State initiatives such as the 2012 Oregon Cannabis Tax Act are aimed at decriminalizing or even legalizing the possession and use of small amounts of cannabis, especially for medical purposes.

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you have almost certainly heard the term “drug czar,” which actually refers to the Director of the Office of National Drug Control Policy. At the time of this writing, our drug czar is Richard Gil Kerlikowske, who was selected by President Barack Obama to replace the former director, John P. Walters. If you thought that the existence of a drug czar and the current “War on Drugs” are relatively recent phenomena, you would be wrong by more than 80 years. The first federal official who might have been called a drug czar by our generation was Harry J. Anslinger, a man who was appointed in 1930 to be the first Commissioner of Narcotics in the Bureau of Narcotics of the United States Treasury Department.

We mention Harry Anslinger here because in the 1930s, he spearheaded a public relations campaign to portray marijuana as a social menace capable of destroying the youth of America. In congressional hearings that preceded passage of the 1937 Marijuana Tax Act, the first federal legislation passed to control marijuana sales, Anslinger testified as follows: “Those who are habitually accustomed to use of the drug [marijuana] are said to develop a delirious rage after its administration, during which they are temporarily, at least, irresponsible and liable to commit violent crimes. The prolonged use of this narcotic is said to produce mental deterioration. It apparently releases inhibitions of an antisocial nature which dwell within the individual” (Schaffer Library of Drug Policy). At the same time, Anslinger’s Bureau of Narcotics was feeding information to the popular media about the evils of marijuana use. This stream of propaganda resulted in magazine articles with titles such as “Marihuana: Assassin of Youth” (American Magazine) and “Sex Crazing Drug Menace” (Physical Culture), as well as antimarijuana movies such as Reefer Madness (Figure 14.1) that are now regarded as cult classics.
Few people still believe the lurid stories spread so widely during the antimarijuana campaign of the 1930s. And yet marijuana remains a highly controversial subject in our society—castigated by many as a gateway to the so-called hard drugs (see Chapter 9), but praised by others as an unappreciated medical marvel. Where does the truth lie? In this chapter, we will attempt to separate the myths of marijuana from the scientific reality of this ancient drug.

Background and History of Marijuana

Marijuana (alternate spelling: marihuana) is produced from the flowering hemp, a weedlike plant given the botanical name of *Cannabis sativa* by Linnaeus in 1753 (Figure 14.2). Historically, hemp has served an important function in many cultures as a major source of fiber for making rope, cloth, and even paper. At times, its seeds have been used for their oil content and as bird feed. More importantly, for neuropharmacologists, cannabis plants contain 70 unique compounds that are collectively known as cannabinoids, as well as more than 400 other identified compounds (ElSohly and Slade, 2005). The psychoactive properties of some of these compounds, particularly a substance called Δ⁹-tetrahydrocannabinol (THC), account for the use of cannabis as a drug. Although cannabinoids can be found to some extent in all parts of the plant, they are concentrated in a sticky yellowish resin that is secreted in particularly large amounts by the flowering tops of female plants.

Cannabis can be obtained in a number of different forms for the purpose of consumption. The most familiar to us is marijuana, which is derived from the Mexican word *maraguango*, meaning “an intoxicating plant.” Marijuana refers to a crude mixture of dried and crumbled leaves, small stems, and flowering tops. Although marijuana can be consumed orally, as in cookies or brownies, it is usually smoked in rolled cigarettes known as “joints,” in various kinds of pipes, or in hollowed-out cigars called “blunts.” Marijuana potency (in terms of THC content) varies widely, depending on the genetic strain of the plant, as well as its growing conditions. One method of significantly increasing potency is to prevent pollination and hence seed production by the female plants. Marijuana produced by this method is called sinsemilla (meaning “without seeds”).

Another type of cannabis derivative is hashish, which also may be smoked or eaten (Figure 14.3). Hashish potency greatly depends on how it has been prepared. In the Middle and Far East, for example, hashish generally refers to a relatively pure resin preparation with a very high cannabinoid content. Alternatively, the term may be used to describe solvent
extracts of leaves or resin that are more variable in their potency. A particularly powerful type of hashish is called hash oil. This is an alcoholic extract that has been reduced to an oily, viscous liquid ranging in color from amber to black. A single drop of hash oil may be placed on a standard tobacco cigarette and smoked, or a drop may be added to a marijuana cigarette to effectively double the dose.

Cannabis is believed to have originated in central Asia, probably in China. There is archeological evidence for the use of hemp fibers 8000 years ago (Figure 14.4). Medical and religious use of cannabis can be traced back to ancient China, India, and the Middle East (Russo, 2007). From there, the substance spread to the Arab world, where the consumption of hashish became commonplace. Indeed, hashish is frequently mentioned in the Arabian folk stories that constitute The Thousand and One Nights. However, Western interest in this substance did not begin until the early to mid-nineteenth century, when some of Napoleon’s soldiers reportedly brought hashish from Egypt back with them to France. Around the same time, a French physician named Jacques-Joseph Moreau encountered the intoxicating effects of hashish in the course of several trips to the Middle East. After returning to Paris, Moreau helped found a notorious association of French writers and artists known as Le Club des Hashischins (“club of the hashish eaters”), which included such notables as Victor Hugo, Alexandre Dumas, Théophile Gautier, and Charles Baudelaire.

The history of cannabis in the United States dates back to the colonial era, when hemp was an important agricultural commodity. No less than George Washington himself was a hemp farmer, which is ironic in view of the patriotic fervor associated with the contemporary “War on Drugs.” Yet domestic hemp growers of the seventeenth and eighteenth centuries apparently had little awareness of the plant’s intoxicating properties. Rather, historians believe that the social practice of consuming cannabis (mainly marijuana smoking) was brought into the United States in the early 1900s by Mexican immigrants crossing the Mexican–American border, and by Caribbean seamen and West Indian immigrants entering the country by way of New Orleans and other ports on the Gulf of Mexico. Marijuana use rapidly spread outward from these points of origin. As a consequence of the antimarijuana campaign described earlier, the federal government passed the Marijuana Tax Act in 1937. This legislation instituted a national registration and taxation system aimed at discouraging all use of cannabis for commercial, recreational, and medical purposes. Although the Marijuana Tax Act was overturned as unconstitutional by the U.S. Supreme Court in 1969, marijuana and other forms of cannabis remain tightly regulated by state laws and by the federal Controlled Substances Act of 1970.

Basic Pharmacology of Marijuana

Modern cannabinoid pharmacology began in 1964, when two Israeli researchers named Gaoni and
Mechoulam identified THC as the major active ingredient of *C. sativa* (Figure 14.5). Among the many other cannabinoids present are cannabinol and cannabidiol, but these compounds are not thought to contribute to the psychoactive properties of cannabis. Later on, we will discuss the brain’s own chemicals that mimic the effects of THC, and we will also consider the development of selective cannabinoid antagonists that have contributed significantly to research in this area.

A typical hand-rolled marijuana cigarette (“joint”) consists of around 0.5 to 1 gram of cannabis. If the THC content is 4% (although it can be even higher depending on the strain and growing conditions), then a 1-gram joint contains 40 mg of active ingredient that is available to the smoker. As in the case of nicotine in tobacco leaves (see Chapter 13), burning of the marijuana causes the THC to vaporize and to enter the smoker’s lungs in small particles. But because of a variety of factors, only about 20% to 30% of the original THC content is absorbed in the lungs. In practice, the amount of THC absorbed is affected not only by the initial amount of plant material used and the potency of this material but also by the pattern of smoking. The effective dose and latency to onset of effects of smoked marijuana are influenced by puff volume, puff frequency, inhalation depth, and breath-hold duration (Gorelick and Heishman, 2006).

THC is readily absorbed through the lungs, resulting in rapidly rising levels in the blood plasma of the smoker (Figure 14.6). After peak levels are reached, plasma THC concentrations begin to decline as a result of a combination of metabolism in the liver and accumulation of the drug in the body’s fat stores. In contrast, oral consumption of marijuana leads to prolonged but poor absorption of THC, thus resulting in low and variable plasma concentrations. The reduced bioavailability of THC following oral consumption compared with smoking probably results from both degradation in the stomach and first-pass hepatic metabolism, that is, once orally ingested THC has been absorbed from the gastrointestinal tract, it must pass through the liver, where much of it is metabolized before it can enter the general circulation. THC is converted into several metabolites, notably 11-hydroxy-THC and 11-nor-carboxy-THC (THC-COOH). These substances as well as various minor metabolites are excreted primarily in the feces (about two-thirds of the administered dose) and the urine (about one-third of the administered dose). Even though THC levels in the bloodstream decline fairly rapidly after one smokes marijuana, complete elimination from the body is much slower because of persistence of the drug in fat tissue. Consequently, the elimination rate, or half-life (t½), of THC is generally estimated at around 20 to 30 hours. Furthermore, the gradual movement of THC and fat-soluble metabolites back out of fat stores means that sensitive urine screening tests for THC-COOH can detect the presence of this metabolite more than 2 weeks following a single marijuana use.

**Section Summary**

- *Cannabis sativa*, the flowering hemp plant, exudes a resin containing a number of unique compounds known as cannabinoids.
- Cannabis can be obtained in several different types of preparations, including marijuana and hashish, both of which may be smoked or taken orally.
- The consumption of cannabis for its intoxicating effects is thought to date back thousands of years in Eastern cultures. The practice of marijuana smoking was introduced into the United States in the early 1900s by Mexican and West Indian immigrants.
• The most important naturally occurring cannabinoid is Δ⁹-tetrahydrocannabinol (THC).

• Inhaled THC is rapidly absorbed from the lungs into the circulation, where it is almost completely bound to plasma proteins. Oral THC consumption yields slower absorption and a lower plasma peak than occurs following smoking.

• THC is extensively metabolized in the liver, and the metabolites are excreted mainly in the feces and urine. Following a single dose of THC, total clearance of the drug and its metabolites may take days because of sequestration of these compounds in fat tissue.

Mechanisms of Action

For many years, researchers interested in how THC and other cannabinoids work in the brain were hampered by the lack of an identified cellular receptor for these compounds. Subsequent discovery of cannabinoid receptors permitted the synthesis of selective cannabinoid agonists and antagonists, as well as elucidation of the endogenous cannabinoid system.

Cannabinoid effects are mediated by cannabinoid receptors

Pharmacological characterization of a central nervous system (CNS) cannabinoid receptor was announced in 1988 by a group of researchers that included William Devane and Allyn Howlett at St. Louis University, and Lawrence Melvin and M. Ross Johnson at the Pfizer pharmaceutical company (Devane et al., 1988).¹ This initial characterization was quickly followed by other studies showing significant expression of cannabinoid receptors in many brain areas such as the basal ganglia (including the striatum, globus pallidus, entopeduncular nucleus, and substantia nigra pars reticularis), cerebellum, hippocampus, and cerebral cortex (Figure 14.7). As discussed later, localization of cannabinoid receptors in these areas is consistent with the recognized behavioral effects of these compounds on locomotor activity, coordination, and memory.

Around the same time that the St. Louis University and Pfizer researchers were first characterizing the cannabinoid receptor pharmacologically, another group of scientists at the National Institute of Mental Health (NIMH) including Lisa Matsuda and Tom Bonner cloned a novel gene from rat cerebral cortex that coded for a membrane protein with the characteristics of a G protein–coupled receptor. Further studies revealed that these investigators, who were working on an unrelated problem, had actually cloned the gene for the rat brain cannabinoid receptor (Matsuda et al., 1990). This is a good example of an approach that is sometimes called reverse pharmacology, namely, the cloning of a novel receptor gene, the identity of which must then be determined by more classical pharmacological methods. The CNS cannabinoid receptor is currently designated CB₁. An additional cannabinoid receptor, CB₂, was discovered later, first in the immune system and then in other tissues such as bone, adipose (fat) cells, and the gastrointestinal tract (Atwood and Mackie, 2010). CB₂ receptors are also expressed by microglia (the brain’s immune cells), especially when those cells have been activated by neuroinflammatory or neurodegenerative events occurring in the brain. Recent evidence further suggests that CB₂ receptors may be expressed by neurons in some areas of the brain (Atwood and Mackie, 2010).

Cannabinoid receptors belong to the large family of metabotropic receptors, and they exert their cellular effects primarily through coupling to the G proteins Gᵢ and Gₛ. The most important of these effects involve inhibition of cyclic adenosine monophosphate (cAMP) formation, inhibition of voltage-sensitive Ca²⁺ channels, and activation of K⁺ channel opening (Howlett, 2007).¹

¹Readers interested in more information on the history of the discovery and characterization of cannabinoid receptors are referred to the excellent review by Mackie (2007).
Cannabinoid receptors can also influence gene expression through a complex system of protein kinases known as the mitogen-activated protein kinase (MAPK) system. Electron microscopy in conjunction with antibodies against the CB1 receptor have been used to determine the location of these receptors within the synapse. In most instances, CB1 receptors have been shown to exist on the axon terminal instead of the postsynaptic cell. By activating these presynaptic receptors, cannabinoids can inhibit the release of many different neurotransmitters including acetylcholine, dopamine, norepinephrine, serotonin, glutamate, and GABA (γ-aminobutyric acid) (Iversen, 2003).

**Pharmacological studies reveal the functional roles of cannabinoid receptors**

Various synthetic cannabinoid agonists and antagonists have been developed for both research and potentially also therapeutic use. These compounds include CP-55,940 and WIN 55,212-2, which are full agonists at both CB1 and CB2 receptors (Svíženská et al., 2008). Interestingly, THC has been shown to be a partial rather than a full CB1 and CB2 receptor agonist since this substance produces lower peak receptor-mediated effects than the above mentioned synthetic agonists. The first selective CB1 antagonist was **SR 141716A** (also known as rimonabant), which was developed by the French pharmaceutical firm Sanofi Recherche. Besides its obvious value in determining CB1-dependent effects of cannabinoids in animal model systems, rimonabant is easily administered to human subjects because it is orally active.

Administration of THC to mice leads to a classical “tetrad” of effects consisting of (1) reduced locomotor activity, (2) hypothermia (a decrease in core body temperature), (3) catalepsy as indicated by immobility in the ring test (a test that measures the animal’s behavior after it is placed on a horizontal wire ring), and (4) hypoalgesia (reduced pain sensitivity) measured using the hot-plate or tail-flick test. These effects are mediated primarily by CB1 receptors because they are largely absent in CB1 knockout mice and they can be duplicated in wild-type animals by administration of a selective CB1 receptor agonist (Pertwee, 2008; Valverde et al., 2005). CB1 receptors also play an important role in the reward system, as shown by the reinforcing effects of CB1 agonists in both animals and humans. This topic is discussed in greater detail later in the chapter.

We shall also see later that cannabinoids adversely affect human cognitive function, which has led to considerable interest in the effects of these compounds on learning and memory in laboratory animals. The results of this work indicate that cannabinoids disrupt memory in several different kinds of learning tasks, including the radial arm maze, the Morris water maze, and the delayed non-match-to-position task (Riedel and Davies, 2005). Memory consolidation in the passive avoidance task may also be adversely influenced by cannabinoid administration. A recent study by Wise and coworkers (2009) found that either systemic administration or microinjection of THC or the synthetic cannabinoid agonist CP-55,940 directly into the dorsal hippocampus produced significant memory deficits in the radial arm maze. Moreover, these effects could be completely blocked by microinjection of rimonabant (0.06 μg) into the dorsal hippocampus (Rim-CP), whereas rimonabant by itself had no effect on maze performance (Rim-V) (After Wise et al., 2009).

**Figure 14.8 Hippocampal CB1 receptors are responsible for memory impairment** in the radial arm maze produced by cannabinoid agonist administration. Rats were trained to a high degree of performance on an 8-arm radial arm maze (see Chapter 4). After training was complete, intra-peritoneal injection of CP-55,940 (0.05 mg/kg) along with a vehicle microinjection into the hippocampus (V-CP) produced a significant number of errors on the task compared with the control group (V-V), indicating an impairment in working memory. This effect was completely blocked by microinjection of rimonabant (0.06 μg) into the dorsal hippocampus (Rim-CP), whereas rimonabant by itself had no effect on maze performance (Rim-V) (After Wise et al., 2009).
Endocannabinoids are cannabinoid receptor agonists synthesized by the body

The discovery and characterization of cannabinoid receptors finally enabled pharmacologists to study the cellular mechanisms by which marijuana produces its behavioral effects. Yet why should our brain possess receptors for substances made by a plant? This situation is reminiscent of the quandary faced by opiate researchers when opioid receptors were first identified as mediating the actions of morphine, which comes from a poppy plant (see Chapter 11). Accordingly, the same assumption was made that there must be an endogenous neurotransmitter-like substance that acts on the newly discovered receptors. Within a few years, a group headed by Raphael Mechoulam, the same Israeli scientist involved in the discovery of THC almost 30 years earlier, announced that they had isolated a substance with cannabinoid-like activity from pig brain (Devane et al., 1992). Chemical analysis revealed the substance to be a lipid with a structure related to that of arachidonic acid. The formal chemical name of this substance is arachidonoyl ethanolamide (AEA), but the researchers gave it the additional name anandamide, from the Indian Sanskrit word ananda, meaning “bringer of inner bliss and tranquility” (Felder and Glass, 1998, p. 186). Later studies demonstrated the existence of other arachidonic acid derivatives such as 2-arachidonoylglycerol (2-AG) that also bind to and activate CB1 receptors (Figure 14.9). Together, these substances came to be known as endocannabinoids, meaning endogenous cannabinoids. However, subsequent studies showed that 2-AG is present in the brain at much higher levels than anandamide, and it also exerts greater efficacy than anandamide on cannabinoid receptors (Sugiura, 2009). This combined with other evidence strongly suggests that 2-AG, not anandamide, is the principal endocannabinoid for both CB1 and CB2 receptors.

The endocannabinoids are generated from inositol phospholipids in the membrane that contain the fatty acid arachidonic acid within their structure. Unlike the classical neurotransmitters, however, endocannabinoids are too lipid soluble to be stored in vesicles since they would just pass right through the vesicle membrane. Consequently, current evidence indicates that these substances are made and released when needed. One mechanism for triggering endocannabinoid release is a rise in intracellular Ca2+ levels, which follows from the fact that some of the enzymes involved in the generation of these compounds are Ca2+ sensitive.

After being released, endocannabinoids are removed from the extracellular fluid by an uptake mechanism that is still under debate. Most of the research on endocannabinoid uptake has come from studies on anandamide. On the basis of these studies, three potential uptake mechanisms have been proposed by different investigators: (1) uptake by means of a protein carrier in the cell membrane, (2) uptake by simple passive diffusion across the cell membrane, and (3) uptake by means of anandamide binding to a membrane protein followed by endocytosis of the anandamide–protein complex (Yates and Barker, 2009). It is clear that proof for a protein-mediated uptake mechanism will ultimately require cloning of the relevant gene and characterization of the gene product as a true carrier protein for anandamide (and possibly also 2-AG).

Once inside the cell, the endocannabinoids can be metabolized by several different enzymes. For anandamide, the best known enzyme involved in its degradation is called fatty acid amide hydrolase (FAAH). In contrast, 2-AG is thought to be broken down primarily by a different enzyme known as monoacylglycerol lipase (MAGL) (Ueda et al., 2010). Indeed, a recent study by Chanda and colleagues (2010) showed that mutant mice lacking MAGL exhibited a huge increase in brain 2-AG concentrations, and these mice also developed a desensitization of central CB1 receptors. The latter effect is further evidence for a key role for 2-AG in activating CB1 receptors within the brain.

On the basis of the discovery that many cannabinoid receptors are localized presynaptically, we might suspect that endocannabinoids are often released from postsynaptic cells to act on nearby nerve terminals. When a signaling molecule carries information in the opposite direction from normal (i.e., postsynaptic to presynaptic), it is called a retrograde messenger. One such retrograde messenger discussed in Chapter 3 is the gas nitric oxide. There is now overwhelming...
evidence that endocannabinoids are also retrograde messengers at specific synapses in a number of brain regions, such as the hippocampus and the cerebellum (Piomelli, 2003; Wilson and Nicoll, 2002). These substances are synthesized and released in response to depolarization of the postsynaptic cell due to the influx of Ca\(^{2+}\) through voltage-gated Ca\(^{2+}\) channels. Following their release, the endocannabinoids cross the synaptic cleft, activate CB\(_1\) receptors on the nerve terminal, and inhibit Ca\(^{2+}\)-mediated neurotransmitter release from the terminal (Sugiura, 2009). In the hippocampus, for example, the endocannabinoids are generated by the pyramidal neurons, which are the principal output neurons of the hippocampus. The endocannabinoids diffuse to the nearby terminals of GABAergic interneurons that normally inhibit the pyramidal cells. The resulting inhibition of GABA release temporarily permits the pyramidal cells to fire more readily (Figure 14.10).

Examples of retrograde signaling by endocannabinoids have also been discovered, including cases in which stimulation of endocannabinoid synthesis and release cause presynaptic long-term depression (LTD) of neurotransmission (Chevaleyre et al., 2006). These findings are consistent with the widespread distribution of cannabinoid receptors in the brain.

The discovery of anandamide and 2-AG has raised interesting questions about whether this signaling system might be involved in the normal regulation of the same behavioral and physiological functions influenced by exogenous cannabinoids such as THC. This question has been addressed in two different ways: (1) by examining the effects of administering the CB\(_1\) receptor antagonist rimonabant in the absence of an exogenous cannabinoid agonist (thus blocking the effects of the endogenous cannabinoids), and (2) by studying the phenotypic characteristics of CB\(_1\) and CB\(_2\) knockout mice. A few examples will be given...
from this large literature to illustrate some of the key functions of the central endocannabinoid system.

A number of studies have demonstrated that genetically normal animals given rimonabant as well as both CB₁ and CB₂ knockout mice exhibit hyperalgesia (increased pain sensitivity) to several different types of pain stimuli. These findings clearly demonstrate a role for endocannabinoids acting on both cannabinoid receptor subtypes in the modulation of pain perception (Buckley, 2008; Calignano et al., 1998; Valverde et al., 2005). The potential use of cannabinoid drugs in the treatment of pain disorders as well as many other medical conditions is discussed in Box 14.1.

Endocannabinoids have additionally been shown to play a significant role in hunger and eating behavior. CB₁ receptor antagonists reliably reduce food consumption in both experimental animals and human subjects, and more detailed studies suggest that endocannabinoids enhance both the incentive motivational properties of food and food-mediated reward (Kirkham, 2009). Recent work by DiPatrizio and coworkers (2011) further showed that endocannabinoids in the gut provide a signal that controls dietary intake of fat. Because of the early success of CB₁ antagonism in reducing food intake, rimonabant (under the trade name Accomplia) was approved and released by Sanofi-Aventis in the European Union in June 2006 as an anti-obesity agent. Unfortunately, reporting of adverse psychiatric side effects by some users resulted in voluntary suspension of marketing of Accomplia by the company in December 2008, followed shortly by withdrawal of approval of the medication by the European Medicines Agency. Nevertheless, targeting the cannabinoid system for the treatment of obesity has continued to be of interest to researchers and pharmaceutical companies (Lee et al., 2009). For example, Cluny et al. (2010) recently showed that AM6545, a CB₁ antagonist with limited penetration across the blood–brain barrier, significantly reduced food consumption and body weight in both rats and mice with a behavioral profile suggesting a lack of CNS-mediated aversive effects (Figure 14.11). Thus, future clinical testing may yet reveal that peripherally acting cannabinoid antagonists can successfully treat obesity without the side effects that compromised earlier attempts to use rimonabant in this capacity.

Potential endocannabinoid involvement in learning and memory has been investigated by comparing the performance of CB₁ knockout mice with that of their wild-type counterparts and by examining the influence of rimonabant treatment on normal animals (Marco et al., 2011; Zanettini et al., 2011). Although the literature shows some inconsistencies, a number of studies suggest that endocannabinoids play a greater role in the extinction of learned responses than in response acquisition. This phenomenon has been particularly well demonstrated in the case of extinction of auditory fear conditioning of rats and mice. This task
Therapeutic Uses of Cannabinoids

Medicinal use of cannabis in various cultures can be traced back for many hundreds, perhaps thousands, of years. During the late-nineteenth and early-twentieth centuries, crude cannabis extracts were accepted pharmaceuticals in Europe and the United States. Indeed, six different types of cannabis preparations were listed in an early edition of *The Merck Index* (1896) of pharmaceutical compounds. However, the medicinal use of cannabis gradually declined, in part because the available preparations tended to be unstable and had inconsistent potency.

Interest in the possible therapeutic benefits of cannabinoids was later revived following the discovery of THC and the subsequent manufacture and testing of various synthetic compounds. At present, both dronabinol, a synthetic form of THC sold under the trade name Marinol, and the THC analog nabiximols (trade name Cesamet) are prescribed in oral form for the treatment of nausea and emesis (vomiting) in cancer chemotherapy patients who are not helped by other antiemetics. Dronabinol is also approved for use as an appetite stimulant in AIDS patients suffering from anorexia–cachexia (wasting syndrome). Patients contemplating use of these drugs should be aware that they can produce various side effects such as sedation, dizziness, confusion, dry mouth, and mild euphoria. Alternatively, dysphoria may occur in people unfamiliar with the effects of smoked marijuana. Fortunately, such side effects tend to be greatest when the drug is first taken and generally diminish within a few days or weeks.

Nabiximols (trade name Sativex) is a cannabis extract containing THC and cannabidiol (a cannabinoid that exerts biological effects independent of either CB₁ or CB₂ receptors) that is taken as an oral spray. This medication is currently licensed in a number of countries (not including the United States) for the treatment of neuropathic pain and spasticity in multiple sclerosis patients. At the time of this writing, nabiximols was undergoing Phase III clinical trials in the United States for the treatment of neuropathic pain in cancer patients. A number of years ago, Jamaican researchers also prepared eye drops from cannabis extracts (trade name Canasol) for the purpose of reducing ocular pressure in glaucoma patients. However, Canasol apparently was never licensed by the FDA for legal marketing in the United States.

New knowledge regarding the anatomy and functioning of the endocannabinoid system as well as the need for effective medications for numerous clinical disorders has led to an upsurge in research on cannabinoid medications. Novel cannabinoid drugs that do not cross the blood–brain barrier or that work as modulators instead of cannabinoid receptor antagonists or as inverse agonists are under development not only for the treatment of obesity (as noted earlier in the text) but also for irritable bowel syndrome and other disorders of the gastrointestinal system (Schicho and Storr, 2011). Other areas of medicine in which cannabinoid-based compounds might prove useful include pain (Sagar et al., 2009), cancer (Grimaldi and...
Box 14.1 (continued)

Capasso, 2011), neurodegenerative diseases (Scotter et al., 2010), and psychiatric disorders (Hill et al., 2009; Roser et al., 2010). For example, Piscitelli and Di Marzo (2012) provide an instructive example of how various features of endocannabinoid biochemistry, particularly reuptake and metabolism, are potential targets of medication development for the treatment of pain. With respect to psychiatric disorders, it is noteworthy that CB1 receptors are located in many parts of the neural circuitry that control mood (see figure). Thus, compounds targeting the central endocannabinoid system might be useful as novel medications for patients suffering from major depression or other mood disorders.

Lastly, we come to the issue of medical marijuana, meaning the use of smoked marijuana as a medication. As reviewed by Cohen (2009a, 2009b), the notion of medical marijuana has been dominated much more by political considerations than by scientific evidence. Indeed, a number of states currently permit legal use of medical marijuana when approved by a physician, despite the fact that the DEA still classifies cannabis as a Schedule I substance. This puts the states in question (and residents of those states who use marijuana medicinally) in direct conflict with federal regulations. Most of the support for medical marijuana comes from anecdotal reports from patients that smoking cannabis gives them greater symptom relief than is obtained from oral cannabinoid preparations such as dronabinol or naboline. There have been a few clinical studies, such as those reviewed by Rog (2010), regarding the use of marijuana versus oral cannabinoid medications for alleviation of multiple sclerosis symptoms, but the results were equivocal. Given the potential for adverse health effects and abuse potential of smoked marijuana, most researchers currently favor the development of cannabinoid-based medications that avoid these negative consequences (Seely et al., 2011). This is an especially important consideration when the proposed medication will be taken on a daily basis over a long time.

...involves the pairing of an auditory stimulus such as a tone with a foot shock as illustrated in Figure 14.12A. As a result, the tone becomes a conditioned fear stimulus that elicits freezing behavior (i.e., no movement except for breathing), which is the species-typical response to a fearful situation in rats and mice, and which is known to depend on a neural circuit involving the amygdala. A number of studies have shown that the endocannabinoid system is not required for acquisition of auditory fear conditioning. However, Marsicano and coworkers (2002) demonstrated that unlike mice possessing functional CB1 receptors, CB1 knockout mice do not show normal extinction of the freezing response when the tone alone without additional foot shock pairing is presented over a series of several days (Figure 14.12B). These investigators performed a number of additional experiments to determine the potential mechanism underlying this effect. One of their findings was that both anandamide and 2-AG levels were greatly increased in the basolateral amygdala complex immediately following the tone presentation on the first extinction day, but not under various control conditions (Figure 14.12C). No change in endocannabinoid levels was observed in the medial prefrontal cortex—another brain area implicated in the extinction of learned aversive responses. These and other findings not shown suggest that endocannabinoids released during extinction and acting on CB1 receptors in the basolateral amygdala alter synaptic plasticity in a manner that enables the animals to learn that the tone is no longer dangerous. Indeed, on the basis of the results from a number of fear extinction studies, Moreira and Wotjak (2009) hypothesized that the endocannabinoid system is involved in the alleviation of fear, thereby functioning to prevent fear responses from becoming too pervasive.

Recent findings have extended this rodent work on fear extinction to humans. Researchers have discovered a single nucleotide polymorphism (SNP) in the FAAH gene (C385A) that changes the amino acid proline at position 129 of the FAAH protein to a threonine. This amino acid substitution leads to a reduction in enzymatic activity, thereby increasing endogenous anandamide levels. Gunduz-Cinar and colleagues (2012) compared people who had at least one copy of the A allele (i.e., with an AA or AC genotype) with individuals homozygous for the C allele (CC genotype) on a fear habituation test in which the subjects were repeatedly exposed to threatening faces during a functional magnetic resonance imaging (fMRI) session. The results showed that the amygdala responses to these faces habituated much more rapidly in the subjects carrying at least one copy of the low-expressing A allele than in the homozygous CC subjects. Such findings are consistent with the hypothesis that increased anandamide levels due to reduced FAAH activity enhance the ability to turn off neural and behavioral responses to threatening stimuli.
Section Summary

- Two cannabinoid receptors, CB₁ and CB₂, have been identified and their genes cloned.
- The CB₁ receptor is the principal cannabinoid receptor in the brain, where it is expressed at a high density in the basal ganglia, cerebellum, hippocampus, and cerebral cortex.
- The CB₂ receptor was first identified in the immune system, but it is also found in a number of other tissues including the brain, where it is mainly localized in microglial cells.
- Cannabinoid receptors belong to the G protein–coupled receptor superfamily. Receptor activation can inhibit cAMP formation, inhibit voltage-sensitive Ca²⁺ channels, and activate K⁺ channels.
CB₁ receptors are typically located on axon terminals, where they act to inhibit the release of many different neurotransmitters.

Agonists at the CB₁ receptor include the synthetic full agonists CP-55,940 and WIN 55,212-2, and the partial agonist THC. The first selective CB₁ antagonist was SR 141716A, also known as rimonabant.

THC administration to mice causes a classical tetrad of CB₁ receptor–mediated effects that consist of reduced locomotor activity, hypothermia, catalepsy, and hypoalgesia. CB₁ agonists also impair learning and memory consolidation in several different kinds of tasks.

CB₂ receptor activation in the immune system causes cytokine release and changes in immune cell migration toward an inflammatory site.

The brain synthesizes several substances, called endocannabinoids, that are neurotransmitter-like agonists at cannabinoid receptors. Anandamide was the first endocannabinoid to be discovered, but a potentially more important endocannabinoid is 2-AG.

Endocannabinoids are generated on demand from arachidonic acid–containing membrane lipids by a Ca²⁺-dependent mechanism and are released from the cell by a process that does not involve synaptic vesicles. They are removed from the extracellular space by an uptake process that has yet to be fully defined.

Anandamide and 2-AG are degraded primarily by FAAH and MAGL, respectively.

Endocannabinoids function as retrograde messengers since they are synthesized and released from postsynaptic cells and act on nearby nerve terminals to inhibit neurotransmitter release by inhibiting the opening of voltage-gated Ca²⁺ channels.

Studies using rimonabant administration to genetically normal animals or mutant mice lacking functional CB₁ receptors have demonstrated that the endocannabinoid system plays a role in pain sensitivity, hunger and eating behavior, and learning and memory. This system seems to be particularly important in the extinction of learned fear responses.

There are accepted therapeutic uses for orally administered dronabinol (synthetic THC) and the THC analog nabilone in treating nausea and vomiting in cancer chemotherapy patients, as well as the wasting syndrome in AIDS sufferers. In addition, the endocannabinoid system is being actively studied as a target in the treatment of many kinds of disorders, including obesity, pain disorders, cognitive dysfunction, drug addiction, and psychosis.

**Acute Behavioral and Physiological Effects of Cannabinoids**

Cannabinoid use produces a range of behavioral and physiological effects that vary depending on the dose, the frequency of use, the characteristics of the user, and the setting in which use occurs.

**Cannabis consumption produces a dose-dependent state of intoxication**

The earliest recorded clinical studies on the intoxicating properties of cannabis were performed by Moreau, the French physician mentioned earlier who introduced hashish to nineteenth-century Parisian literary society. Moreau, who is sometimes called the “father of psychopharmacology,” became interested in the possible relationship between hashish intoxication and the characteristics of mental illness. Consequently, he and his students meticulously recorded their subjective experiences after consuming varying amounts of hashish. Because of the potency of their preparation, these individuals reported profound personality changes and perceptual distortions, even frank hallucinations. Hallucinogenic responses have also been reported either following a high dose of pure THC administered to subjects in a research setting, or as an occasional side effect of ingesting a synthetic cannabinoid for medicinal purposes (Koukkou and Lehmann, 1976; Timpone et al., 1997).

The lower cannabis doses associated with smoking one or two marijuana cigarettes produce a somewhat more modest reaction, although many of the same kinds of effects are found across the dose–response curve. As summarized in Iversen (2000), the subjective and behavioral effects commonly associated with marijuana use can be separated into four stages: the “buzz,” the “high,” the stage of being “stoned,” and finally the “come-down.” The “buzz” is a brief period of initial responding during which the user may feel lightheaded or even slightly dizzy. Tingling sensations in the extremities and other parts of the body are commonly experienced. The marijuana “high” is characterized by feelings of euphoria and exhilaration, as well as a sense of disinhibition that is often manifested as increased laughter. If the user has taken a sufficiently

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2Moreau’s work culminated in a book entitled *Du Hachich et de l’aliénation mentale* (Hashish and Mental Alienation), major excerpts of which can be found in Nahas (1975).
large amount of marijuana, his level of intoxication progresses to the stage of being “stoned.” In this stage, the user usually feels calm, relaxed, perhaps even in a dreamlike state. Indeed, relaxation is the most common effect reported by cannabis users in self-report studies involving open-ended questions (Green et al., 2003). Sensory reactions experienced by users in the stage of being stoned include floating sensations, enhanced visual and auditory perception, visual illusions, and a tremendous slowing of time passage. Sociability can undergo different types of changes, in that the user may experience either an increased desire to be with others or a desire to be alone. The “come-down” stage is the gradual cessation of these effects, which varies in length depending on the THC dose and the individual’s rate of THC metabolism.

Marijuana and other forms of cannabis also produce several physiological responses. There is increased blood flow to the skin, which leads to sensations of warmth or flushing. Heart rate is stimulated, which may be experienced by the user as a pounding pulse. Finally, marijuana increases hunger (the infamous “munchies”), an effect that is more than just street lore but has actually been documented in controlled laboratory studies of both humans (Foltin et al., 1988) and rats (Williams et al., 1998; also see Kirkham, 2000). Indeed, appetite stimulation is one of the recognized therapeutic uses for cannabinoids (see Box 14.1).

Not surprisingly, the marijuana “high” and its other subjective and physiological effects are dose dependent, in that the concentration of THC in a smoked marijuana cigarette has a direct relationship to the intensity of these effects (Cooper and Haney, 2008). Moreover, these effects are at least partially mediated by CB1 receptors. Huestis and colleagues (2001, 2007) found that self-reported ratings of intoxication following the smoking of a single marijuana cigarette were significantly although not completely inhibited by prior treatment with rimonabant (Figure 14.13). Similar results were found for the heart rate–elevating effects of the drug. Either a higher dose of the antagonist is needed to fully block the effects of marijuana or some other mechanism in addition to CB1 receptor activation (e.g., activation of central CB2 receptors) is involved in producing these effects.

Smoking marijuana can also transiently evoke psychotic symptoms such as depersonalization (feeling separated from the self), derealization (feeling that the external world is unreal), agitation, and even paranoia (Sewell et al., 2009). Adverse reactions are most likely to occur in first-time users, although regular users may also experience these effects if they consume an unusually high dose. Flashbacks, which are widely known to occur in LSD users, have occasionally been reported for marijuana as well (Iversen, 2000).

Although some authors have suggested the existence of a specific cannabis-induced psychosis, that concept remains questionable.

As with most psychoactive drugs, the psychological effects of marijuana vary greatly as a function not only of dose but also of the setting, the individual’s past exposure to the drug, and his mental set, which refers to the expectation of what effects the drug will produce. The influence of expectancy was demonstrated by Kirk and coworkers (1998), who gave subjects capsules containing either THC or a placebo. The subjects were instructed beforehand that the capsules would contain placebo or one of several types of psychoactive compounds, but only for the “informed” group were cannabinoids included in the list of possible drugs. When asked to rate their responses to the substance they had consumed, the “informed” group gave higher ratings than the “uninformed” group in the categories of “like” drug and “want more drug.” The expectation of consuming cannabinoids not only enhanced the pleasurable effects of actual cannabinoid administration, it also elicited a more positive reaction when the subjects were given placebo instead.

Plasma THC levels peak much more rapidly following intravenous (IV) THC injection or marijuana smoking than after oral ingestion (Figure 14.14). Consequently, users reach the peak “high” sooner with the first two routes of administration. Nevertheless, users
Marijuana use can lead to deficits in cognition and psychomotor performance

Clinical accounts of marijuana intoxication have often noted deficits in thought processes and in verbal behavior. These may include illogical or disordered thinking, fragmented speech, and difficulty in remaining focused on a given topic of conversation. The early descriptive work later gave rise to quantitative experimental assessments of marijuana’s effects on learning, memory, and other cognitive processes. Marijuana or THC administration does not appear to impair subjects’ ability to recall simple, “real-world” information. On the other hand, drug-induced performance decrements have been noted for a variety of verbal, spatial, time estimation, and reaction time tasks. With respect to memory, cannabinoids appear to interfere with all aspects of memory processing, namely, encoding, consolidation, and retrieval (Ranganathan and D’Souza, 2006), and some researchers have argued that adolescents are more vulnerable than adults to the influence of these substances on cognitive function (Schweinsburg et al., 2008). One example of THC’s effects on memory can be seen in a study by Valerie Curran and colleagues at University College of London. These investigators demonstrated dose-dependent deficits in two different verbal memory tasks at 2 and 6 hours following oral THC administration to infrequent cannabis users (Curran et al., 2002) (Figure 14.15). It is interesting to note that significant prior marijuana usage may reduce the adverse cognitive effects of acute marijuana exposure, which has led to the hypothesis that behavioral (“cognitive”) tolerance develops in heavy marijuana smokers (Hart et al., 2001).

Although memory and other cognitive functions are impaired shortly after smoking marijuana, most people do not smoke marijuana while they’re at work or in class, or at other times when a high level of functioning is required. If marijuana is used only during recreational times (e.g., evenings and weekends), and if drug-related cognitive deficits do not outlast the period of use, then one could argue that such deficits are harmless. On the other hand, is it possible that heavy recreational use over a long period who are smoking marijuana do not reach this peak until some time after the cigarette has been finished. This delay means that the maximum level of intoxication occurs when plasma THC concentrations are already declining, suggesting that the brain and plasma THC concentrations are not yet equilibrated at the time when the plasma level is peaking. Another possible factor is the contribution of active THC metabolites (whose peak does not coincide with that of THC itself) to the psychoactive properties of marijuana.
of time somehow compromises brain function such that cognitive problems persist even after drug use is stopped? The question of residual cognitive deficits from marijuana use is a controversial one, but a recent review by Crean and coworkers (2011) summarizes the current state of the field. Heavy cannabis use for a long period of time may lead to impaired executive functioning for at least 2 to 3 weeks following cessation of use. The affected functions include attention, the ability to concentrate, and inhibitory control. The adverse effects of cannabinoids on memory processes seem to have recovered by this time. Less information is available on truly long-term effects of prior cannabis use, ranging from 3 weeks to a few years. However, some of the data suggest that heavy, long-time users may continue to show impairment in decision making, planning, and concept formation.

In addition to its deleterious effects on cognitive/executive functioning, marijuana can negatively influence psychomotor performance. This has been demonstrated not only under controlled laboratory conditions but also in real-world tasks such as driving an automobile. Low doses of marijuana generally produce relatively few psychomotor effects, particularly in subjects who have previous experience with the substance. However, even regular users show impaired psychomotor functioning under demanding task conditions (including driving) following a moderate or high dose of marijuana, or when a low dose of marijuana is combined with alcohol. It is not surprising, then, that recent (shortly prior to driving) use of cannabis with or without alcohol has been implicated as a risk factor in automobile accidents (Ramaekers et al., 2004). On the basis of these results, it is prudent for individuals to avoid driving and other activities requiring operation of heavy machinery for a significant period after smoking marijuana.

**Cannabinoids are reinforcing to both humans and animals**

Cannabinoids are obviously reinforcing to users who smoke marijuana recreationally or who consume cannabis by other means. However, cannabinoid reinforcement in humans has also been studied under controlled laboratory conditions. For example, Chait and Zacny (1992) found that regular marijuana users could discriminate THC-containing marijuana cigarettes from placebo cigarettes containing no THC, and that all subjects preferred the marijuana with THC when given a choice. In the same study, pure THC taken orally in capsule form was also preferred over a placebo. Chait and Burke (1994) subsequently related marijuana preference to THC content, as users reliably selected marijuana with a 1.95% THC content over marijuana containing only 0.63% THC.

As we have seen in earlier chapters, the rewarding and reinforcing properties of drugs can also be studied in animals using the techniques of drug-induced place conditioning and IV drug self-administration. Although most drugs that are abused by humans are rewarding or reinforcing in these experimental paradigms, cannabinoids were initially thought to be among the exceptions to this general principle. However, it now appears that the early negative studies were compromised by several factors, particularly the presence of aversive reactions that can result from initial cannabinoid exposure, particularly at high doses.

Perhaps the most convincing evidence for cannabinoid reinforcement in animals has come from a series of studies from the National Institute on Drug Abuse that demonstrated reliable self-administration of THC by squirrel monkeys (reviewed by Panlilio et al., 2010). The key factor in these experiments was the use of low drug doses that are within the range of

![Figure 14.15 Oral THC produces a dose-dependent impairment in explicit memory.](image-url)
estimated human THC intake from a single puff on a
typical marijuana cigarette (Figure 14.16). Lever
pressing for THC was completely blocked by pretreatment
with rimonabant, indicating that the reinforcing effect
was dependent on CB₁ receptor activation. These
same investigators showed that THC can induce drug-
seeking behavior (a model of relapse in human drug
users) in monkeys (Justinová et al., 2008), and that the
endocannabinoid 2-AG is also self-administered (and
thus reinforcing) in the squirrel monkey model (Justi-
nová et al., 2011). Other studies have also found that
THC can produce a conditioned place preference in
mice (Valjent and Maldonado, 2000), and that rats and
mice will self-administer low doses of the synthetic
CB₁ receptor agonist WIN 55,212-2 (Fattore et al., 2001;
Martellotta et al., 1998). It is interesting to note that in
the place-conditioning study, the rewarding proper-
ties of THC could be demonstrated only in mice that
had been preexposed once to the drug in their home
cage. This was interpreted by the authors to mean that
first exposure to THC involves aversive responses that
mask its rewarding effects. Preexposure outside of the
experimental apparatus presumably reduces the
occurrence of these responses when the THC is subse-
quently administered during the conditioning trials.

Once cannabinoids were shown to be reinforcing
under appropriate conditions, researchers began to
investigate the mechanisms underlying the reinforcing
effects. One factor in cannabinoid reinforcement
may be activation of the mesolimbic dopamine (DA)
system, as cannabinoids have been found to stimu-
late the firing of DA neurons in the ventral tegmental
area (VTA), and to enhance DA release in the nucleus
accumbens. More surprisingly, there is substantial
evidence for close interactions between the cannabi-
noid and opioid systems that play a critical role in can-
nabinoid reward and reinforcement. Various studies
have found that opioid agonists enhance cannabinoid
self-administration, whereas opioid antagonists exert
the opposite effect (Cooper and Haney, 2009). Nev-
ertheless, we must be cautious in extrapolating the
results to human users, as a similar opioid modulation
of cannabinoid reward (as determined by self-report)
has not been reliably demonstrated in human studies.

This section has focused on the rewarding and rein-
forcing properties of cannabinoids themselves. Howev-
er, in recent years, a number of studies have examined
the effects of either genetic deletion of CB₁ receptors
or administration of rimonabant on responses to other
drugs of abuse. The results of these studies suggest that
the endocannabinoid system may play a significant
role in the processes of reinforcement, dependence,
and/or relapse for a number of other drugs, includ-
ing ethanol (Colombo et al., 2005), opioids (Fattore et
al., 2005; Robledo et al., 2008), nicotine (Castañé et al.,
2005; Maldonado and Berrendero, 2010), and psycho-
stimulants such as cocaine (Arnold, 2005; Wiskerke et
al., 2008). Most previous findings have indicated that
“cross-talk” between the endocannabinoid system and
the neurochemical systems associated with other drugs
of abuse involves the action of CB₁ receptors. However,
a recent study by Xi and coworkers (2011) surprisingly
found that systemic administration or microinjection
into the nucleus accumbens of JWH133, a selective CB₂
receptor agonist, dose-dependently inhibited various
effects of cocaine in mice, including cocaine-induced
hyperactivity and cocaine self-administration. The
effects of JWH133 could be blocked either by pretreat-
ment with a CB₂ receptor antagonist or by administra-
tion to CB₂ receptor knockout mice instead of wild-
type animals. Thus, future treatment approaches for
drug dependence based on manipulating the endo-
cannabinoid system might conceivably target either
or both of the CB₁ and CB₂ receptors.

**Figure 14.16 Acquisition of THC self-administration by squirrel mon-
keys** Monkeys were initially trained in drug
self-administration on a fixed-ratio (FR) 10
schedule using cocaine as the reinforcer
(not shown). They were then switched
to saline, which led to a nearly complete
elimination of lever-pressing behavior.
When THC (2.0 μg/kg/injection) was sub-
stituted for saline, lever pressing immedi-
ately increased to an amount sufficient to
deliver approximately 30 drug injections
per 1-hour session. Substitution with the
vehicle again reduced operant responding
until the active drug was made available
once again. (After Tanda et al., 2000.)
Section Summary

- The subjective characteristics of cannabis intoxication include feelings of euphoria, disinhibition, relaxation, altered sensations, and increased appetite. The euphoric effects produced by smoking marijuana appear to be mediated at least partly by CB₁ receptors. Psychopathological reactions can occur, particularly at high doses, or in the case of inexperienced users.

- Cannabis adversely affects memory, psychomotor performance, and other cognitive functions. The strongest effects occur during and for several hours after consumption. However, there is evidence for residual deficits that may last several weeks or possibly even longer.

- Although early studies failed to demonstrate cannabinoid reward or reinforcement in laboratory animals, more recent work has shown that THC can support self-administration and drug-seeking behavior in squirrel monkeys. Other cannabinoids, including the major endocannabinoid 2-AG and the synthetic CB₁ agonist WIN 55,212-2, are also self-administered by animals.

- Cannabinoid reinforcement has been shown to depend on the CB₁ receptor and may also involve dopamine, since cannabinoids stimulate the firing of DA neurons in the VTA and enhance DA release in the nucleus accumbens.

Cannabis Abuse and the Effects of Chronic Cannabis Exposure

According to Copeland and Swift (2009), about 4% of adults worldwide use cannabis in some form, with the greatest prevalence in North America, Australia, and New Zealand. Indeed, marijuana is the most widely used illicit drug in the United States. According to the 2011 National Survey on Drug Use and Health, more than 18 million Americans aged 12 or older were current marijuana users at the time of the survey (Substance Abuse and Mental Health Services Administration, 2012). This represented an increase from an estimated 14.4 million users in 2007, suggesting that government efforts to dissuade young people from trying marijuana have not been particularly successful.

Initial marijuana use typically occurs in adolescence and peaks during young adulthood. If an individual has not yet tried marijuana by his or her mid-twenties, he or she is unlikely to begin at a later age. This is shown in Figure 14.17, which is derived from a longitudinal study of 976 subjects drawn from upstate New York. In this cohort, the peak age for initiating marijuana use was 17, although a few children began as early 10 or 11 years of age. It is also the case that the prevalence of illicit drug use (including marijuana) declines with age. In the 2011 National Survey, for example, the percentage of respondents who were current users of at least one illicit drug (typically marijuana) was 23.8% at 18 to 20 years of age, 11.1% at 30 to 34 years of age, and only 1.0% at 65 years or older.

Several factors seem to influence the likelihood of early marijuana use, including lax parental monitoring and early behavioral problems. For example, a recent study by Falls and colleagues (2011) found a significant association between early conduct problems and early initiation of marijuana use (i.e., before 15 years of age) in a large sample of college students. In addition, most adolescents have prior experience with alcohol and/or cigarettes before trying marijuana. For this reason, alcohol and tobacco have been hypothesized as “gateway” drugs to marijuana use, although not all findings are consistent with this hypothesis (e.g., see van Leeuwen et al., 2011). Some evidence also exists that marijuana, in turn, may serve as a gateway to other illicit drugs (e.g., cocaine) or to prescribed psychoactive drugs such as sedatives (Mayet et al., 2012). However, it is difficult to determine whether marijuana actually facilitates the progression to “hard drugs,” or whether certain users are already predisposed to seek out these more dangerous substances because of some combination of personality traits, life circumstances, and other factors independent of their exposure to marijuana (see Web Box 9.1).

A further issue to consider is the progression from initial to regular (i.e., daily or near daily) marijuana use. Risk factors in the development of heavy marijuana use by adolescents include emotional problems in the family, heavy drug use in the household and/or by peers, dislike of school and poor school performance, and an early age of first use of marijuana (Gruber and...
Pope, 2002). On the other hand, rates of marijuana use tend to be lower among adolescents from stable families with close parental supervision, as well as those who have strong career aspirations or assume adult responsibilities such as marriage and parenthood. Another important factor may be the degree to which the young person experiences positive reactions to his or her early use of cannabis. Researchers in New Zealand examined the relationship between the subjective responses to early cannabis use at 14 to 16 years of age and the likelihood of becoming cannabis-dependent by the age of 21, according to criteria of the Diagnostic and Statistical Manual of Mental Illness (DSM-IV) (Fergusson et al., 2003b). Individuals who reported more positive responses (i.e., feeling happy, feeling relaxed, laughing a lot, doing silly things, or getting very “high”) to their early experience with cannabis were at greater risk of later dependence than those who reported fewer of these positive reactions. Finally, there is recent work by Brook and coworkers (2011) examining much longer-term trajectories of marijuana use frequency in a cohort of subjects from upstate New York over a period from 14 to approximately 37 years of age. The investigators identified five different patterns that they called (1) non-users or experimenters, (2) occasional users, (3) quitters or decreasers, (4) chronic users, and (5) increasing users (Figure 14.18). Programs aimed at reducing marijuana use and the development of dependence clearly need to identify and specifically target the factors that influence the usage patterns of the latter two groups.

**Tolerance and dependence can develop from chronic cannabinoid exposure**

For many drugs of abuse, regular heavy use leads to powerful tolerance as well as to physical and/or psychological dependence. Is this also the case for marijuana? We will first consider studies of cannabinoid tolerance in humans and animals.

**TOLERANCE** The human literature on cannabis tolerance is somewhat variable. There are some reports that the “high” produced by a given dose of THC is similar in heavy or frequent marijuana users compared with light or infrequent users (Kirk and de Wit, 1999; Lindgren et al., 1981), suggesting an absence of tolerance to this effect. However, controlled laboratory studies involving 4 consecutive days of high doses of either smoked marijuana or oral THC provided evidence of tolerance to several (although not all) self-reported cannabinoid effects, including drug “high” and “good drug effect” (Haney et al., 1999, 1999b).

Studies in laboratory animals have been even more consistent, showing that animals exposed repeatedly to THC and other CB1 agonists develop a profound tolerance to the behavioral and physiological effects of these compounds (González et al., 2005; Panagis et al., 2008). The rate of tolerance development depends on a variety of factors, including the species, choice of cannabinoid and dosing regimen, and which effect is being studied. Cannabinoid tolerance appears to be largely pharmacodynamic in nature, involving a combination of desensitization and down-regulation of CB1 receptors. For example, Breivogel and coworkers (1999) found that rats given daily THC injections (10 mg/kg) over a 3-week period showed gradual reductions both in regional CB1 receptor density and in cannabinoid agonist-mediated receptor activation (Figure 14.19). In some brain areas, the cannabinoid receptors were almost entirely desensitized following 3 weeks of THC exposure.

Interestingly, the results of a recent brain imaging study demonstrated a significant decrease in cortical but not subcortical CB1 receptor binding in regular marijuana smokers (Hirvonen et al., 2012). The magnitude of the reduction was correlated with the number of years of smoking, and the effect was reversible by 4 weeks of continuous abstinence from cannabis. These findings provide a neurochemical basis for cannabinoid tolerance in humans (at least with respect to those drug effects that are cortically mediated) and
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may also have relevance for the production of cannabis dependence and withdrawal symptoms.

DEPENDENCE AND WITHDRAWAL On the basis of a number of epidemiological studies, it has been estimated that approximately 10% of individuals who have ever used cannabis will eventually become dependent (Copeland and Smith, 2009). Not surprisingly, the risk of dependence is related to drug use patterns. Thus, people who progress to daily use have a 50% probability of becoming dependent. The 2011 National Survey estimated that 4.2 million individuals in the United States were abusing or dependent on marijuana at the time of the survey (Substance Abuse and Mental Health Services Administration, 2012).

Cannabinoid withdrawal symptoms were first reported in laboratory studies in the 1970s. Later research began to recognize the existence of cannabis dependence in some marijuana users. Such dependence is manifested as a difficulty in stopping one’s use, a craving for marijuana, and unpleasant withdrawal symptoms that are triggered by abstinence. Controlled studies of abstinence in long-term heavy marijuana users have reported a number of withdrawal symptoms, including irritability, increased anxiety, depressed mood, sleep disturbances, heightened aggressiveness, and decreased appetite (Cooper and Haney, 2008, 2009). These withdrawal symptoms resemble those seen with several other drugs of abuse, most notably nicotine. Overall symptomatology is greatest during the first 1 to 2 weeks of withdrawal (Figure 14.20), but some symptoms may persist for a month or longer. Moreover, recent research has shown that exposure to marijuana-related cues can elicit increased craving in cannabis-dependent individuals (Lundahl and Johanson, 2011). Cannabinoid withdrawal can be alleviated by providing either smoked marijuana or oral THC, demonstrating a key role for this compound in both the development of dependence and the manifestation of withdrawal symptoms.

Early experimental studies in which animals were administered THC chronically and then were examined after the treatment was stopped found few if any signs of withdrawal. Although these results may seem to be at odds with reports of an abstinence syndrome in humans, researchers recognized that the absence of withdrawal symptoms might have been due to the long elimination half-life of THC, which causes the cannabinoid receptors to remain partially occupied for a significant time even after termination.
of drug treatment. Once the CB₁ receptor antagonist rimonabant was developed, it could be used to test for dependence and withdrawal, since administration of the antagonist would abruptly block the receptors despite the continued presence of THC in the animal. This approach, which is called precipitated withdrawal, enabled researchers to demonstrate an abstinence syndrome characterized by tremors, wet-dog shakes, increased grooming behaviors (facial rubbing, licking, and scratching), ataxia, and hunched posture (González et al., 2005; Panagis et al., 2008). As expected, no withdrawal symptoms were observed in CB₁ knockout mice given chronic THC and then challenged with rimonabant. Although the precipitated withdrawal studies have convincingly shown that chronic treatment with THC or a synthetic cannabinoid can produce physical dependence in animals, there has been some criticism that these studies used very high cannabinoid doses compared with typical human recreational use patterns. Nevertheless, the reports of human abstinence symptoms confirm that dependence and withdrawal occur under naturalistic conditions, thereby supporting at least the basic conclusions drawn from the animal research.

The neurochemical mechanisms underlying the marijuana abstinence syndrome are not yet fully understood. Some of the important findings (using the precipitated withdrawal paradigm) include decreased DA cell firing in the VTA and reduced DA release in the nucleus accumbens, increased corticotropin-releasing factor (CRF) release in the central nucleus of the amygdala, increased secretion of stress hormones such as corticosterone, and various changes in the endocannabinoid system (González et al., 2005; Panagis et al., 2008). Together, these alterations could contribute to the mood reduction, irritability, and stress experienced by dependent cannabis users during periods of abstinence. Moreover, at least some of the same responses have been reported to occur during withdrawal from cocaine, alcohol, and opiates, thereby linking cannabinoids with substances generally considered to have greater abuse potential.

**TREATMENT OF CANNABIS DEPENDENCE** Although most cannabis users do not become dependent and do not seek treatment, those who do develop cannabis dependence report many problems (besides craving and withdrawal symptoms) that adversely influence their functioning, including social problems, financial difficulties, and poor general satisfaction with life (Budney et al., 2007; Copeland and Swift, 2009). Some, although not all, such individuals eventually seek professional treatment for their problems.

Dependent marijuana users seeking treatment are typically entered into an outpatient program that may involve cognitive-behavioral therapy, relapse prevention training, and/or motivational enhancement therapy. These approaches can also be combined with an incentive program in which participants who submit cannabinoid-negative urine samples earn vouchers redeemable for various goods and services. Although these different treatment programs have all met with some success, patients are highly vulnerable to relapse even after an initial period of abstinence (Kadden et al., 2007) (Figure 14.21). Thus, marijuana appears to be similar to other drugs of abuse with regard to the difficulty in achieving long-term treatment success in dependent individuals.

The idea of pharmacotherapy for cannabis dependence has not received a large amount of attention, but a few small-scale studies have used this approach to attempt to alleviate withdrawal symptoms. Medications tested to date include the antidepressants nefazodone and buspirone, the norepinephrine uptake inhibitor atomoxetine, the mood stabilizers divalproex and lithium carbonate (used to treat bipolar disorder), oral THC, and a combination of THC with the α₂-adrenergic agonist lofexidine (Budney et al., 2007; Copeland and Swift, 2009). Of these, the best success has been reported for THC, which suppresses cannabinoid withdrawal symptoms in a dose-dependent manner, and the combination of THC and lofexidine.

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Motivational enhancement therapy is a type of psychotherapy that seeks to elicit a desire for behavioral change on the part of the patient.
Because chronic marijuana use leads to cognitive impairments, Sofuoglu and colleagues (2010) recently suggested that cognitive enhancers such as those acting on the cholinergic system should be considered as potentially playing a useful role in mitigating such impairments.

**Chronic cannabis use may lead to adverse behavioral and health effects**

It is not unusual for dedicated cannabis users to consume the drug on a regular, even daily, basis for many years. Concern naturally has arisen over whether such lengthy periods of chronic drug exposure might lead to adverse psychological, neuropsychiatric, or physiological effects. Evidence for such effects is discussed in this final section of the chapter.

**EDUCATIONAL PERFORMANCE** Survey studies indicate that the amount of cannabis use by young people is inversely related to educational performance. That is, greater use is associated with poorer grades, more negative attitudes about school, and increased absenteeism (Lynskey and Hall, 2000). Furthermore, prospective longitudinal studies suggest that regular cannabis use beginning relatively early in life is a significant risk factor for poor performance in school and even dropping out (Brook et al., 2008; Townsend et al., 2007).

At the present time, we do not know whether there is a causal relationship between amount of cannabis use and educational achievement. Even if there is, the direction of causation would still need to be established. Does early cannabis use cause a lack of success in school, or does a lack of success early in one’s academic career cause an increase in cannabis use? One hypothesis is that heavy cannabis use leads to persistent cognitive deficits, thereby impairing school performance (Jacobus et al., 2009). It is possible that students who use cannabis heavily over a long period of time could perform poorly in school because of the cognitive impairment. Recent findings of Meier and colleagues (2012) support this hypothesis. These researchers conducted a prospective study of cognitive function in approximately 1000 people in New Zealand, who were recruited into the study at 3 years of age and were subjected to neuropsychological testing at 13 (before the onset of cannabis use) and again at 38 years of age. The amount of cannabis use and the appearance of symptoms of cannabis dependence were significantly associated with neuropsychological impairment (including lower IQ) at 38 years, even after controlling for level of education. These are among the first data to suggest a causal relationship between long-term cannabis use and cognitive deficits. Despite these findings, it is important to consider alternate hypotheses, including the notion that the social context surrounding heavy cannabis use at a relatively early age promotes the rejection of mainstream social values such as educational achievement in favor of a more unconventional lifestyle (Fergusson et al., 2003a; Lynskey et al., 2003). This hypothesis attempts to account for poor school performance in heavy users without postulating a direct effect of cannabis on their performance.

Another possibility involves drug-related motivational changes that would have a negative impact on performance in the classroom. Indeed, research going back more than 30 years has found evidence for apathy, aimlessness, loss of achievement motivation, lack of long-range planning, and decreased productivity in chronic marijuana users. Together, these symptoms have been termed the amotivational syndrome.

![Figure 14.21](image-url)
(Lynskey and Hall, 2000). We cannot rule out the possibility that some users experience a loss of drive and achievement motivation as a result of chronic, heavy exposure to cannabis. However, one could argue just as plausibly that such personality characteristics are a cause, rather than a consequence, of adopting a marijuana-centered lifestyle.

**NEUROPSYCHIATRIC EFFECTS**  In recent years, various imaging methods have begun to examine the potential influence of chronic marijuana use on the brain. A recent review of structural magnetic resonance imaging (MRI) studies on long-term cannabis users found some evidence of alterations in temporal lobe structures such as the hippocampus, although the findings across studies were inconsistent (Lorenzetti et al., 2010). Research using other imaging techniques such as functional MRI and proton magnetic resonance spectroscopy (which measures regional concentrations of several different neurochemicals) has found abnormalities in several other structures, including the anterior cingulate cortex, a brain area rich in CB₁ receptors that plays an important role in emotional processing and behavioral inhibition (Gruber et al., 2009; Prescott et al., 2011). Thus, imaging methods suggest that chronic marijuana use is associated with several different kinds of abnormalities in the brain.

Over the past 15 years, several large-scale epidemiologic studies have found a significant relationship between early heavy marijuana smoking and increased risk for the later development of psychotic disorders such as schizophrenia. This has become an important new area of research that is discussed in greater detail in Box 14.2.

**HEALTH EFFECTS**  In considering the potential health consequences of cannabis use, there is both good and bad news. The good news is that there is no published report of anyone dying as a result of cannabis overdose. This means that the use of this substance has a margin of safety that is lacking with many other substances of abuse such as heroin, cocaine, and sedative–hypnotic drugs. The bad news is that the lack of fatal overdosing does not mean that cannabis use, particularly in large amounts or for long periods of time, is without risk.

Because cannabis is almost always consumed by smoking, the possibility of lung damage is one obvious area of concern. Although marijuana joints and tobacco cigarettes contain different psychoactive ingredients (cannabinoids versus nicotine), the smoke they produce has the same kinds of irritants and carcinogens. Tar from cannabis smoke actually contains higher concentrations of certain carcinogens known as benzanthracenes and benzpyrenes. Even so, one might think that marijuana smoking is not harmful because users typically smoke only one or a few joints a day, compared with the one or more packs of cigarettes smoked by regular tobacco users. Unfortunately, it appears that the amounts of tar and carbon monoxide taken in per cigarette are much greater for marijuana joints than for tobacco cigarettes (Wu et al., 1988). It is not surprising, therefore, that regular marijuana smoking is associated with various respiratory symptoms, including chronic cough, increased phlegm production, wheezing, and even bronchitis in some cases (Howden and Naughton, 2011; Tetriault et al., 2007). Furthermore, microscopic examination of bronchial biopsy specimens from marijuana users has revealed several kinds of cellular abnormalities, some of which are considered precancerous (Tashkin et al., 2002). Researchers have not yet established a relationship between long-term marijuana smoking and lung cancer (Mehra et al., 2006). Nevertheless, heavy use has definite risks for the respiratory system, and future studies may show that development of lung cancer is one such risk.

Evidence has also been accumulating that cannabinoids influence the immune system. Both CB₁ and particularly CB₂ receptors are expressed by various immune cells, and activation of these receptors generally suppresses immune function (Tanasescu and Constantinescu, 2010). Importantly, THC has been found to impair an organism’s resistance to bacterial and viral infections under controlled experimental conditions (Cabral and Pettit, 1998). We don’t yet know, however, whether marijuana use leads to an increased incidence of infectious disease under real-life conditions.

Another system susceptible to interference by cannabis use is the reproductive system. It is now clear that the endocannabinoid system plays an important role in both the male and female reproductive systems (Bari et al., 2011; Sun and Dey, 2012), raising the possibility that marijuana smoking could have an adverse influence on reproduction. In support of this possibility, animal studies have consistently shown that THC suppresses the release of luteinizing hormone (LH), an important reproductive hormone secreted by the pituitary gland, in both males and females (Maccarone and Wenger, 2005). Other animal work has demonstrated pregnancy failure, retarded embryonic development, and even fetal death associated with THC administration, although similar findings have not yet been reported in controlled human studies. However, regular marijuana smoking by men has been shown to reduce testosterone levels, sperm counts, and possibly sperm motility (Rossato et al., 2008). Thus, marijuana seemingly has the potential to produce reproductive abnormalities, but more
BOX 14.2  The Cutting Edge

Is There a Relationship between Early Heavy Marijuana Smoking and Later Risk for Developing Psychosis?

Earlier in this chapter, we saw that heavy marijuana smoking causes short-term cognitive deficits, but any effects that persist after stopping seem to be modest. Similarly, immediate psychotic-like responses to cannabis are usually transient in nature. But what if young people knew that heavy marijuana use significantly increased their risk for developing a psychotic disorder such as schizophrenia later in life?

This important issue has now been addressed by a number of longitudinal cohort studies that tested whether there is a relationship between early marijuana smoking and a later onset of psychosis (Moore et al., 2007; Murray et al., 2007; Sewell et al., 2009). These studies were conducted in a number of different locations worldwide, including Germany, the Netherlands, the United Kingdom, Sweden, New Zealand, and the United States. The figure summarizes the findings from six studies according to the odds ratio of developing psychotic symptoms in heavy cannabis users compared with non-using control subjects. All studies found an increased odds ratio (increased risk) in the cannabis users, with this increase being statistically significant in five of the six since the 95% confidence intervals (depicted as the error bars) do not reach an odds ratio of 1 (represented by the controls) in those studies. Also shown in the figure is that a meta-analysis performed on the studies taken together found an overall odds ratio of approximately 2. This is interpreted to mean that heavy (e.g., daily) marijuana use, which typically occurs during the adolescent to young adult period of life, is related to a doubling of the risk of later developing psychotic symptoms (including in some cases a full-blown schizophrenia). Recent studies conducted in the Netherlands have additionally suggested that a younger age of onset of cannabis use is related to a younger age of appearance of psychosis-related symptoms (Dragt et al., 2010, 2012).

Although many investigators are convinced that these studies conclusively demonstrate a relationship between early marijuana smoking and increased risk for later psychosis, others have questioned the methodology used in at least some of the research (McLaren et al., 2010; Minozzi et al., 2010). Furthermore, even if we accept that such a relationship is real, there are several possible interpretations of the results. For example, Sewell and colleagues suggest three possible models to account for the findings of these cohort studies: (1) an association model, in which individuals who are already vulnerable to developing psychosis have an increased likelihood of using cannabis when they’re young; (2) a causal model, in which cannabis use (especially heavy use)

<table>
<thead>
<tr>
<th>Study (use)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHDS (daily)</td>
<td>1.56 (1.20–2.03)</td>
</tr>
<tr>
<td>ECA (daily)</td>
<td>2.00 (1.27–3.16)</td>
</tr>
<tr>
<td>EDSP (daily)</td>
<td>2.23 (1.30–3.83)</td>
</tr>
<tr>
<td>NEMESIS (weekly)</td>
<td>6.81 (1.79–25.91)</td>
</tr>
<tr>
<td>NPMS (dependence)</td>
<td>1.47 (0.55–3.93)</td>
</tr>
<tr>
<td>Swedish (&gt;50 times)</td>
<td>3.10 (1.72–5.58)</td>
</tr>
<tr>
<td>Overall</td>
<td>2.09 (1.54–2.84)</td>
</tr>
</tbody>
</table>

Increased probability of developing psychosis in heavy cannabis users  The graph illustrates the odds ratio (the probability compared with a reference group) of developing any psychotic disorder in six separate epidemiological studies relating cannabis use to later psychosis. The criterion for heaviest cannabis use is specified for each study in parentheses. The blue squares and accompanying lines represent the odds ratio for that study along with the 95% confidence interval (CI; a 95% probability that the real odds ratio lies within the specified range). The open diamond shows the overall odds ratio from the six studies taken together and shows that heavy cannabis use is related to an increased risk of subsequently developing a psychotic disorder. CHDS, Christchurch Health and Development Study (New Zealand); ECA, Epidemiological Catchment Area (U.S.A.); EDSP, Early Developmental Stages of Psychopathology (Germany); NEMESIS, Netherlands Mental Health Survey and Incidence Study (Netherlands); NPMS, National Psychiatric Morbidity Survey (United Kingdom). (After Moore et al., 2007.)
predisposes individuals to develop psychosis later in life, and (3) an indicator-variable model, in which one or more other factors lead jointly to cannabis use and psychosis proneness. Current data do not permit us to choose one model over another, although it is worth noting that some investigators have proposed plausible biological mechanisms whereby heavy cannabis exposure during adolescence might perturb the brain in ways that could predispose the person to developing psychotic symptomatology (e.g., Murray et al., 2007). But even if we adopt some version of a causal model, it seems likely that significant cannabis use is a component factor that interacts with other factors (including genetics and the early environment) to increase the risk of later psychosis development. Thus, this relationship is a strong reason (besides the adverse health consequences discussed elsewhere in this section) for young people to abstain from using cannabis, or at least to minimize such use.

research is needed to confirm and extend the existing findings.

A number of studies have been performed on the offspring of women who smoked marijuana during pregnancy. These studies found few negative effects of these offspring at birth or at early ages. On the other hand, cognitive deficits, poor school achievement, and increased risk for tobacco and/or marijuana use later in life have all been associated with prenatal marijuana exposure (Minnes and Singer, 2011). Such findings highlight the importance of educating women about the dangers of continuing to smoke marijuana during pregnancy, as well as the development of treatment programs to serve marijuana-dependent women who become pregnant.

Finally, Aryana and Williams (2007) have briefly reviewed evidence that marijuana use may be associated with cardiovascular problems, even including myocardial infarction (heart attack) in some patients. This is a relatively poorly studied area that clearly needs more work for these ideas to be substantiated.

ADVERSE EFFECTS OF ABUSED DESIGNER CANNABINOIDS Beginning in 2004, advertisements began to appear on the Internet for new herbal preparations containing synthetic designer cannabinoids that were legal at the time. These substances were typically sold under the names “K2” or “Spice.” Indeed, many of these preparations were found to contain potent CB1 agonists when they were tested by forensic laboratories, and thus smoking the plant material would provide a powerful marijuana-like “high” (Seely et al., 2011). Moreover, these products were reported to produce a number of adverse physiological and psychological effects in users, and they could be expected to exhibit significant dependence potential if used repeatedly. In response to these concerns, in 2011 the U.S. Drug Enforcement Agency (DEA) placed the synthetic cannabinoids previously identified in K2 or Spice under Schedule I, which bans their recreational use. Nevertheless, at the time of this writing, there are still numerous ads on the Internet for herbal products using the same names, and it is unclear whether any such products continue to contain illegal synthetic cannabinoids.

Section Summary

- Marijuana is the most heavily used illicit drug in the United States.
- Early behavioral (e.g., conduct) problems have been associated with an increased likelihood of early marijuana use.
- Initial exposure to marijuana usually occurs during adolescence, after the individual has already had experience with alcohol and/or cigarettes. Some investigators have hypothesized that alcohol and tobacco are “gateway” drugs to marijuana, which then serves as a potential gateway to other illicit drugs. However, it is difficult to determine whether marijuana actually facilitates the progression to these more dangerous substances.
- Other factors such as family issues, poor school performance, and a strong positive response to early marijuana experience are risk factors for the transition to regular use and possibly dependence.
- Controlled laboratory studies have demonstrated tolerance to repeated THC exposure in both humans and experimental animals. Such tolerance is related to a desensitization and down-regulation of central CB1 receptors.
- Heavy (e.g., daily) marijuana users are at significant risk for developing dependence on the drug and for undergoing withdrawal symptoms upon becoming abstinent. Withdrawal symptoms
include heightened irritability, anxiety, aggressiveness, depressed mood state, sleep disturbances, reduced appetite, and craving for marijuana.

- Chronic THC exposure in laboratory rodents also causes the development of dependence that can be demonstrated using the procedure of precipitated withdrawal with rimonabant. Neurochemical studies of cannabinoid-dependent animals undergoing withdrawal have found reduced DA cell firing, increased CRF release, and endocannabinoid system changes that could contribute to some of the symptoms of cannabis withdrawal in human users.

- Individuals who have developed cannabis dependence report a number of life problems, which leads some of these individuals to seek treatment.

- Some success has been achieved with various kinds of psychotherapeutic interventions, and additional improvement in outcome has been reported by adding a voucher-based incentive program to the standard treatment approach. Nevertheless, most dependent individuals find it difficult to maintain long-term abstinence.

- Pharmacotherapeutic approaches to the treatment of cannabis dependence are now being investigated. Oral THC has been shown to reduce withdrawal symptoms in heavy marijuana users, but this approach has not yet been incorporated into any established treatment programs.

- Concerns have been raised over possible adverse consequences of chronic cannabis consumption. There is a negative association between the amount of cannabis use by young people and their educational performance, although it is not yet known whether this association is causal. It is possible that heavy cannabis use can produce persistent cognitive deficits and/or an amotivational syndrome characterized by apathy, loss of achievement motivation, and decreased productivity. Alternatively, early cannabis use may be linked to the adoption of an unconventional lifestyle that devalues educational striving and achievement.

- Neuroimaging studies of heavy cannabis users have reported structural and biochemical changes in certain brain regions (including the hippocampus and anterior cingulate cortex). Epidemiologic studies have found a positive relationship between early heavy cannabis use and later risk for developing psychosis.

- Health consequences of heavy marijuana smoking include respiratory problems, possible suppression of immune function, interference with the reproductive system in both men and women, and adverse effects on offspring development (when used by pregnant women).

- Synthetic designer cannabinoids marketed as “K2” or “Spice” began to be sold over the Internet in 2004. Because of the dependence potential of these substances, as well as reports of adverse effects, the DEA designated these cannabinoids as Schedule I in 2011.

**Recommended Readings**


Go to the COMPANION WEBSITE

sites.sinauer.com/psychopharm2e
for Web Boxes, animations, flashcards, and other study resources.