavior therapy that may be effective in treating this disorder.

Worldwide Use Of Marijuana

For a number of years, the United Nations has been compiling annual surveys of worldwide drug use, including cannabis. Reflecting the difficulties and uncertainties associated with developing estimates of the number of people who use drugs (such as the quality of the data gathered and the methodologies used to sample populations), the latest United Nations estimates are presented in ranges, reflecting the lower and upper estimates indicated through the array of surveys

available. In their 2012 report (covering 2010), the United Nations estimated that between 119.4 and 224.5 million people between the ages of 15 and 64 had used cannabis in the past year, representing between 2.6% and 5.0% of the world's population.[22]

In 2014, approximately 22.2 million people ages 12 and up reported using marijuana during the past month. Also in 2014, there were 2.6 million people in that age range who had used marijuana for the first time within the past 12 months.[33] Based on a report of people between the ages of 12 and 49, the average age a person first uses the drug is 18 and a half. In the past year, 4.2 million people ages 12 and up met criteria for a substance use disorder based on marijuana use.[25]

Use by Regions

Looking at specific regions of the world, surveys have found that the highest per capita rate of use in the past year was in Oceania (the countries and territories in the Pacific Ocean, including Australia), where between 9.1% and 14.6% of adults reported past-year use. Past-year prevalence estimates for other regions were 10.8% for North America, 7.0% for western and central Europe, and 5.2% to 13.5% for West and Central Africa. Although the prevalence of cannabis use in Asia (1.0% to 3.4%) was lower than the global average, the absolute number of users in Asia, estimated between 26 million and 92 million, was the highest worldwide due to Asia's large population.[5]

As in most other countries, marijuana is the most frequently used illicit drug in the United States. Its use rose dramatically throughout the 1960s and 1970s, followed by steady decreases into the early 1990s.

However, the use of marijuana by high school seniors increased again in 1993, although it has been decreasing since the late 1990s.

Data gathered as part of the 2011 National Survey on Drug Use and Health revealed that just over 107 million Americans (41.9% of the population) have used marijuana at least once in their lives. An estimated 18 million Americans were current marijuana users (that is, they used marijuana in the last 30 days), representing 7% of the U.S. population aged 12 and older.[23]

Use by Age, Gender and Ethnicity

The breakdown by age for current use of marijuana was 7.9% among those aged 12 to 17; 19.0% among those aged 18 to 25; 10.2% among those aged 26 to 34; and 3.6% among those 35 and older. Three other findings from the 2011 National Survey on Drug Use and Health are noteworthy. First, men were more likely than women to be current users of marijuana (9.3% versus 4.9%). Second, current marijuana use varied by race or ethnicity; marijuana prevalence was 8.7% among Native Hawaiians or other Pacific Islanders, 8.6% among American Indians/Alaska Natives, 8.4% among blacks, 7.1% among whites, 6.3% among Hispanics, and 2.9% among Asians. The rate of current use among individuals describing themselves as being of two or more races was 11.8%. Notably, a third finding concerned the frequency of marijuana use. Among those who smoked marijuana in the past year, 32% reported using marijuana on 1 to 11 days, 18% on 12 to 49 days, 11% on 50 to 99 days, 23% on 100 to 299 days, and 17% on 300 or more days.[23]

What is Marijuana?

Marijuana is an illicit psychoactive sedative drug from the cannabis (hemp) plant. The name marijuana is thought to have its origins in the Portuguese word *mariguango*, which translates as intoxicant.[1] Marijuana consists of the dried and crushed leaves from the cannabis plant, which are typically smoked, but can also be eaten in baked goods or consumed as tea. In the United States, marijuana is typically smoked in rolled cigarettes ("joints"), in pipes or water pipes, or in hollowed-out cigars ("blunts").[2]

Marijuana is known by many names including pot, reefer, grass, weed, and many others. People's experiences with marijuana can differ considerably depending on the potency of the drug. Many users experience sedative effects such as relaxation and drowsiness. The psychoactive chemical in marijuana is delta-9-tetrahydrocannabinol (delta-9-THC or THC). THC is also the active ingredient in several FDA-approved medications such as dranabinol and nabilone. These medications are used to treat medical conditions including glaucoma, severe nausea, vomiting, weight loss, and pain.[3]

The Marijuana Plant

The cannabis (hemp) plant, Cannabis sativa, is the source of marijuana and hashish. The cannabis plant contains more than 400 chemicals. At least 60 of the chemicals are cannabinoids (as they bind to cannabinoid receptors in the brain), but the most important of these cannabinoids is delta-9-tetrahydrocannabinol (THC). Delta-9-tetrahydrocannabinol is the plant's main psychoactive chemical, although researchers are examining some of the other chemicals found in this plant for potential additional medicinal use. Various marijuana

plants can significantly differ in how much THC is contained in each. Marijuana can contain 1% to 3% THC all the way up to 20% THC in the sinsemilla variety.[4]

The cannabis plant is a hardy plant that grows quickly in a variety of environments. Cannabis is highly resistant to pests and grows easily. In favorable environments, the plant can reach a height of 20 feet. The leaves consist of five or more narrow leaflets extending from a slender stem attached to a thick, hollow stock. The leaflets are arranged *palmately*, which means they radiate from a common center like fingers of a hand spreading apart. Closer examination of the jagged edge of each leaflet reveals a resemblance to the blade of a serrated knife. Cannabis is considered an herbaceous annual, since it both has nonwoody stems and will die at the end of the growing season if in the natural environment. The plant has flowers from late summer to mid fall.

There are male and female varieties of cannabis, which are partly distinguishable because the female plant tends to be shorter than the male. The male and female also have different types of flowers. The male has flowers that are elongated clusters that turn yellow and die after blossoming. The female has flowers that grow in spike-like clusters and retain their green color after blossoming. The female plant's flowers are larger than the male's, which help the female plant catch pollen. The female plant produces seeds and a sticky resin that protects those seeds.

By comparison, hashish is produced through removing and drying resin found on the tops (flowers) of the hemp plant. Hashish is much more potent than marijuana because it contains a higher proportion of

the main psychoactive ingredient in the plant, THC. The plant produces this resin as a protective mechanism against sun, heat, and dehydration, which partly explains why cannabis is hardy in a variety of growing conditions.[5]

Marijuana is the general common name for most parts of the plant C. sativa L., including the seeds, the resin extracted from any part of the plant, and every compound, salt, derivative, or mixture derived from the plant, but it does not include the mature stalks, fiber produced from the stalks, or oil or cake prepared from the seeds. "Marijuana" is also the nonchemical name given to the crude drug derived from the plant. Additionally, cannabis is grown commercially to produce hemp. The bulk of the commercial plant consists of stalks with very little foliage, except at the apex. In contrast, wild plants, and those cultivated illegally, possess many branches and the psychoactive ingredient is concentrated in the leaves and flowering tops. There may be significant differences in the gross appearance of marijuana plants due to climatic and soil conditions, the closeness of the plants to other plants during growth, and the origin of the seed stock grown.[1]

The stiff and fibrous stalks of the cannabis plant can be used to produce various consumer products. The fiber (also referred to as hemp) is used to make rope, cloth (used in clothing), canvas (used for ship sails), paper, and shampoos. The fiber tends to be stronger and more resistant to mildew than similar fibers such as cotton. The seeds can be eaten as food and are often found in granola and cereal. The seeds can also be made into oils. Both hemp oils and seeds contain trace amounts of THC. Industrial hemp (cannabis) plants grown for industrial uses have very low concentrations of THC (less than 0.15%

THC as compared to 2% THC found in psychoactive cannabis plants). Thus, a person might try to smoke a whole field of industrial hemp plants and still be unable to get high. Owning hemp products such as clothing or food items is legal. While dozens of products are made from industrial cannabis, industrial cannabis is a far smaller agricultural product than it was one hundred years ago. Currently, it is illegal (per U.S. federal law) to grow or possess marijuana in plant or drug form.

Forms of Marijuana

Marijuana and hashish have been administered in a number of ways in their use as psychoactive agents. The route of administration refers to the method by which a drug enters the body. Marijuana is typically administered either by inhalation or oral administration. Inhalation of marijuana via smoking is the most rapid and efficient means of drug administration. Marijuana can be smoked with joints or blunts. Marijuana can also be smoked using pipes (also referred to as bowls) or water pipes, colloquially referred to as *bongs*. The drug is absorbed through the lungs, and users experience the effects of THC within minutes. Peak blood levels of THC are experienced about 10 minutes after initiation.

The duration of drug action for smoked marijuana is 2 to 3 hours. The other major route of administration for marijuana is oral. Marijuana can be eaten in food such as brownies or taken in pill form, such as in synthetic THC medications. The onset of the drug effect with orally administered marijuana is much slower and less efficient than smoked marijuana. Oral administration requires the drug to be passed through the digestive tract until THC is absorbed in the small intestine. The

onset of drug action for orally administered marijuana is 30 to 60 minutes after swallowing. Peak blood levels of THC are observable at 2 to 3 hours after oral administration. The duration of drug action for orally administered marijuana is approximately 4 to 6 hours. It is estimated that the dose must be three times higher to achieve the same effect with oral administration as experienced when marijuana is smoked.[4,7,8]

Chemicals in the Cannabis Plant

Studies have shown cannabis to be a complex plant. More than 400 individual chemical compounds have been identified in the plant. Over 60 of these chemicals, collectively called cannabinoids, are unique to the cannabis plant. Continued research will likely identify additional cannabis chemical compounds and cannabinoids. Despite years of study, the principal psychoactive agent in cannabis was not isolated until 1964. This substance has been labeled delta-9-tetrahydrocannabinol but is more commonly known as D-9-THC, or simply THC.

The THC compound was first reported by Gaoni and Mechoulam, two researchers working in Israel. Research since 1964 has shown that the D-9-THC cannabinoid accounts for the vast majority of the known specific pharmacological actions of marijuana. Although THC is the prime psychoactive agent in cannabis, other cannabinoids, such as cannabidiol and cannabinol, can be biologically active and can modify THC effects. However, they tend not to be psychoactive in and of themselves.[9-11]

Potency of Cannabis

The strength of cannabis varies considerably, and most of the marijuana grown in the United States has a lower THC content than the marijuana grown in other countries. Marijuana smoked in the United States today is considerably stronger than that used three decades ago (8% to 10% THC is now the average versus around 2% in 1980). Comparable figures are reported for marijuana smoked in the United Kingdom.

Higher THC potency is generally found in "homegrown" cannabis — that is, marijuana grown in large-scale domestic indoor environments. The THC content in sinsemilla (a seedless variety of marijuana) is now in the range of 10% to 20% and sometimes reaches 30%. Similar variations and increasing average potencies have been found as well for hashish. A third form of cannabis is hash oil, a concentrated liquid marijuana extract derived from the cannabis plant using solvents. This oil has been available on the streets for a number of years and is more potent than the marijuana leaf material or resin. Estimates are that hash oil can contain as much as 60% THC, although the potency is more generally found to be around 20%.[12,13]

The Pharmacokinetics Of Tetrahydrocannabinol

Several factors can influence the amount of tetrahydrocannabinol absorbed through smoking. One important variable, of course, is the potency of the cannabis being smoked. Only about half of the THC available in a marijuana cigarette is in the smoke, and the amount ultimately absorbed into the bloodstream is probably less. Another variable is the amount of time the inhaled smoke is held in the lungs; the longer the smoke is held, the more time for absorption of the THC. An additional factor that influences intake is the number of people who

share the cigarette because more smokers may decrease the amount of marijuana available to any one user.

The amount of THC in a marijuana cigarette that is actually absorbed by smoking averages around 20%, with the other 80% lost primarily through combustion, side stream smoke, and incomplete absorption in the lungs.[1] The pharmacokinetics of THC are further elaborated on below relative to its absorption, distribution, metabolism and excretion.

Absorption

The absorption of THC depends primarily on the mode of consumption. The most rapid and efficient absorption of marijuana occurs through smoking. Inhalation results in absorption directly through the lungs, and the onset of the THC action begins within minutes. Assessments of blood plasma reveal that peak concentrations occur 30 to 60 minutes later. The drug effects can be experienced for two to four hours.[8]

Oral ingestion of marijuana is much slower and relatively inefficient. The onset of action is longer than when smoked, taking as long as an hour. The marijuana is absorbed primarily through the gastrointestinal tract, and peak plasma levels can be delayed for as long as two to three hours following ingestion. An important difference from absorption through smoking is that blood containing orally ingested marijuana goes through the liver before going to the brain. The liver processes or clears much of the THC so that lesser amounts have the opportunity to exert action in the brain; however, the drug effects following oral ingestion can be experienced for longer periods of time, generally four to six hours. The dose needed to create a comparable

high when orally ingested is estimated as three times greater than that needed when smoking.

Distribution, Metabolism, and Excretion

Using peak plasma THC levels to assess cannabis effects can be misleading because the psychoactive cannabinoids are highly lipid-soluble; that is, the cannabinoids are lipids, which means they are almost entirely insoluble in water. The cannabinoids instead are a dark, viscous, oil-like substance. Plasma levels of THC decrease rapidly because the THC is deposited in the tissues of various organs, particularly those that contain fatty material. Assessments of organs following cannabis ingestion reveal marked concentrations of THC in the brain, lungs, kidneys, and liver. Thus, even when blood levels of THC are zero, the levels of THC in other organs can be substantial. Also, THC is capable of crossing the placental barrier and reaching the fetus.[8]

As noted, THC is carried through the bloodstream and deposited within various organs. The THC is then metabolized to less active products over time. Although this process occurs primarily in the liver, it can occur in other organs as well. The THC metabolites are excreted slowly through feces and urine. Approximately half of the THC is excreted over several days and the remainder by the end of about a week. However, some metabolites of the THC, a number of which may still be active in the system, can be detected in the body at least 30 days following ingestion of a single dose and in the urine for several weeks following chronic use.[13,14]

Hepatic metabolism is the major route by which THC is eliminated from the body. Hepatic metabolism consists primarily of hydroxylation by CYP2C9 to form 11-hydroxy- THC (abbreviated as HO-THC), which is also a psychoactive compound. Hydroxylation is followed by oxidization, probably by alcohol dehydrogenase or, possibly, a microsomal enzyme known as aldehyde oxygenase, another member of the CYP2 subfamily. This compound is eventually excreted as THC-COOH in the urine after first forming a glucuronide at the carboxyl group.[16]

In humans, over 20 metabolites have been identified in urine and feces of marijuana users. Metabolism in humans involves allylic oxidation, epoxidation, aliphatic oxidation, decarboxylation, and conjugation. The two monohydroxy metabolites, 11-hydroxy (OH)-THC and 8-β-hydroxy THC, are active, with the former exhibiting similar activity and disposition to THC, while the latter is less potent. Plasma concentrations of 11-OH-THC are typically <10% of the THC concentration after marijuana smoking. Two additional hydroxy compounds have been identified, namely, 8-α-hydroxy-THC and 8,11-dihydroxy-THC, but they are believed to be devoid of THC-like activity. Oxidation of 11-OH-THC produces the inactive metabolite, 11-nor-9-carboxy-THC, or THC-COOH. This metabolite may be conjugated with glucuronic acid and is excreted in substantial amounts in the urine.[16]

The average plasma clearance for THC is 600–980 mL/min with a blood clearance of 1.0–1.6 L/min, which is very close to hepatic blood flow. This indicates that the rate of metabolism of THC is dependent on hepatic blood flow. Approximately 70% of a dose of THC is excreted in the urine (30%) and feces (40%) within 72 hours. Because significant

quantities of the metabolites are excreted in the feces, enterohepatic recirculation of THC metabolites may occur. This would also contribute to the slow elimination and hence long plasma half-life of THC. Unchanged THC is present in low amounts in the urine along with 11-OH-THC, but accounts for only 2% of a dose.

The other urinary metabolites consist of conjugates of THC-COOH and unidentified acidic products. Following a single smoked 10-mg dose of THC, urinary THC-COOH concentrations peaked within 16 hours of smoking, at levels of 6–129 ng/mL (n = 10). Huestis and Cone reported a mean (± SEM) urinary excretion half-life for THC-COOH of 31.5 ± 1 hour and 28.6 ± 1.5 hour for six healthy volunteers after administration of a single marijuana cigarette containing 1.75% or 3.55% THC, respectively. Passive exposure to marijuana smoke may also produce detectable urinary metabolite concentrations. In one earlier study, Cone *et al.*, exposed five volunteers to the smoke of 16 marijuana cigarettes (2.8% THC content) for 1 hour each day for 6 consecutive days. After the first session, THC-COOH concentrations in urine ranged from 0 to 39 ng/mL. A maximum THC-COOH concentration of 87 ng/mL was detected in one subject on Day 4 of the study.

Tetrahydrocannabinol may be ingested orally by consuming food products containing the seeds or oil of the hemp plant. Ingestion of 0.6 mg/day (equivalent to 125 mL hemp oil containing 5 µg/g of THC or 300 g hulled seeds at 2 µg/g) for 10 days resulted in urine THC-COOH concentrations of < 6 ng/mL. In another study the maximum urinary concentration of THC-COOH after ingestion of hemp oil containing 0.39–0.47 mg THC/ day for 5 days was 5.4–38.2 ng/mL (n

= 7). After oral administration of a higher dose (7.5 and 14.8 mg THC/day), peak urinary concentrations of THC-COOH ranged from 19.0 to 436 ng/mL.[8,16,18]

Mechanisms of Action

The psychotropic actions of marijuana occur in the brain and are a result of the drug's effect on chemical neurotransmission. Much of the early research in this area (typically performed with animals) focused on the effects of marijuana on acetylcholine, a chemical transmitter involved in memory. THC in relatively small doses has been shown to decrease the turnover in acetylcholine, particularly in the hippocampus, resulting in a decrease in neurotransmitter activity. Similar inhibitory effects of THC have been observed on a variety of neurotransmitters, including L-glutamate, GABA, noradrenaline, dopamine, and 5-HT. In addition, THC facilitates release of the neurotransmitter serotonin and produces changes in the dopamine system, thus enhancing activation of movement.[12,15]

Although specification of the drug action remains somewhat speculative, important advances are occurring. Foremost among these has been research on THC receptors in the brain. Two types of cannabinoid receptors (called CB1 and CB2) have been identified, and these receptors are uniquely stimulated by THC. CB1 receptors are located predominantly in brain areas that control memory, cognition, the motor system, and mood. CB2 receptors are most prevalent in the immune system.[17,18]

Research on cannabinoid receptors opened the door to efforts to study pathways in the brain that may be involved in cannabinoid actions and to the search for naturally occurring chemicals in the body (called

endogenous chemicals) that normally would interact with the identified receptors. One research team identified such a chemical (named "anandamide" from the Sanskrit word for "bliss") that binds to the same receptors on brain cells, as do cannabinoids. Researchers are now using the compound anandamide to study how the cannabinoid receptors affect functions such as memory, movement, hunger, and pain, which are affected by marijuana use. Another endogenous chemical identified as interacting with cannabinoid receptors is 2-arachidonoyl-glycerol, or 2-AG.

Newer research methods, such as positron emission tomography (PET), which assesses cerebral blood flow, have opened new avenues for exploring marijuana effects. For example, it has been shown that THC increases blood flow in most brain regions in both the cerebral cortex and deeper brain structures. Such blood flow is greatest in the frontal cortex, which is critical to executive brain functions. Other recent research has focused on identifying and investigating areas of the brain that have greater densities of cannabinoid receptors, such as the cerebral cortex.[1]

Medical And Psychotherapeutic Uses Of Cannabis

Cannabis has a long history of use for medical and health purposes, with the earliest documented use attributed to Shen Nung in the 28th century B.C. Shen Nung purportedly recommended that his people use cannabis for its medicinal benefits. The earliest physical evidence of marijuana used as a medicine was uncovered recently by Israeli scientists who found residue of marijuana buried with the body of a young woman who apparently died in childbirth 1,600 years ago. They suggested that the marijuana was used to speed the birth process and

to ease the associated pain. Indications that cannabis had been used during childbirth had been found earlier in Egyptian papyri and Assyrian tablets.

More systematic uses of cannabis as a therapeutic agent did not occur until the 1800s. For example, the Paris physician Jacques Moreau used cannabis in the mid-1800s to treat mental illnesses. Dr. William O'Shaughnessy, the Irish physician who, in an 1838 treatise, described the use of cannabis to treat such problems as rheumatism, pain, rabies, convulsions, and cholera, provided much greater legitimization of the medical use of marijuana. Cannabis also was used widely in the United States for many complaints. It was recognized as a therapeutic drug well into the 1900s. At that time, cannabis extract was listed for varying periods of time in the United States Pharmacopeia, the National Formulary, and the United States Dispensatory. In the Dispensatory, for example, cannabis was recommended for treating neuralgia, gout, rheumatism, rabies, cholera, convulsions, hysteria, mental depression, delirium tremens, and insanity.

Well into the 1930s, cannabis was an ingredient in a variety of over-the-counter medicines, such as remedies for stomach pain and discomfort, restlessness, and coughs. One company marketed cannabis cigarettes for the treatment of asthma; however, these medicinal uses of cannabis rapidly began to decline for two reasons. The first was the advances made in medicine and specific knowledge about various diseases and their treatments. The second factor was the *Marijuana Tax Act of 1937*. This legislation markedly decreased prescribed medicinal uses of marijuana.[26-28]

The therapeutic uses of marijuana today are much more circumscribed. For the most part, synthetic products such as dronabinol and nabilone that chemically resemble the cannabinoids have been used in current treatment efforts because they provide the active elements of THC in a more stable manner. Synthetics also can provide better solubility. Unfortunately, a downside to the synthetics is the absence of the rapid effect experienced when marijuana is smoked.

When synthetic THC is taken orally, it is broken down prior to entering the bloodstream and absorption thus is delayed. A recent development with promise is a cannabis oral spray, which has been approved in several countries for use as a painkiller for sufferers of multiple sclerosis. Sativex also holds promise for alleviating pain associated with rheumatoid arthritis and may even suppress the disease. Sativex has also shown some promise in animal research for improving memory loss in Alzheimer's disease.[28,29,30]

The discovery of the cannabinoid receptor has important implications for future medical and psychotherapeutic uses of cannabis. The identification of the cannabinoid receptor also has advanced knowledge about the neurobiology of cannabis use. Perhaps more importantly, therapeutic uses of cannabis have caused an increase in the examination of compounds related to the endogenous cannabinoid system for potential applications with multiple disorders. For example, a medication based on the cannabinoid CB1 receptor, the antagonist rimonabant, is being used in the treatment of complicated obesity.

Other medications based on the endogenous cannabinoid system are now in development or under evaluation. Meanwhile, in the past several decades, there have been sustained efforts to legalize marijuana use for medicinal purposes. Much of this effort has been spurred by an increased use of marijuana by patients with autoimmune deficiency syndrome (AIDS) who claim that marijuana reduces the nausea and vomiting caused by the disease and that it stimulates appetite, thus helping them to regain weight lost during their illness. The passage of propositions related to marijuana use in a number of states demonstrates public sympathy for those positions. An offshoot of these efforts has been the establishment of "cannabis clubs" in several major U.S. cities. These organizations purchase marijuana in bulk and provide it (free or at cost) to patients with AIDS, cancer, and other diseases. The debate over legalizing marijuana for medicinal purposes is not likely to be resolved in the near future.[31,32,33] In the meantime, there are several disorders — especially nausea and cachexia — for which cannabis is prescribed in synthetic form. They are described briefly in the following table:[1,33-36]

Nausea and Vomiting	Cannabis and THC synthetics have been used to counter the nausea and vomiting frequently associated with chemotherapies (and some radiation treatments) for cancer. These side effects, which can last for several hours or even several days, often are not ameliorated by traditional antiemetic medications (although significant advances are being made in the development of more powerful anti-sickness drugs). Researchers in the 1970s began more systematic study of the antinausea and antivomiting effects of THC (usually administered orally), and their results were favorable. This research, incidentally, followed anecdotal reports by chemotherapy patients that their private use of marijuana had reduced the aversive side effects of their treatments.

	Positive outcomes have emerged in subsequent research. Furthermore, there are indications that children undergoing cancer chemotherapy may particularly benefit from orally administered high doses of cannabinoids. More recent studies have included the use of THC synthetics. The main drawback to the use of cannabis and THC synthetics is the resultant mental effects, which some patients have viewed as uncomfortable and disorienting. Nevertheless, many patients undergoing chemotherapy find the THC side effects an acceptable price to pay for reduced side effects. An increasing amount of research is now being conducted, thanks in part to the classification of synthetic THC as a Schedule III drug, which means some medical value is recognized. The synthetic had once been classified as a Schedule I drug, meaning it was a prohibited substance with no recognized medical benefit. Marijuana not in synthetic form remains a Schedule I drug. Meanwhile, advances have been occurring with newer antiemetic drugs, not cannabis-based, that have been well tolerated and effective.
Cachexia	Cachexia is a disorder in which an individual physiologically "wastes away," often due to HIV infection or cancer. Based partly on anecdotal reports that marijuana use is associated with increased frequency and amount of eating, it has been proposed that patients with cachexia use marijuana to stimulate appetite and thus weight gain. These anecdotal reports have some empirical support. Plasse *et al.*, found a relationship between marijuana ingestion and appetite. Accordingly, some individuals who have disorders that include cachexia have been turning to marijuana to stem the tide of weight loss and to gain weight. Abrams, *et al*., for example, found that smoked marijuana or oral THC each effectively induced weight gain among HIV-infected adults.

	A caution on the use of smoked marijuana is that patients with HIV, for example, might be uniquely vulnerable to any immunosuppressive effects of the drug. More study in this area appears justified.
Glaucoma	Glaucoma is a generic term used to denote ocular diseases that involve increases in intraocular pressure. This pressure damages the optic nerve and represents the leading cause of blindness in the United States. More than 2 million Americans over age 35 have developed glaucoma, and an estimated 300,000 new cases are diagnosed yearly. Almost 67 million people are affected by glaucoma worldwide. Although drug and surgical interventions are available, their effectiveness is variable. Cannabis has been shown to decrease intraocular pressure, although patients have experienced side effects regardless of whether the cannabis was administered orally, through injection, or by smoking. These side effects include increased heart rate and psycho- logical effects. Some effects dissipate with extended exposure to the cannabis. Of more concern, marijuana may also reduce blood flow to the optic nerve and possibly exacerbate the loss of vision. The mechanisms through which the cannabis reduces intraocular pressure have not been determined. Cohen and Andrysiak suggested that cannabis dilates the vessels that drain excess fluids from the eyeball. This draining is thought to prevent fluid buildup and the resultant pressure that causes optic nerve damage. Clinical research on the potential benefits of cannabis as a treatment for glaucoma is continuing, with two emphases. The first is on developing synthetic formulas that reduce side effects, and the second emphasis is on modes of application. Particular attention is given to developing a topical preparation that could be applied directly onto the eye. Meanwhile, most experts believe that existing non-THC medications have equal or greater benefit in the treatment of glaucoma.

Other Uses	Cannabis and THC synthetics have been used to a lesser extent or in exploratory fashion in the treatment of several other disorders. For example, ajulemic acid, a synthetic analog of THC, is receiving attention as an analgesic that does not produce feelings of being "high". Other clinical areas for which THC and cannabis-based treatments are being studied include muscle spasticity, convulsant activity, epilepsy, chronic pain, insomnia, hypertension, asthma, anxiety, cardiovascular diseases, Tourette's syndrome, Alzheimer's disease, and depression. However, the data in support of these uses so far have been preliminary or mixed, and more research is needed to specify the potential utility of cannabis in these areas.

Defining Harmful Drug Use

A substance use disorder develops over time and has been described as evolving through five distinct stages of progression. The length of time for each stage, and the duration of the progression to full-blown addiction will vary by individual. In some instances, the progression will occur quickly, with the individual spending brief periods in each stage. In other instances, the individual will slowly progress through the stages and will not reach the stage of addiction for an extended period of time. The following table provides a description of each stage of progression, however the learner is encouraged to keep in mind that the new DSM-5 criteria replaces prior quantitative models to evaluate substance use severity with a pooled set of "dependence" and "abuse" criteria that exist along a severity continuum. Quantitative measures of a substance use disorder in DSM-5 continue to be debated and controversial in the field of addiction medicine; however, the general

concepts in the table will help to elucidate phases leading to behavioral consequences and addiction severity as relates to the progression beginning with early consumption of a substance to craving and addiction.

Stage	Description
Stage One: Experimentation	The first stage, experimentation, is the voluntary use of alcohol or other drugs. Quite frequently, the person experimenting is trying to erase another problem. The substance seems solve the problem. So the person takes more, and moves from experimentation to regular use, the next stage.
Stage Two: Regular Use	Some people stay in the regular use stage indefinitely. They will not develop a problem, and stop by themselves. Others start using substances in a manner that is risky or hazardous to themselves or to others.
Stage Three: Risky Use	When and how the transition from regular to risky use happens differs for every individual. So, what constitutes "risky behavior" by another person can be difficult to gauge. People can pass quickly from risky use to stage four of a substance use disorder.
Stage Four: Substance Use Disorder/Craving	Characteristics of substance use disorder/craving include: • Repeated use of alcohol or other drugs that leads to failure to fulfill major responsibilities related to work, family, school or other roles. • Repeatedly drinking or using drugs in situations that are physically hazardous, such as driving while intoxicated or using heavy machinery when intoxicated. • Repeated legal problems. Many people with a craving/substance use disorder are able to work, maintain family relationships and friendships, and limit their use of alcohol or other drugs to certain time periods, such as evenings or weekends.

Stage Five: Addiction	The last phase of the spectrum of substance use problems is addiction. Addiction is a medical condition involving serious psychological and physical changes from repeated heavy use of alcohol, other drugs, or both. Symptoms include uncontrollable alcohol or other drug craving, seeking, and use, that persists even in the face of negative consequences.

Dimensions of Addiction

There are seven dimensions of substance addiction that are interrelated but can, and do, operate independently. The dimensions are thought to be on a continuum from less severe/low risk to more severe/high risk. Knowledge of where a client falls on each continuum can provide useful clinical information and strengthen the assessment process.[36,37,38]

Clinicians can use the seven dimensions of addiction as a starting point when assessing their clients. They are useful in determining the extent or severity of one's substance use. For example, a client might self-report moderate use but be extremely high on consequences, behavioral and medical harm. Subsequent treatment could focus on "higher" dimensions with an eye on reducing or eliminating use.[39] Assessing the dimensions could be accomplished as part of a clinical interview or as seven lines drawn on a piece of paper, ranging from low to high, for each dimension. If using seven lines, the clinician could place an X on each line indicating the extent of the problem related to a particular dimension. Once completed, the clinician has a documented snapshot of the client's addiction pattern, which can inform placement and treatment-planning decisions. The seven dimensions are as follows:[40,41]

- Use:

Three behaviors characterize use: *quantity, frequency, and variability*. Quantity refers to how much one uses a substance on a "typical occasion," frequency refers to how often one uses on a typical occasion, and variability addresses the pattern of using a substance.

- Consequences:

  Clients do not often come to counseling because they are using a substance but rather because their use-behaviors have gotten them into trouble. Exploring the consequences of substance use can lead to enhanced motivation and is a key part of *motivational interviewing*. The consequences of substance use range from none to many within a typical day.

- Physical adaptation:

  Another dimension of addiction is the presence or absence of physical tolerance. The presence of tolerance and/or withdrawal is usually the hallmark of a physical addiction.

- Craving:

  In the DSM-5 the definition of substance dependence (previously referenced in DSM-IV) is discussed in terms of *craving* (discussed later), and tolerance or withdrawal does not have to be present for someone to crave a substance. Clients may psychologically crave a substance, in which case they develop a mental need for the drug to get through the day or cope with stress. They believe they cannot do this without the substance.

- Cognitive impairment:

Drug use alters brain chemistry. Even relatively brief stints with substance use can have noticeable negative cognitive effects. Long-term use of some chemicals, such as alcohol, can result in permanent damage to memory, motor skills, and attention.

- Medical harm:

  Substance use also impacts physical health. For example, smoking marijuana is especially dangerous due to high levels of carcinogens that enter the bloodstream. Cocaine and other stimulant drugs can have deleterious effects on cardiovascular functioning, and, similarly, excessive, long-term alcohol use can become highly physically damaging, affecting almost every organ system in the body.

- Motivation for change:

  Lack of client motivation can make treatment planning and movement toward goals a difficult process. Knowing how important making a change in substance use is to the client can help clinicians gauge what strategies might be most helpful. Many techniques are available that can assist in enhancing motivation to change.

In the United States and other countries, providers of care for physical and mental illness have handled problems of definition by developing systems of definitions of illnesses, or diagnostic systems. A diagnosis typically is based on a cluster of symptoms that is given a name (the diagnosis). The advantage is that, for example, if two health providers are communicating about pneumonia in a patient and they are following the same diagnostic system, then each knows exactly what

the other is referencing when the term pneumonia is used; that is, a specific cluster of symptoms is being referred to. It also is possible to create diagnostic systems of mental illnesses.

In the U.S., the primary organization responsible for doing that has been the American Psychiatric Association (APA). Since the early 1950s, the APA has published formal diagnostic systems of different mental illnesses or disorders in its Diagnostic and Statistical Manual (DSM). The most recent version (in which systems are revised because of ongoing research that provides new information about different disorders) appeared in May 2013, and is called the DSM-5. The DSM-5 has a section called "substance-related" (alcohol- or other drug-related) disorders, which includes definitions of "substance use disorders."[41,42]

The table below lists the criteria for defining substance use disorder according to DSM-5. It is important to make a few comments about the criteria. Most generally, the same criteria are applied in defining substance use and addiction for all drugs and drug classes that people tend to use for nonmedical reasons. Another important point is that prior editions of the DSM distinguished between "dependence" and "abuse". However, that distinction is not made in DSM-5, due to research findings since the last major DSM was published in 1994. Criteria 1 through 9 focus on what traditionally has been called "compulsive drug use," or drug addiction. In essence, the individual's life centers on drug use and its procurement to the point of reduced attention to or outright neglect of other aspects of life. Similarly, drug use persists despite the risk of incurring serious consequences by doing so. Individuals with addictions also have an inability to stop or to

reduce drug use for any length of time. This phenomenon has been called "loss of control." The last two criteria introduce two terms: *tolerance and withdrawal*. At least 2 of the 11 criteria listed in the table below must be met for the diagnosis of substance use disorder.[41,42,43]

DSM-5 Diagnostic Criteria for Current Substance Use Disorder

Substance use disorder is a problematic pattern of substance use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

1. The substance is often taken in larger amounts or over a longer period than was intended.
2. Users have a persistent desire or unsuccessful efforts to cut down or control use of the substance.
3. A great deal of time is spent in activities necessary to obtain the substance (*i.e.*, visiting multiple doctors or driving long distances), to use the substance (*i.e.*, chain-smoking), or to recover from its effects.
4. Users have cravings, or strong desires to use the substance.
5. Recurrent use of the substance results in a failure to fulfill major role obligations at work, school, or home.
6. Use of the substance is continued despite having persistent or recurrent social or interpersonal problems caused, or exacerbated, by the substance.
7. Use of the substance is recurrent so that important social, occupational, or recreational activities are given up or reduced.
8. Use of the substance is recurrent in situations in which it is physically hazardous.
9. Use of the substance 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; and,
10. Tolerance has developed, as defined by either of the following: (a) Need for markedly increased amounts of the substance to achieve intoxication or desired effect, or (b) Markedly diminished effect with continued use of the same amount of the substance.
11. Withdrawal is experienced, as manifested by either of the following: (a) The characteristic withdrawal syndrome for the substance, or (b) The same (or closely related) substance is taken to relieve or avoid withdrawal symptoms.

Specify current severity: *Mild, presence of two to three symptoms; Moderate, presence of four to five symptoms; Severe, presence of six or more symptoms.*

Although DSM-5 no longer includes substance "dependence" as a separate substance use disorder, the term drug dependence still is, and likely will continue to be, widely used. In this regard, it is important for clinicians to be aware of an additional term that is commonly used within the circle of addiction medicine, which is *psychological dependence*. Like many terms used in communicating aspects of drug use, the term "psychological dependence" has had different meanings. In this instance, psychological dependence is defined as the emotional state of craving a drug either for its positive effect or to avoid negative effects associated with its use. As noted earlier, it is important for clinician's during patient evaluation of a substance use issue to be aware that "craving" (for a substance) is one of the 11 criteria for a diagnosis of substance use disorder according to DSM-5, which increasingly has replaced the DSM-IV definition of dependence.[41,44]

The DSM-5 criteria, which are based on the most current knowledge about substance use disorders that comes from research and clinical practice, ease existing problems of describing substance use because the DSM-5 criteria are clearly written and descriptive. This does not mean that the criteria are perfect; indeed, the expectation is that the criteria will continue to evolve as new knowledge accrues. This is important for clinicians to understand because having an understanding of a generally accepted definition of substance use makes it far more likely to acquire new knowledge about a substance use and addiction disorder and eventually have a good understanding of it. Another point to consider is that the DSM-5 provides no definition of drug use. In DSM-5 terms, drug use would be any consumption of

alcohol or other drugs and related events that do not meet the criteria for a *use disorder*.[45,46]

Drug Tolerance, Withdrawal, and Drug Use Behavior

The DSM-5 criteria for substance use disorder include the term *drug tolerance*, which was defined in parts (a) and (b) of criterion 10 in the table above. Another new term is *withdrawal symptoms*. Withdrawal is a definable illness that occurs with a cessation or decrease in drug use after the body has adjusted to the presence of a drug to such a degree that it cannot function without the drug. Not all drugs are associated with an identifiable withdrawal syndrome (also called abstinence syndrome). For any drug associated with withdrawal symptoms, the severity of those symptoms may change with the characteristics of the users and their history of use of that drug. Furthermore, psychological symptoms, such as anxiety, depression, and craving for drugs, are often part of withdrawal syndromes. These psychological symptoms strongly influence whether the individual can stop using drugs for any length of time.[46]

Tolerance and withdrawal are addressed as part of any evaluation or study of a drug, as they are central topics in psychopharmacology. It is critical to understand that tolerance and withdrawal affect drug-use patterns. For example, if tolerance to a drug develops, the individual must consume increasing amounts of it to achieve a desired drug effect. Such a trend in use may affect how much time the person devotes each day to acquiring the drug and to using it. Furthermore, with greater quantities and frequencies of drug use, the person

becomes more susceptible to experiencing various negative physical, social, or legal consequences.[47]

Drug withdrawal also makes a person more likely to continue or resume the use of a drug after a period of abstaining. Many studies have shown that relief from withdrawal is a powerful motivator of drug use. In this regard, drug withdrawal may begin when the level of drug in the blood drops. If the user takes more of the drug at this point, the withdrawal symptoms are relieved. Here the motivating force is the "turning off" of unpleasant withdrawal symptoms, which works to perpetuate a powerful cycle of drug use, drug withdrawal, and drug use again. Withdrawal is also associated with a higher likelihood of resuming drug use following a period of abstinence because of learned reactions to cues in the environment.[47,48]

Another factor that may be critical to the development of addictive drug-use patterns is "sensitization." The sensitization hypothesis is that one result of repeated use of a drug in interaction with environmental factors is changes in the brain neural pathways that may heighten (sensitize) the reward value of that drug. This means that the drug's effects become more appealing to an individual, and therefore procurement of the drug may assume increasing control over his/her behavior. Critically, the brain changes resulting from repeated drug use may be permanent, which is one reason why drug addiction may be such an intractable problem for many people.[10,48]

Using a drug for a long time alters the patterns of use for that drug. Long-term use also relates to the DSM-5 criteria. Tolerance, withdrawal, and sensitization may result not only in changes in drug

use and preoccupation but also in the likelihood that the person's life and the lives of those around that person are affected by the drug in a snowballing effect, with one consequence building on another. The outcome can reflect some of the criteria included in the DSM-5 definition of substance use disorder.[10,11]

As mentioned, with the publication of DSM-5, cannabis abuse and dependence are now considered part of the same substance use disorder, or simply, cannabis use disorder. When soliciting information related to marijuana use, both acutely and chronically, clinicians are advised to keep in mind the diagnostic criteria of DSM-5, as outlined below.[41]

Cannabis Intoxication

Cannabis intoxication, a cannabis-related disorder coded as 292.89, is defined by DSM-5, as the following:

- Recent use of cannabis
- Clinically significant problematic behavioral or psychological changes (*i.e.*, impaired motor coordination, euphoria, anxiety, sensation of slowed time, impaired judgment, social withdrawal) that developed during, or shortly after, cannabis use
- At least 2 of the following signs, developing within 2 hours of cannabis use:
    - Conjunctival injection
    - Increased appetite
    - Dry mouth
    - Tachycardia
- Symptoms not due to a general medical condition and not better accounted for by another mental disorder

Clinicians are instructed to specify if this is occurring with perceptual disturbances — hallucinations with intact reality testing or auditory, visual, or tactile illusions occur in the absence of delirium.

Cannabis Use Disorder

Cannabis use disorder, a cannabis-related disorder coded as 305.20 for mild or 304.30 for moderate or severe, is defined by DSM-5 as the following:

- A problematic pattern of cannabis use leading to clinically significant impairment or distress, as manifested by at least 2 of the following, occurring within a 12-month period:
    - Cannabis 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 cannabis use.
    - A great deal of time is spent in activities necessary to obtain cannabis, use cannabis, or recover from its effects.
    - Craving, or a strong desire or urge to use cannabis.
    - Recurrent cannabis use resulting in a failure to fulfill major role obligations at work, school, or home.
    - Continued cannabis use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of cannabis.
    - Important social, occupational, or recreational activities are given up or reduced because of cannabis use.

- Recurrent cannabis use in situations in which it is physically hazardous.
- Cannabis 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 cannabis.
- Tolerance, as defined by either a (1) need for markedly increased cannabis to achieve intoxication or desired effect or (2) markedly diminished effect with continued use of the same amount of the substance.
- Withdrawal, as manifested by either (1) the characteristic withdrawal syndrome for cannabis or (2) cannabis is taken to relieve or avoid withdrawal symptoms.

Clinicians are instructed to specify the following:

- Early remission:

  After full criteria for cannabis use disorder were previously met, none of the criteria for cannabis use disorder has been met for at least 3 months but for less than 12 months (with an exception provided for craving).

- Sustained remission:

  After full criteria for cannabis use disorder were previously met, none of the criteria for cannabis use disorder has been met at any time during a period of 12 months or longer (with an exception provided for craving).

Cannabis Withdrawal

DSM-5 provided criteria for cannabis withdrawal, coded as 292.0 and defined as follows:

- Cessation of cannabis use that has been heavy and prolonged (*i.e.*, usually daily or almost daily use over a period of at least a few months).
- Three or more of the following signs and symptoms develop within approximately 1 week after cessation of heavy, prolonged use:
    - Irritability, anger or aggression
    - Nervousness or anxiety
    - Sleep difficulty (*i.e.*, insomnia, disturbing dreams)
    - Decreased appetite or weight loss
    - Restlessness
    - Depressed mood
    - At least one of the following physical symptoms causing significant discomfort: abdominal pain, shakiness/tremors, sweating, fever, chills, or headache
- The signs or symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication or withdrawal from another substance.

Compared with other illicit substances with clearly defined withdrawal states and associated symptoms, the definition of a cannabis withdrawal syndrome (CWS) had remained controversial. Previously, as no evidence was available of increasing tolerance associated with cannabis use, the diagnosis of cannabis dependence (as identified in DSM-IV) with physiological dependence was controversial, if not impossible. Although prior studies have attempted to illustrate the existence of CWS, these studies have had significant limitations. Additionally, until recently, there has been a dearth of any prospective studies assessing the occurrence of CWS. However, a prospective study more recently focused on assessing the course of CWS symptoms among patients using cannabis who were seeking detoxification. This study appears to support evidence of a clinically relevant CWS that the authors qualify as being only expected in a subgroup of patients using cannabis at a high enough level to qualify as a substance use disorder. Its definition and inclusion in DSM-5, is consistent with the symptoms described by these researchers. While DSM-5 defined the timeframe as occurring within 1 week after cessation of prolonged, heavy use, the authors of this prospective study on CWS specified symptoms are believed to occur following a 24-hour period of abstinence, peaking at day 3 following abstinence and lasting 1-2 weeks.[42,43,44]

The authors recommended subgrouping "cannabis-dependent" patients undergoing detoxification into those with no or only very mild CWS and those with moderate-to-strong CWS. Risk factors that seemed to predict which subgroup patients could be classified by included recent cannabis intake and last amount of cannabis consumed prior to hospitalization, with patients reporting recent and more cannabis

consumption before hospitalization as more likely to report symptoms of CWS. A withdrawal scale predicated on a study of 49 "cannabis-dependent subjects" may have reliability in assessing the severity of cannabis withdrawal symptoms.

Other Cannabis-Induced Disorders

This section provides a basic review of other cannabis-induced disorders that health team members should be aware of during the course of patient care and when developing a treatment plan that includes varied or co-morbid conditions existing with a substance use disorder.

Cannabis Intoxication Delirium

Cannabis intoxication delirium, a cannabis-induced disorder coded as 292.81, relies on the definition of delirium and this diagnosis is appropriate when the following 2 symptoms predominate:

- Disturbance in attention (*i.e.*, reduced ability to direct focus, sustain, and shift attention) and awareness (reduced orientation to the environment).
- An additional disturbance in cognition (*i.e.*, memory deficit, disorientation, language, visuospatial ability, or perception).

Cannabis-Induced Psychotic Disorder

Cannabis-induced psychotic disorder is coded as 292.9 and defined by DSM-5 as follows:

- Presence of one or both of the following symptoms:
    - Delusions
    - Hallucinations

- Evidence from the history, physical examination, or laboratory findings of either one of the following:
    - The symptoms in the first criterion developed during or soon after substance intoxication or withdrawal.
    - The involved substance is capable of producing these symptoms.
- The disturbance is not better accounted for by a psychotic disorder that is not substance induced. Evidence that the symptoms are better accounted for by a psychotic disorder that is not substance induced might include the following:
    - The symptoms precede the onset of the substance use (or medication use).
    - The symptoms persist for a substantial period (*i.e.*, about a month) after the cessation of acute withdrawal or severe intoxication or are substantially in excess of what would be expected given the type or amount of the substance used or the duration of use.
    - Other evidence suggests the existence of an independent non–substance–induced psychotic disorder (*i.e.*, a history of recurrent non–substance–related episodes).
- The disturbance does not occur exclusively during the course of a delirium.
- The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Cannabis-Induced Anxiety Disorder

Cannabis-induced anxiety disorder**,** categorized as a cannabis-induced disorder and coded as 292.89, is defined by the DSM-5 as follows:

- Panic attacks or anxiety predominate in the clinical picture.
- Evidence from the history, physical examination, or laboratory findings of either of the following:
    - The symptoms in the first criterion developed during or soon after substance intoxication or withdrawal.
    - The involved substance is capable of producing the symptoms in the first criterion.
- The disturbance is not better accounted for by an anxiety disorder that is not substance induced. Evidence that the symptoms are better accounted for by an anxiety disorder that is not substance induced might include the following:
    - The symptoms precede the onset of the substance use (or medication use).
    - The symptoms persist for a substantial period (*i.e.*, about a month) after cessation of acute withdrawal or severe intoxication or are substantially in excess of what would be expected given the type or amount of the substance used or the duration of use.
    - Other evidence suggests the existence of an independent non–substance–induced anxiety disorder (*i.e.*, a history of recurrent non–substance–related episodes).
- The disturbance does not occur exclusively during the course of a delirium.

- The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Cannabis-Induced Sleep Disorder

The DSM-5 defines cannabis-induced sleep disorder as follows:

- A prominent and severe disturbance in sleep.
- There is evidence from the history, physical examination, or laboratory findings of both of the following:
    - The symptoms in the first criterion developed during or soon after cannabis intoxication or after withdrawal from or exposure to it.
    - Cannabis is capable of producing the symptoms in the first criterion. The disturbance is not better explained by a sleep disorder that is not substance/medication induced. Such evidence of an independent sleep disorder could include that symptoms precede the onset of the cannabis use; symptoms persist for a substantial period (*i.e.*, about a month) after the cessation of acute withdrawal or severe intoxication; or there is other evidence suggesting the existence of an independent nonsubstance/medication-induced sleep disorder (*i.e.*, a history of recurrent nonsubstance or medication-related episodes).
- The disturbance does not occur exclusively during the course of delirium.

- The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Unspecified Cannabis-related Disorder

Coded as 292.9, this category applies to presentations in which symptoms characteristic of a cannabis-related disorder that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning predominate but do not meet the full criteria for any specific cannabis-related disorder or any of the disorders in the substance-related and addictive disorders diagnostic class.

Short And Long-Term Effects Of Marijuana Use

Marijuana has general effects on mood, memory, coordination, cognitive ability, and sense perception. It is difficult to classify marijuana properly given its range of effects on humans. At low doses, the person might experience mild euphoria. At moderate doses, perceptual and time distortions may set in along with low motivation; and, at high doses, hallucinations and distortions of body image can occur. Technically, marijuana does not fit neatly into any particular class of drugs; however, it is legally considered a Schedule I narcotic in the United States. Thus, according to the U.S. government, marijuana has high use potential and no accepted medicinal value.

Clearly, marijuana is not in the same class as heroin (also a Schedule I substance). Compared to other substances, the dangers associated with marijuana use are perceived to be relatively mild. However, that does not mean that THC is completely safe. THC does appear to interfere with short-term memory, but there is no conclusive evidence of disruptions in long-term memory.[6]

Smoking marijuana increases the risk of respiratory problems, including lung cancer. This is because marijuana smoke may contain from 50–100 percent more carcinogens than cigarette smoke. In fact, three to four joints a day can do about as much damage as about 20 cigarettes. Also, pot smokers tend to smoke unfiltered joints and hold the smoke in their lungs longer to achieve a more intense effect, thus contributing to potential pulmonary problems. THC impairs reaction time, making it a dangerous drug to consume while operating a motor vehicle. Marijuana and alcohol may potentiate each other, making the combination of these two drugs especially concerning. At high doses, marijuana can be toxic, but lethal overdose is virtually impossible.

Concern has been reported about marijuana's effects on adolescent users and their developing brains. Preliminary evidence suggests that marijuana may negatively impact learning and memory and, among chronic users during adolescence, produce negative effects on psychological functioning later in life.[12,13]

The following is a list of the general short and long term effects of marijuana use. They are discussed in detail in the sections below:[49]

Short-term effects:

- Sensory distortion
- Panic
- Anxiety
- Poor coordination of movement
- Lowered reaction time
- After an initial "up," the user feels sleepy or depressed
- Increased heartbeat (and risk of heart attack)

Long-term effects:

- Reduced resistance to common illnesses (colds, bronchitis, *etc.*)
- Suppression of the immune system
- Growth disorders
- Increase of abnormally structured cells in the body
- Reduction of male sex hormones
- Rapid destruction of lung fibers and lesions (injuries) to the brain could be permanent
- Reduced sexual capacity
- Study difficulties: reduced ability to learn and retain information
- Apathy, drowsiness, lack of motivation
- Personality and mood changes
- Inability to understand things clearly

Short-term and long-term effects are more broadly defined as acute and chronic effects. In these categories, the impact of marijuana use is identified based on the impact it has on the user and his/her body.

Acute Effects

The acute effects of marijuana are changes that take place after ingesting the drug one time. Acute effects can be objective, including observable changes in behavior or physiology. Acute effects can also be subjective, such as when individuals report how high they feel. Of course, the baseline state of the individual can influence response to the drug. Individuals using marijuana (or THC medications), primarily for medical reasons, are often nauseous or in pain at the time of drug administration. The baseline state will have an effect on the individual's response to the drug. For those who are nauseated or in pain, relief from aversive symptoms may be central to the acute experience of the drug. Recreational users of marijuana may be primarily motivated to achieve a subjective state such as feeling high, although the drug also produces several objective changes, including changes to the body. Regardless of the reason for use of marijuana, the risk of fatal overdose is extremely small when marijuana is used alone.[18]

Although there are a number of acute effects that may occur when an individual smokes or ingests marijuana (discussed in further detail in the following sections), the following are three of the most common effects:

- Distorted perception
- Difficulty with thinking and problem solving
- Loss of motor coordination

Acute effects are categorized into two groups, which are outlined in the table below:[7,14,49-51]

Objective	Marijuana is a sedative drug, with acute effects impairing both

Effects	cognitive and behavioral functions. Multiple aspects of cognitive processing are impaired by marijuana. The ability to pay attention in a sustained manner is decreased. In addition, errors on psychomotor tasks tend to increase. When marijuana users drive, their driving skill is impaired in part because they are less able to concentrate on the driving task and avoid distraction. Road-traffic accidents are more likely for individuals having used marijuana, with higher risk for individuals having had higher doses of marijuana. The problem of impaired driving under the influence of marijuana is a serious concern. However, statistics do indicate that alcohol-impaired driving is a much greater societal problem, in part because marijuana is used less frequently than alcohol. A study in France between 2001 and 2003 found that 3% of fatal road-traffic accidents were attributable to marijuana, whereas 30% of accidents were attributable to alcohol. Of course, either type of fatal crash (marijuana- or alcohol-related) is entirely preventable. Researchers have estimated that the impairment resulting from a 2.6% to 4.0% THC concentration is comparable to a blood alcohol concentration of .05 g%. The decrements in attention following marijuana administration lead to impairments in memory. When one does not pay attention, new information is not stored in memory for later retrieval. Marijuana's contribution to interference with memory processing is highly reliable, particularly in relation to the ability to form new memories, rather than recalling old well-learned memories. For example, an individual who has smoked marijuana may have a conversation with a friend and mutually decide to meet at 7 p.m. at a certain restaurant. This memory may be poorly encoded and the individual who smoked marijuana may not remember the time, the location, or anything else about the

	conversation. However, the marijuana-smoking individual would still be able to recall information from earlier events when not under the influence of marijuana, such as how the friends had decided to attend a concert and had purchased tickets for the event earlier that week. Thus, the acute effects of marijuana decrease attention, which limits how much new information can be encoded and stored in long-term memory during the time marijuana is in the body. Beyond memory impairment, individuals who are under the influence of marijuana exhibit diminished motor activity. Marijuana users also tend to interact with others less frequently in social situations, although that observation can depend on context. In laboratory settings, decreased verbal interactions occur among research subjects who have smoked marijuana, although these individuals may still spend time with others. However, some users also demonstrate the opposite outcome, in which talkativeness increases, even while most other aspects of motor behavior are reduced. In addition, aggression is reduced, and subjects in research studies are less likely to exhibit aggressive responses to highly provoking actions by others. Finally, another reliable outcome with marijuana administration is increased appetite. Individuals feel hungry and eat more food when using marijuana. This objective change in appetite stimulation is sometimes referred to as "the munchies" and is therapeutically useful in medical patients. Increased food intake can also lead to weight gain among recreational users of the drug. Increases in food intake tend to be similar whether marijuana is smoked or orally administered as THC in pill form.
Subjective Effects	The acute effects of marijuana can cause several changes in subjective state. However, the one constant about the acute

	effects of marijuana on subjective state is that reported experiences are highly variable. Thus, conclusions about the typical subjective effects for users are somewhat difficult to make. For example, many who use marijuana may report feeling almost nothing the first few times they tried marijuana. It has been argued that the lack of subjective change among initial users could reflect anything from inexperience in smoking technique to the necessity for sensitization to occur in the brain. When subjective effects are experienced, users report euphoria or a feeling of being high, but the effects tend not to be dramatic and the users may also characterize themselves as feeling mellow, drowsy, relaxed, or carefree. Users tend to be prone to laughter and loquaciousness (talkativeness). Subjective effects from smoking marijuana tend to be experienced within a few minutes after initiation of smoking. Subjective effects may peak at approximately 15–30 minutes and then dissipate within 2–3 hours. The experience of marijuana intoxication is routinely described as intellectually interesting or emotionally pleasant. Users may describe transient perceptual alterations whereby visual images may seem more intense, colorful, or meaningful. Others describe a relaxed and open experience in which normal feelings and thoughts can be processed more fully. The user's perception of time may also seem to slow down. Subjective changes tend to be similar whether marijuana is smoked or administered orally as THC in pill form. However, not all subjective effects are positive, and some users report anxiety, panic attacks, or other negative symptoms. Less commonly, paranoid thoughts and other psychotic symptoms occur. The acute effects of synthetic illicit THC and similar compounds,

	found in Spice and K2, are similar to marijuana. However, in some cases acute anxiety and psychosis have been reported to be higher with synthetic marijuana than with plant-based marijuana.

Chronic Effects

Despite the widespread use of marijuana, the literature on the chronic effects of marijuana is oddly sparse. However, there are indications that chronic use of marijuana leads to several important health concerns. First, chronic marijuana use can result in various cognitive deficits. Cognitive impairments can be observed, from basic motor coordination to more complex executive functions such as planning, organizing, solving problems, and making decisions. Memory problems and difficulty controlling emotions and behavior have also been reported. Of course, the deficits vary considerably in severity, with one's history of drug use playing an important role.

Quantity, frequency, and duration of use, as well as age of onset of use, are all factors that contribute to the likelihood that cognitive deficits emerge. Users who have used more marijuana, more recently, for a longer duration of time, and with a younger age of initiation are more likely to experience problems. Moreover, chronic marijuana users may also use other drugs that increase the likelihood that cognitive deficits develop.[50,52]

Physiological Effects

Acute Effects

Although cannabis produces physiological effects, most of these actions are different for different users, not only in strength or intensity of the effect but also in duration. In general, the acute physiological effects of marijuana in a healthy individual are not dramatic. In fact, the LeDain Commission reported that the typical cannabis dose resulted in short-term physiological effects that was generally benign and apparently of little clinical significance in the average person; a finding often reported in subsequent research.

The most commonly experienced effects are cardiovascular. Predominant among these is injection of the conjunctiva, or bloodshot eyes. This effect, a result of vasodilation, is most obvious about an hour after smoking, and it is generally dose related. Although some cite a concomitant dilation of the pupil, research does not support this claim. It appears more likely that the dilation is a consequence of smoking the marijuana in a darkened room. There does, however, tend to be a cannabis-induced sluggish reaction to light.[31]

The second most common cardiovascular effect is an increase in heart rate and pulse rate. Both of these effects last for about an hour, and each appears to be dose related. The peak heart rate occurs around 20 minutes after smoking. In addition to these effects, blood pressure tends to become slightly elevated. No evidence indicates that these effects create any permanent damage within the normal cardiovascular system.[32]

The most significant acute effect of smoking marijuana is its action as a bronchodilator, which increases vulnerability to the smoke by decreasing airway resistance and increasing specific airway conductance. Marijuana-induced bronchodilation has been demonstrated with healthy control participants and asthmatics, and under conditions of experimentally induced asthma. Marijuana's effect, which is bronchodilation, distinguishes it from tobacco smoking, which produces bronchoconstriction.

Marijuana smoking also increases absorption of carbon monoxide, resulting in elevated levels of blood carboxyhemoglobin (COHb). Although smoking tobacco also boosts COHb, the increase found with smoking marijuana is as much as four times greater than with tobacco. These elevated levels of COHb lead to reduced oxygen in the blood and impairment in oxygen release from hemoglobin. Reduced blood oxygen levels can stress a number of organs including the heart. Another general effect following cannabis use is a generalized decrease in motor activity. The only real exception to this is the talkative behavior of many following smoking. Some users also report drowsiness. Cannabis use also can have a marked effect on sleep stages, tending in part to decrease the total REM sleep achieved. However, this effect typically occurs only with higher doses of cannabis.[49,51]

Other effects have also been reported, but they tend to be minor or infrequent and often variable from person to person. These other effects include (but are not limited to) dry mouth, thirst, fluctuations in respiration and body temperature, hunger or "the munchies" (peaking two to three hours after smoking), nausea, and headache or dizziness.

Chronic Effects

Data on the longer-term effects of marijuana unfortunately are sparse and difficult to interpret. The research that has been conducted has focused on four central systems: respiratory, cardiovascular, immune, and reproductive.[18,52,54,56-58]

Respiratory System	The impact of chronic marijuana smoking on respiratory health has many similarities to that of tobacco smoking. Compared with nonsmokers, chronic marijuana smokers show increased likelihood of outpatient visits due to respiratory illness and exhibit respiratory symptoms of bronchitis at comparable rates to tobacco smokers. Chronic bronchitis can be moderately debilitating and increases the risk of additional infections. As THC appears to suppress immune system function, recurrent bronchitis may further increase the risk of opportunistic respiratory infections such as pneumonia and aspergillosis. This is of concern particularly for those individuals with already compromised immune functions such as cancer and AIDS patients. Airway obstruction and symptoms of chronic cough, sputum production, shortness of breath, and wheezing characterize chronic bronchitis. These symptoms are the result of airway inflammation and tissue damage caused by marijuana smoke that results in increased fluid production, cellular abnormalities, and reduced alveolar permeability. This damage begins long before overt symptoms such as cough or wheezing are evident. Cellular abnormalities include reductions in ciliating surface cells of the lungs that function to clear fluid from the lungs to the mouth and throat.

	As a result, marijuana smokers have substantially higher bronchitis index scores than nonsmokers, and comparable scores to tobacco smokers, even at young ages with only short histories of marijuana use. Investigations of chronic obstructive pulmonary disease (COPD) in chronic marijuana smokers have been inconclusive. A common severe consequence of tobacco smoking, COPD includes chronic obstructive bronchitis or emphysema, and is characterized by impairment in small airway function rather than large airways. Marijuana smokers exhibit almost identical degrees of histopathologic and molecular abnormalities associated with progression to COPD in tobacco smokers and several case reports have been identified. However, two earlier large-scale studies of COPD in chronic marijuana users have been inconclusive. Bloom, *et al.* (1987) reported some indication of reduced small airway function suggestive of COPD, while Tashkin, *et al*. (1987) found no evidence of small airway obstruction or other indicators of COPD. Chronic cannabis smoking is likely associated with respiratory cancer, although this link is not definitive. Cannabis smoking is clearly associated with similar processes and patterns of disease that lead to aerodigestive cancers among tobacco smokers. As noted previously, marijuana smoke contains more carcinogens than cigarette smoke. Marijuana interferes with normal cell function, including synthesis and functions of DNA and RNA, and appears to activate an enzyme that converts inactive carcinogens found in marijuana smoke into active carcinogens. Chronic marijuana smokers also show substantial cellular mutation associated with tumor progression. Marijuana also reduces the ability of pulmonary alveolar macrophages to kill pathogens, including

	tumor cells, allowing tumors to grow more rapidly. Clinical reports of aerodigestive cancers in individuals who had a history of marijuana smoking with limited or no tobacco exposure have provided suggestive evidence of a link between marijuana use and cancer. In addition, Zhang, *et al*., (1999) found increased risk for squamous-cell carcinoma of the head and neck for marijuana smokers compared with nonsmokers when tobacco smoking was statistically controlled. Similarly in a case-controlled hospital study in Casablanca, Morocco, Sasco, *et al*., (2002) found that the use of hashish was independently predictive of lung cancer. The only epidemiological study that directly examined the risk of aerodigestive cancer in marijuana users reported no significant risk associated with cannabis. This study, however, included a relatively young cohort comprised of primarily experimental and light marijuana users rather than chronic heavy users. Individuals who began smoking marijuana in the late 1960s are now approaching ages that are more likely to be associated with aerodigestive cancer; hence, future epidemiological studies should clarify better the risk of cancer associated with chronic cannabis use. Smoking both cannabis and tobacco warrants mention as this combination most likely produces an additive adverse effect on the respiratory system. Tobacco smoking is common among cannabis users, as almost half of daily marijuana users also smoke tobacco. This subgroup of marijuana smokers merits careful study as they may be at particularly high risk for respiratory disease.
Cardiovascular System	Relatively little research has been conducted on the long-term cardiovascular effects of chronic cannabis use. Most studies have focused on acute changes and suggest a limited cardiovascular health impact associated with cannabis use. The

	primary acute effect of smoked marijuana or oral THC is tachycardia. The increase in heart rate appears dose dependent, is observed with nonusers and chronic users, and is reduced as tolerance develops. Cannabis or oral THC can produce small increases in supine blood pressure and impair vascular reflexes. Smoking marijuana also results in increased inhalation of carbon monoxide and subsequent COHb, which in combination with tachycardia, increases the work required of the heart. Cannabis use also may reduce exercise tolerance, which is likely due to the combination of tachycardia, reduced thermoregulation caused by decreased vascular reflexes, and the increase in carbon monoxide. Although these findings show clear changes in cardiovascular functioning due to marijuana or THC use, the effects have not been associated with short-term or long-term cardiovascular or cerebrovascular injury/disease. Case reports suggest that regular cannabis smoking may increase risk for some serious disorders such as arteritis and transient ischemic attacks, but no controlled studies support these reports. For most healthy young marijuana smokers, the stress to the heart produced by marijuana use does not appear clinically detrimental. However, for individuals with cardiovascular or cerebrovascular disease, the additional cardiac stress may increase the risk for chest pain, heart attack, or stroke. Additional research is needed to further elucidate the effects of chronic cannabis use on cardiovascular health, including interactions with other risk factors.
Immune System	Chronic use of cannabis appears to compromise the immune system, particularly the immune defense systems of the lungs. This suppressive effect occurs in a variety of immune cells including killer cells, T cells, and macrophages. Most research has focused on pulmonary alveolar macrophages (PAMs), which

	are killer cells destroying infectious microorganisms in the lungs. Compared with tobacco smokers and non-smokers, PAMs of chronic cannabis smokers exhibit a reduced ability to kill tumor cells and many microorganisms, including fungi and bacteria. As with tobacco, cannabis smoking produces an inflammatory response in the lungs, which increases growth in the number and concentration of PAMs. However, their efficacy for destroying microorganisms is compromised. Cannabis smoking also appears to impair phagocytosis and cytokine function of the PAMs. Recent studies have begun to explore the mechanisms that may be involved in the inhibitory responses associated with chronic cannabis smoking. The functional consequences of cannabis's effect on the suppression of the immune system in humans are poorly understood. Nonetheless, clinical findings suggest that such effects warrant some concern. Chronic cannabis smoking is associated with increased bronchitis and other respiratory illnesses. Chronic use may also increase risk of exposure to infectious organisms, as cannabis and tobacco plants are often contaminated with a variety of fungi and molds including aspergillus. Lung illnesses in marijuana smokers have been attributed to fungal infection. Decreased immune system response could increase the vulnerability and risk of developing these respiratory illnesses and lung diseases. More research is needed to determine whether chronic marijuana use is directly responsible for an increased incidence of disease via its effects on immune system function. It is worth noting that the medical use of marijuana has now been legalized in ten U.S. states and legislation is pending in others.

	Many of the patients deemed appropriate candidates for medical marijuana have illnesses that involve already compromised immune systems such as AIDS wasting syndrome and chronic pain from various types of cancer. A better understanding of the functional significance of marijuana's effects on the immune system is imperative as attempts are made to develop safe and effective models for the medical use of marijuana.
Reproductive System	*Hormones and Fertility* Research examining the effects of cannabis use on reproductive function in women or men has been sparse. In women, marijuana smoking can affect some reproductive hormones (*i.e.*, luteinizing hormone, prolactin), but this effect may occur only when they smoke during specific phases of the menstrual cycle. Chronic cannabis use appears to alter male reproductive hormones, but these effects are not conclusive. Some studies have demonstrated marijuana-related decreased levels of gonadotropin, testosterone, prolactin, and luteinizing hormones in men, while others have reported negative findings. For both men and women, the functional significance of these findings remains elusive. Although one might suspect that these purported effects on the reproductive system would adversely influence fertility, this has not been carefully studied in humans. *Perinatal Effects* Pregnant women who use cannabis expose the fetus to its effects, as THC is known to cross the placenta. Here we provide an overview of the perinatal effects of cannabis use, focused primarily on cognitive functioning. It is estimated that 10 to 20 percent of women use marijuana during pregnancy. Thus, understanding the effects on fetal development is vital.

	Studying cannabis use during pregnancy in humans has proven difficult, as pregnant users generally have many additional risk factors for adverse effects such as tobacco smoking, alcohol use, other illicit drug use, poorer nutrition, and lower socioeconomic status SES. Moreover, multiple factors deterring self-disclosure in this population raise concern regarding the validity of self-reports of cannabis use. A number of studies have made efforts to control for these influences other than cannabis that impact perinatal outcomes, hence, certain tentative conclusions appear justified. Risk of major congenital anomalies is not increased due to cannabis use in pregnant women. However, some reports suggest that risk of developing minor anomalies, particularly related to the visual system, may be related to heavy cannabis use, but these data are not robust. Cannabis use during pregnancy may be related to reduced birth weight and length, and possibly shortened length of gestation, although studies have reported conflicting findings. Overall, these perinatal effects, if valid, are clearly not as severe as those observed with tobacco smokers. The cognitive and behavioral effects of prenatal exposure to cannabis are perhaps best addressed in one study, the Ottawa Prenatal Prospective Study (OPPS). This study collected birth data on 700 women and has periodically assessed the children of a subsample of 150 to 200. Adverse effects of prenatal cannabis use were observed in testing the neonate during the first month. Possible indicators of an impact on the nervous system included increased tremors, decreased visual habituation, exaggerated startle, and increased hand-to-mouth behavior. However, at one and two years of age, no cannabis-related effects were

	observed when children were assessed using the Bayley Scales. No cannabis-related effects were observed at three years on tests of language expression, comprehension, and other general cognitive abilities, after controlling for confounding variables. Age four assessments of OPPS children revealed cannabis-related performance decrements on verbal and memory tasks.

It appears the majority of effects associated with marijuana use are more acute than chronic and that longer-term effects tend to be reversible with the termination of drug use. Significant exceptions may occur, however. Smoking marijuana may be linked to various respiratory disorders, including cancer. Most of the negative effects found are correlated with higher doses and frequency of use than those described by most cannabis smokers in this country. Nevertheless, these indications are tentative and await confirmation from more systematic and controlled research.[24,25]

Psychological Effects

Although cannabis can produce the varied effects previously noted, most marijuana users use the drug to experience its psychological effects, some of which are reported consistently and others more idiosyncratically. The psychological effects that marijuana users generally experience can be divided into three domains: behavioral, cognitive, and emotional.[6,7]

Some cannabis effects, especially those associated with the "marijuana high" that users describe, are learned. This learning process has

distinct steps. The first step is mechanical, when the smoker learns to inhale the smoke and hold it in the lungs to maximize intake and absorption. The second step is to learn to perceive the effects of the cannabis, which can be physical as well as psychological. The final step is learning to label these effects as pleasant. This learning process accounts for the frequent finding that experienced users are more sensitive to cannabis effects than would be the case with novice smokers.[32]

Behavioral Effects

The most common behavioral effect is a generalized decrease in psychomotor activity and decrements in some domains of psychomotor performance. These effects appear to be dose related, with more pronounced changes associated with greater amounts of marijuana taken in. The general decrease in motor activity appears to be pervasive, and the state is described as associated with feelings of relaxation and tranquility. The only exception to this effect appears to be speech because marijuana use is associated with rapid or slurred speech, circumstantial talk, and loquaciousness. These speech effects often are observed more in the early smoking phase, followed by the more traditional relaxation.[17,18]

Although relaxation and a sense of wellbeing are the usual responses to cannabis, some users first experience a stage in which they feel excited and restless. Fairly soon, however, these users virtually always experience a transition to the relaxation stage. Furthermore, despite feeling relaxed, users sometimes also feel their senses are markedly keener. Many users, for example, describe more intense perceptions of touch, vision (especially in perceiving colors), hearing, and smell. The

research cited to support these reports is not strong, though. Finally, other research has shown a decreased sensitivity to pain during marijuana intoxication. Concomitant with the feelings of relaxation and decreased motor activity is a subtle impairment in some areas of psychomotor performance. There appear to be dose-related dysfunctions in motor coordination, signal detection, and the ability to monitor a moving object. The data on reaction time are not conclusive. Taken together, these findings have implications for driving a motor vehicle after using cannabis.[13,14,21]

Laboratory studies that use a driving simulator have revealed detrimental effects of marijuana on driving skill, and research findings indicate a significantly increased risk of a motor vehicle crash when under the influence of cannabis. Some of these impairments may be cognitively mediated in that drivers under the influence of marijuana showed impaired judgment and concentration along with other general driving skills. Others have suggested that some of the detriments in driving skill may be due to decreased vigilance and thus less awareness of peripheral stimuli. Therefore, it appears that cannabis can cause psychomotor impairment and that this impairment becomes more apparent in tasks that require thinking and concentration.[8,14,15,16]

The influence of marijuana on sexual behavior and functioning is not fully understood, but its effects vary considerably from user to user. Some report that sexual pleasures are more intense and enjoyable when using marijuana, whereas others describe a disinterest in sex. Those who report increased sexual pleasure when smoking probably are responding to the enhanced sensory sensitivity that frequently accompanies marijuana use. The drug itself produces no known specific physiological response that stimulates sexual drive or

performance. Long-term or heavy use of marijuana has been associated with temporary impotence among men and temporary decreases in sex drive among women.[52]

Cognitive Effects

Two primary cognitive consequences of cannabis intoxication have been documented. The first is impaired short-term memory and the second is the perception that time passes more slowly. The impairment in short-term memory seen following cannabis use can occur with intake of a fairly low dose. The degree of impairment increases rapidly with the complexity of the memory task. This effect has been observed with various types of stimuli, such as word lists and conversational materials. More generally, the evidence indicates that cannabis intake impairs multiple aspects of memory, including the encoding, consolidation, and retrieval of information. There is some evidence to suggest that adolescents may be more vulnerable to these cognitive effects of cannabis than adults.[53]

The mechanisms of marijuana's effects on memory have not been specified, but researchers have identified several possibilities. The first cause simply may be that users are not motivated to attend to or to retrieve the material presented. Although this hypothesis is plausible, indications suggest participants in these experiments perceive the tasks administered as a challenge and respond actively to the task demands. A second possibility is that the perceptual changes created by cannabis produce a *curtain of interference,* which blocks or hinders intake or retrieval of material.

The third hypothesis proposed is that marijuana causes a decreased ability to concentrate and attend to the material presented. This mechanism was advocated by Abel and by DeLong and Levy. These latter researchers have proposed a model of attentional processes as a central key in understanding the cognitive effects of cannabis. Finally, cannabis drug action may interfere with the neurochemical processes that operate in memory and retrieval operations. The exact factor, or set of factors, remains unknown, but it is likely that they operate in concert to affect short-term memory. However, likely mechanisms include cannabis effects on long-term potentiation and long-term depression and the inhibition of neurotransmitter (GABA, glutamate, acetylcholine, dopamine) release.[24,50,54]

Altered perception of the passage of time is the second common cognitive effect of cannabis. This is perhaps best described in statements like *a few minutes seemed to pass like hours*. The effect has been noted in both surveys and the experimental literature. However, the time distortion is not as pronounced in the research reports as it is in more subjective self-reports that marijuana users provided. Other cognitive effects of marijuana have been reported but not as consistently as those already described. One effect is decreased ability to attend and concentrate so that users are easily distracted. Many users report that cannabis produces symptoms of *racing thoughts* and *flight of ideas*, in which various (and sometimes seemingly random) ideas fly in and out of the mind. Another perception sometimes reported is enhanced creativity. Writers and painters have especially noted this.[13]

Finally, some cannabis users describe occasional feelings of unreality and the attachment of increased meaning to events or objects not previously perceived as important. Most of the effects noted are short-term. The effects of long-term cannabis use on cognitive functioning have received much less attention. Research in this area has been increasing, although providing a mixed picture so far. Recent studies reported that a longer history of use was associated with greater cognitive impairment, even after stopping marijuana use. A recent study found that frequent marijuana users (smoking four or more joints per week) performed worse than nonusers on several measures of cognitive functioning, including divided attention (paying attention to more than one task at a time) and verbal fluency.

Among the marijuana users, those who had used marijuana for 10 or more years had more difficulties with their thinking abilities than those who had used marijuana for 5 to 10 years. Other studies comparing the cognitive functioning of current heavy users, former heavy users, light users, and nonusers have not found such a relationship. These studies found that intellectual impairment associated with heavy marijuana use is apparently reversible with abstinence. Although the available research on persistent cognitive effects from long-term marijuana use is equivocal, the distinct possibility of enduring neurocognitive deficits associated with longer-term cannabis use certainly remains.[6,51,55]

Emotional Effects

Positive emotional changes following cannabis intake are cited frequently as key motivators to smoke marijuana. Alterations in mood can occur, but there is uncertainty regarding the extent to which these

are direct drug effects. A host of nonpharmacological factors can contribute to the drug effects experienced. Chief among these nondrug influences are past experiences with cannabis, attitudes about the drug, expectancies regarding the drug use consequences, and the situational context of drug use. These factors must be considered in conjunction with the dose of THC absorbed to understand the emotional changes attributed to the drug.[56]

The typical emotional response to cannabis is a carefree and relaxed state. This feeling has been described in various ways: euphoric, content, happy, and excited. It frequently includes laughter and loquaciousness and may take on the character of a dreamlike state. Most generally, the response is viewed as pleasant and positive. It appears the intensity of the response is positively correlated with the dose. It is noteworthy that negative emotional feelings, such as anxiety or dysphoria, are more common than might be expected. Additionally, a variety of somatic consequences have been experienced, including headache, nausea, and muscle tension; less frequently reported are suspiciousness and paranoid ideation.

About a third of marijuana users at least occasionally experience some negative effects; however, the effects can be transitory. Users may fluctuate between experiencing these negative feelings and the more positive states described earlier. Also, the negative effects often are reported more by inexperienced cannabis users.[4]

In recent years, there has been an increased focus on the relationship between cannabis use and various mental health outcomes, such as schizophrenia, anxiety disorders, and depression. A review of the

literature on this issue concluded that cannabis use increases one's risk for psychotic behavior outcomes (including schizophrenia), and not just among heavy users. In this regard, they found that marijuana users had around a 40% higher chance of developing a psychotic condition later in life, relative to nonusers (although the risk is fairly low overall). Further, it appears that a younger age of onset of marijuana use is associated with a younger age of appearance of psychosis-related symptoms.

Although the data used to address this issue do not prove that marijuana use increases the risk for psychosis (instead, it could be something else about cannabis users, such as their use of other drugs or particular personality traits), the association is still noteworthy. A comparable relationship between cannabis use and anxiety disorders and depressive disorders was not found in the study. In another report, however, a modest link between cannabis use and the risk for a later episode of depression was found. The mechanisms underlying these relationships are not known, although they do not appear to be related to cannabis-induced changes in brain anatomy. Instead, the positive relationship may reflect the impact of cannabis on the dopaminergic pathway, perhaps especially among genetically vulnerable individuals.[8,14,56]

Social and Environmental Effects

Three hypothesized social and environmental consequences of cannabis use have received attention: the role of marijuana in enhancing interpersonal skills, the effect of cannabis on aggression and violence, and the role of marijuana use in what has been called the amotivational syndrome. Many young users of marijuana have said

they use the drug because it enhances their social skills and allows them to be more competent in social situations. Although insufficient data are available to evaluate it fully, this claim has not been supported by the available research. Rather, what seems to occur is that users either are more relaxed in the situation and thus perceive less anxiety or interpret their behavior differently while under the influence of marijuana. In any event, marijuana does not seem to significantly enhance competence in social situations.[2]

A long-standing claim regarding cannabis use is that marijuana causes users to be aggressive and violent. The overwhelming conclusion drawn from data, including surveys, laboratory investigations, and field studies, however, is that cannabis use is not causally related to increased aggression. When aggression is observed, it probably is more a function of the beliefs and characteristics of the individual drug users. In fact, levels of aggression actually decrease following cannabis use.[17,18]

Perhaps the most controversial social/environmental consequence of cannabis use is the *amotivational syndrome*. The term was used independently in the late 1960s by McGlothlin and West and Smith to describe the clinical observation that *regular marijuana use may contribute to the development of more passive, inward turning, amotivational personality characteristics*. Based on case reports, the phenomenon was most likely to be seen among younger users who were using marijuana daily or heavily. The list of behaviors proposed as part of the syndrome includes apathy, decreased effectiveness, lost ambition, decreased sense of goals, and difficulty in attending and concentrating.

Although there does not seem to be much question that these characteristics cluster in some marijuana users, the causal influence of cannabis is not clear. Also, there is some debate about just how commonly the syndrome occurs, with some citing it as fairly infrequent. In addition, anthropological investigations of heavy cannabis users in other countries generally have not found the presence of the amotivational syndrome, and laboratory studies on cannabis use in humans have not supported the hypothesized syndrome. Furthermore, survey studies do not always find the differences between marijuana users and nonusers that would be expected if marijuana caused this clustering of effects. And, the amotivational syndrome has been seen in youths who do not use marijuana and is often not seen in other daily users of marijuana. Thus, both preexisting personality characteristics and some drug effects together probably account for the clustering labeled the amotivational syndrome, when it occurs.[5,21,22]

Marijuana Use And Mental Illness

The relationship between substance use and psychiatric disorders can change over time, and will vary throughout the addiction process. Changes in severity, chronicity, disability, and degree of impairment in functioning are common and must be understood as the patient begins the treatment and recovery process. Each condition will have an individual affect on the patient that will range in severity, yet both conditions will also affect the other, thereby potentially increasing the severity or extent of the symptoms. The extent and severity of both conditions may change over time, depending on the patient's status and adherence to treatment and recovery.[57,58]

It is important to note that patients with mental disorders are at an increased risk of developing a substance use disorder. In addition, substance users are at an increased risk of developing mental health issues.[59] Therefore, each condition must be handled accordingly. When working with patients with co-morbid conditions it is important to note that "*compared with patients who have a mental health disorder or an substance use problem alone, patients with dual disorders often experience more severe and chronic medical, social, and emotional problems. Because they have two disorders, they are vulnerable to both substance relapse and a worsening of the psychiatric disorder. Further, addiction relapse often leads to psychiatric decompensation, and worsening of psychiatric problems often leads to addiction relapse. Thus, relapse prevention must be specially designed for patients with dual disorders. Compared with patients who have a single disorder, patients with dual disorders often require longer treatment, have more crises, and progress more gradually in treatment*."[60] The following section addresses the mental disorders most associated with marijuana use.

Schizophrenia

Schizophrenia is a thought disorder believed to be mostly inherited, characterized by:[61]

- hallucinations (false visual, auditory, or tactile sensations and perceptions)
- delusions (false beliefs)
- an inappropriate affect (an illogical emotional response to any situation
- autistic symptoms (a pronounced detachment from reality)

- ambivalence (difficulty in making even the simplest decisions)
- poor association (difficulty in connecting thoughts and ideas)
- poor job performance
- strained social relations
- an impaired ability to care for oneself

Major Depression

Major depression is classified as an affective disorder along with bipolar affective disorder and dysthymia (mild depression). A major depression is likely to be experienced by 1 in 20 Americans during their lifetime. It is characterized by:[62]

- depressed mood
- diminished interest and diminished pleasure in most activities
- disturbances of sleep patterns and appetite
- decreased ability to concentrate
- feelings of worthlessness
- suicidal thoughts

All of these symptoms may persist without any life situation to provoke them. For the diagnosis to be made accurately, these feelings have to occur every day, most of the day for at least 2 weeks running.[63]

Bipolar Affective Disorder (Manic Depression)

This illness is characterized by alternating periods of depression, normalcy, and mania. The depression phase is described above. The depression is as severe as any depression seen in psychiatry. If untreated, many bipolar patients frequently attempt suicide. The mania, on the other hand, is characterized by:

- a persistently elevated, expansive, and irritated mood

- inflated self-esteem or grandiosity
- decreased need for sleep
- more talkative than usual or pressure to keep talking
- flight of ideas
- distractibility
- increase in goal-directed activity or psychomotor agitation
- excessive involvement in pleasurable activities that have a high potential for painful consequences (*i.e.*, drug use, gambling, or inappropriate sexual advances).

These mood disturbances are severe enough to cause marked impairment in job, social activities, and relationships. Bipolar affective disorder usually begins in a person in his or her twenties, and affects men and women equally. Many researchers believe this disease is genetic.[64]

Anxiety Disorders

Anxiety disorders are the most common psychiatric disturbances seen in medical offices. There are listed below as:[65]

1) Panic disorder with and without agoraphobia (fear of open spaces).
2) Agoraphobia without history of panic disorder (a generalized fear of open spaces).
3) Social phobia (fear of being seen by others to act in a humiliating or embarrassing way, such as eating in public).
4) Simple phobia (irrational fear of a specific thing or place).
5) Obsessive-compulsive disorder (uncontrollable, intrusive thoughts and irresistible, often distressing actions, such as cutting one's hair or repeated hand washing).

6) Post-traumatic stress disorder (persistent re-experiencing of the full memory of a stressful event outside usual human experience, *i.e.*, combat, molestation, car crash). It is usually triggered by an environmental stimulus, *i.e.*, a car backfires and the combat veteran's mind relives the stress and memory of combat. This disorder can last a lifetime and be very disabling.
7) Generalized anxiety disorder (unrealistic worry about several life situations that lasts for 6 months or more).

Sometimes it is extremely difficult to differentiate the anxiety disorders. Many are defined more by symptoms than specific names. Some of the more common symptoms in anxiety disorders are shortness of breath, muscle tension, restlessness, stomach irritation, sweating, palpitations, restlessness, hypervigilance, difficulty in concentrating, and excessive worry. Often anxiety and depression are mixed together. Some physicians think that many anxiety disorders are really an outgrowth of depression.

Organic Mental Disorders

These are problems of brain dysfunction brought on by physical changes in the brain caused by aging, miscellaneous diseases, injury to the brain, or psychoactive drug toxicities. Alzheimer's disease, where older people suffer unusual rapid death of brain cells resulting in memory loss, confusion, and loss of emotions so they gradually lose the ability to care for themselves, is one example of an organic mental disorder. Mental confusion from heavy marijuana use in an elderly patient may mimic symptoms of this disorder.

Addiction Potential Of Marijuana

Many psychoactive drugs can result in tolerance when used regularly. Users may find that their typical dose results in a suboptimal effect, and such users may therefore escalate their dose to achieve the desired effect. However, whether tolerance to marijuana actually develops is currently unclear. In some cases, users do not appear to escalate their dose over time, which suggests that tolerance development may not be a major concern for recreational users or medical patients. Other evidence suggests that tolerance does develop to marijuana.[9,66]

Tolerance to cannabis has been well documented in animal species. The evidence for tolerance to cannabis in humans is less clear, with many studies indicating tolerance but a number of others not. Some of the discrepancies in the human studies can be attributed to the dose of marijuana and the duration of use being studied. Tolerance is more likely to occur with higher doses used over longer periods of time. Research has typically been done in controlled laboratory settings, where the doses and frequencies of use studied are generally much greater than those reported by marijuana users in the general population. The mechanisms by which tolerance occurs are still unknown.[67]

Frequent marijuana smokers may report that they feel less high than an infrequent user given the same dose. This might indicate that tolerance has developed among frequent marijuana users. In one study examining tolerance in a controlled laboratory inpatient setting, marijuana smokers were given 20 mg of THC every 3.5–6 h for a week. The subjective ratings of intoxication following the first THC

dose of the day declined over the week, indicating that the subjects had developed some tolerance to the high that the dose of marijuana induced. Tolerance was limited to subjective effects, however. While THC lowered blood pressure and elevated heart rate over the six days, it did so in a similar manner on each test day, suggesting that tolerance did not develop to the cardiovascular effects of the drug. However, behavioral studies with animals have demonstrated tolerance to THC. If tolerance to marijuana develops, it seems to go away rapidly with abstinence from the drug.[68]

There is an ongoing debate as to whether physical dependence can occur in the context of marijuana use. Some have argued that there is no significant withdrawal syndrome identifiable, and certainly no clustering of withdrawal indicators as identified for other substances such as alcohol or heroin. However, some studies have described several aspects of dependence associated with sustained heavy use of marijuana. These aspects entailed sleep disturbance, nausea, irritability, and restlessness following cessation of marijuana use.

It has been more recently posited that these symptoms reflect a reliable and clinically significant withdrawal syndrome, although debate continues as to whether these symptoms are more indicative of a psychological as opposed to physical dependence on marijuana. At present, it appears that aspects of physical dependence, when they occur, are most likely to be associated with sustained heavy use of marijuana.

Gateway Drug Theory

A marijuana use disorder can lead individuals to seek treatment. However, clinical drug use populations tend not to be dominated by exclusive marijuana users since few patients ever seek treatment for marijuana addiction alone. Individuals who need treatment for drug use problems may use marijuana, but it is unlikely that marijuana was the major concern requiring treatment. However, there does tend to be a natural history of drug initiation, a pattern that has been documented in various countries around the world. Typically, individuals initiate the use of drugs in the following order: alcohol and tobacco first, marijuana second, and then other illicit drugs such as cocaine and heroin.

The gateway drug theory is based on the premise that marijuana control is necessary in order that users not proceed to other highly addictive drugs such as heroin. The gateway drug theory is difficult to study, since it requires prospective cohort studies. For example, researchers might design a prospective cohort study that involves recruitment of children before any of the children had tried marijuana and then follow those children into adulthood to see who became addicted to other drugs. Despite the lack of good prospective cohort studies, it does seem clear that marijuana is frequently a stepping stone to dependence on other more highly addictive illicit psychoactive drugs. However, a large majority of marijuana users do not proceed to develop problem with using other drugs, which has led researchers to question the validity of the gateway drug theory.[69]

There are also clearly cases of a marijuana use disorder. The risk of a marijuana use disorder has been estimated to be approximately 9% among lifetime marijuana users, which is a significant concern but a

rate that is far lower than the risk of a problem with using other illicit drugs. Most often, marijuana leads to a psychological craving rather than a physical need to use. The marijuana user may crave the drug. They may feel irritable, depressed, restless, and agitated if they do not use the drug. However, there are limited illness-like physical withdrawal symptoms indicating physical addiction on the drug.

Some patients may report insomnia, nausea, anorexia, and cramping. If withdrawal symptoms develop, they tend to follow a time-course similar to other drugs like tobacco. The onset of withdrawal symptoms from marijuana begins after 1–3 days of abstinence. Peak effects occur on or before day 6. After 2 weeks of abstinence, withdrawal symptoms have dissipated for most individuals. Both psychological and physical withdrawal symptoms are not particularly aversive, at least in comparison to withdrawal symptoms following use of other psychoactive drugs. Even compulsive marijuana users do not appear to continue to use the drug out of fear of withdrawal symptoms. This makes marijuana quite different than other drugs of use. For example, individuals who have an alcohol or opiate use disorder will become extremely sick, even fatally so, if they suddenly cease use of their drug of use. Such users of alcohol or opiates may continue use of their drug just to avoid the development of withdrawal symptoms.

Withdrawal symptoms can be variable among chronic marijuana users. Some of this variability is a direct result of the typical use pattern. Heavier users are more likely to experience withdrawal symptoms. However, even after typical use variability is taken into consideration, some users experience almost no withdrawal, while others experience significant psychological and physical withdrawal symptoms. Recent

research suggests that genetic factors may play an important role in the variability of withdrawal from marijuana.

There are natural variations in the gene that regulates the endocannabinoid system, which is the receptor system upon which THC acts. In one study, researchers recruited 105 college students who were daily marijuana smokers. Participants were tested once at baseline and then again 5 days after abstinence. As expected, withdrawal symptoms differed considerably. The researchers found a difference among subjects in their cannabinoid receptor 1 (CNR1) genotype. Subjects either had a T/C SNP (single nucleotide polymorphism) or a T/T SNP on the CNR1 gene. The individuals with the T/C genotype had far more pronounced withdrawal symptoms after abstinence. In sum, there is a genetic contribution to withdrawal symptoms from marijuana.[59]

Overview of Cannabis Use Disorder

A problematic pattern of cannabis use can lead to clinically significant impairment or distress. Typically includes a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal state.[20]

Diagnostic Features

Cannabis Use Disorder is a condition characterized by the harmful consequences of repeated cannabis use, a pattern of compulsive cannabis use, and (sometimes) physiological addiction on cannabis (*i.e.*, tolerance and/or symptoms of withdrawal). This disorder is only

diagnosed when cannabis use becomes persistent and causes significant academic, occupational or social impairment.

Cannabis users can develop tolerance to this drug so that it can be difficult to detect when they are intoxicated. Signs of cannabis use include red eyes, chronic cough, cannabis odor on clothing, yellowing of finger tips (from smoking joints), burning of incense (to hide odor), and exaggerated craving and impulse for specific foods.

Cannabis Intoxication causes significant psychological and social impairment. It begins with a "high" euphoric feeling followed by inappropriate laughter and grandiosity, sedation, lethargy, impairment in short-term memory, difficulty carrying out complex mental processes, impaired judgment, distorted sensory perceptions, impaired motor performance, and the sensation that time is passing slowly. Occasionally, anxiety, depression, or social withdrawal occurs. This intoxication has two or more of the following developing within 2 hours of cannabis use: red eyes (conjunctival injection), increased appetite, dry mouth, or rapid pulse.[18]

Cannabis withdrawal occurs after the cessation of (or reduction in) heavy and prolonged cannabis use. This withdrawal syndrome includes three or more of the following: irritability, anger or aggression; nervousness or anxiety; insomnia or disturbing dreams; decreased appetite or weight loss; restlessness; depressed mood; at least one of: abdominal pain, shakiness/tremors, sweating, fever, chills, or headache. These withdrawal symptoms typically don't require medical attention; however, they make quitting cannabis difficult.[70]

Complications of Cannabis Use

About 9% of cannabis (pot) users become addicted to it. Cannabis use disorder in school often causes a dramatic drop in grades, truancy, and reduced interest in sports and other school activities. In adults, this disorder often is associated with work impairment, unemployment, lower income, welfare dependence, and impaired social functioning.

Higher executive functioning is impaired in cannabis use disorder, which contributes to school and work impairment. This disorder also significantly decreases motivation at school or work (*i.e.*, an "amotivational syndrome"). There is an increased risk of accidents while driving, at sports or at work.

Since cannabis smoke contains high levels of carcinogenic compounds; chronic cannabis users face the same cancer and respiratory illness risks, as do chronic tobacco smokers. There is strong evidence that cannabis use can trigger the onset of schizophrenia and other psychotic disorders.[71]

Comorbidity

Individuals with Opioid Use Disorder have higher rates of: Alcohol Use Disorder (50%), Tobacco Use Disorder (53%), Antisocial Personality Disorder (30%), Anxiety Disorder (24%), Obsessive-Compulsive Disorder (19%), Paranoid Personality Disorder (18%), Bipolar I Disorder (13%), and Major Depressive Disorder (11%). Adolescents have higher rates of Conduct Disorder and Attention-Deficit/Hyperactivity Disorder.[72]

Associated Laboratory Findings

Cannabis is detected on routine urine toxicology testing.

Prevalence

The 12-month American prevalence rate for Cannabis Use Disorder is 3.4% among 12- to 17-year-olds and 1.5% among adults age 18 years and older. The prevalence has increased during the past decade.[23]

Course and Prevalence of Cannabis Use Disorder

Onset is usually during adolescence or young adulthood, but it can start in preteens and older adults. The onset is usually gradual. Cannabis use prior to age 15 is a strong predictor of later cannabis use disorder, other substance use disorders and conduct disorder. The prevalence of cannabis use disorder decreases with age, with rates highest among 18- to 29-year-olds (4.4%) and lowest among individuals age 65 years and older (0.01%).[4,5]

Familial Pattern

In cannabis use disorder it is estimated that 30%-80% of the variance of risk is explained by genetic influences. What seems to be inherited is impulsivity and novelty seeking which makes the individual more prone to substance use disorders in general.[67]

Effective Therapies

There is no FDA-approved pharmacological treatment for cannabis use and addiction. There are only two pharmacological, randomized, double-blind, placebo-controlled clinical trials, which had a positive outcome (N-acetylcysteine, gabapentin) - but neither of these clinical

trials has been replicated.

There are no randomized, placebo-controlled clinical trials of any psychosocial treatment. Thus the effectiveness of psychosocial treatment for cannabis use disorder is unknown.

Summary

The history of cannabis use is extensive and goes as far back as ancient societies and continues to be used in the United States both legally (in certain jurisdictions) and illegally. THC is the active chemical in the cannabis plant that causes psychotropic effects in the form of marijuana, which is now available in many forms. While marijuana has been legalized in many states for use to treat neuropathic pain and other conditions discussed in this article, its important for health professionals to recognize its potential physical and psychotropic side effects.

Sustained marijuana use can have negative impacts on the brain as well as the body. Studies have indicated a link between regular marijuana use and certain physical and mental illnesses. No pharmacological treatments with a proven impact on marijuana use disorder are available, however varied screening tools and behavior therapy may be effective during treatment. Clinicians are advised to observe DSM-5 diagnostic criteria during screening/diagnosing a cannabis substance use disorder, including new specifiers that may affect an individual's initial and ongoing plan for recovery. Part II of Marijuana Substance Use Disorder: *recommendations for screening and therapy* will address options for patients and their families seeking support to initiate and continue in a recovery program.

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