5 Marijuana

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A brief introduction to cannabis and its use

Notes on cannabis and its history

The cannabis plant (*Cannabis sativa*) is an annual flowering herb, often referred to as hemp or marijuana. The leaves, stems, and flowering tops have over 60 unique compounds (botanical cannabinoids) that interact with the human body in complex ways, though Δ-9-tetrahydrocannabinol (THC) is the most potent psychoactive constituent in cannabis. Cannabis use dates back to ancient times, when it was thought to have been used by several Eurasian and Middle Eastern civilizations as a medical treatment and as an agent for the induction of altered states of consciousness. The first mention of cannabis as a psychoactive and medicinal substance appears during the 1st and 2nd millennium BC, in the first-known herbal medicine texts in China.

In recent years, perhaps no other illicit recreational drug has received as much social, political, medical, and scientific attention. Whereas some denounce the plant as a neurotoxin that is associated with an array of consequences, including psychosis, cognitive dysfunction, addiction, and all manner of social depravity, others tout cannabis as a benign healing herb. This debate is longstanding (for extensive reviews see Booth, 2003; Guy, Whittle, & Robson, 2005; Iversen, 2000).

Cannabis has repeatedly been classified and reclassified as a recommended medicine and as an outlawed intoxicant. For instance, in the United States, reports documenting the medicinal properties of cannabis were published during the 19th century. Decades later, the 1937 Marihuana Tax Act criminalized the use of cannabis in the United States, yet it remained in the United States Pharmacopoeia until 1941, exemplifying the lack of consensus on its utility and harm.

Methods of consumption, THC content, and pharmacodynamics

Cannabis can be prepared and ingested in various ways. The leaves and flowers of the plant are often dried before consumption. Higher potency can be attained by compressing resin from the flowering heads of the plant to

make hashish or by extracting THC with alcohol to make tinctures and oils. Cannabis preparations are often smoked using cigarette paper to envelop the substance before consumption or it can be smoked directly from a pipe. Apparatus is available that allows individuals to "vaporize" cannabis using a heating element that lets scorching air pass through the dried plant at a temperature that creates a THC vapor without combusting the plant itself. Cannabis can also be eaten. Users have attempted various uncommon methods of delivering THC to the bloodstream, which have included injecting cannabis preparations, placing tinctures on the eyes, or inserting cannabis into the rectum. Additionally, pharmaceutical companies have developed new systems of administration for delivery of cannabinoids or their synthetic analogues to the central nervous system (e.g., transdermal patches, eye drops, sublingual preparations).

Blood plasma levels of THC and its psychoactive effects depend on the potency and method of consumption. Factors influencing potency include the plant strain and method of growing, as well as how cannabis is prepared and consumed. The THC content of dried cannabis leaves and flowering tops typically ranges from 0.5 to 4%; however, the THC content of "sinsemilla" (seedless flowering tops of the female cannabis plant) can reach 20%. The THC levels in hashish and cannabis oil range from 10% to 50%.

Some scientists have suggested that the current potency of cannabis substantially exceeds the potency of cannabis during the 1960s and 1970s, though the findings on this issue are inconsistent and their significance is questioned. For example, a study of cannabis samples seized by the government in New Zealand between 1976 and 1996 reported no changes in average THC content across the 20 years (Poulsen & Sutherland, 2000). In contrast, in the United States, the THC content of cannabis samples seized between 1980 and 1997 rose steadily from less than 1.5% THC during 1980 to 4.47% in 1997 (ElSohly et al., 2000). Furthermore, commercial grade cannabis and sinsemilla confiscated in the United States during 2002 averaged 5.11% and 11.43% THC concentration, respectively (National Drug Intelligence Center, 2005).

Increasing levels of THC in cannabis and greater availability of more potent strains have been cited as a partial contributor to emergent cannabis-related health problems, such as increased psychiatric diagnoses of dependence and abuse (e.g., Compton, Grant, Colliver, Glantz, & Stinson, 2004). John P. Waters, the director of the United States White House Office of National Drug Control Policy, coined the phrase "This is not your father's marijuana," in an effort to convey the dangers associated with using the newly grown forms of cannabis. Others have criticized such claims, however. These critics note that potent strains have been available for many years, recent overall increases in potency have been small, and that smokers adjust the amount of cannabis consumed and frequently titrate their THC exposure to achieve the wanted effects (Earleywine, 2004; Hall & Swift, 2000; Mikuriya & Aldrich, 1988).

The pharmacokinetic and pharmacodynamic properties of THC and other cannabinoids have been well studied and vary according to route of administration (for a recent review, see Grotenhermen, 2003). When cannabis is smoked, THC is detectable in plasma within seconds. Peak concentration is attained in 3–10 minutes. Bioavailability is typically between 10 and 25%, and these values can vary depending on the users' amount of smoking experience. In contrast, consumption of cannabis in pill form results in erratic absorption of THC, with peak concentrations detectable in plasma between 1 to 6 hours and widely varying bioavailability.

It is noteworthy that THC is lipophilic, therefore repeated use of cannabis results in storage of THC in fatty tissue with subsequent slow release into the bloodstream. However, the amount and rate of THC released into the bloodstream from fat stores after cessation of use are not thought to be of enough magnitude or released rapidly enough to produce psychoactive effects. Estimates of THC half-life in plasma after cannabis consumption vary a great deal, ranging from several hours to several weeks depending on the method of use, potency of the preparation, and chronicity of use. Each of these factors is important to consider when attempting to assess last cannabis use through urine toxicology testing.

Prevalence of cannabis use

Despite its illegal status in many countries, prevalence of cannabis use worldwide from 2001 to 2003 is nearly 3.7% (146 million) for individuals 15–64 years old, compared with 0.3% for cocaine and 0.4% for opiates (United Nations Office on Drugs and Crimes, 2004). The highest annual prevalence of cannabis use was reported in Australia/Oceania (16.4%). North America, Africa, and Western Europe reported prevalences of 10.3%, 7.7%, and 6.7%, respectively. The lowest annual prevalences of cannabis use were reported in Eastern Europe (3.6%), South America (2.4%), and Asia (1.9%).

During 2003, in the United States alone, roughly 97 million (33%) Americans over the age of 12 reported ever using cannabis. Twenty-five million (12%) reported use during the last year and about 15 million (5%) during the last month (Substance Abuse and Mental Health Services Administration, 2003). Most Americans first try cannabis before age 18. During 2004, 51.1% of 12th graders reported use (Johnston, O'Malley, Bachman, & Schulenberg, 2005; Substance Abuse and Mental Health Services Administration, 2003). Cannabis use in America is most prevalent among adolescents and young adults between the ages of 15 and 29. Compared to the 30–49 year age group, almost twice as many Americans aged 15–29 reported cannabis use during the past year (approximately 15 million vs. 8 million) and the past month (approximately 9 million vs. 5 million) (Substance Abuse and Mental Health Services Administration, 2003). Fewer than 1.5 million Americans over 50 years old reported using marijuana during the past year.

In Europe, use of cannabis is also most prevalent among young adults

(European Monitoring Centre for Drugs and Drug Addiction, 2004). The proportion of individuals who have tried cannabis on at least one occasion differs substantially across countries. Estimates during 1999–2003 range from about 5% to 10% in Belgium, Estonia, and Portugal, with up to 24–31% prevalence in Denmark, Spain, France, and the United Kingdom. Cannabis use "in the last 12 months" among individuals between the ages of 15 to 34 were lowest in Sweden (1%), with higher rates reported for Estonia (4%), Hungary (5.4%), Poland (6.3%), Portugal (6.3%), Finland (7.1%), Slovakia (7.7%), Latvia (8.1%), Norway (8.1%), Ireland (8.7%), Greece (8.8%), Italy (9.2%), Netherlands (11.8%), Germany (13%), Denmark (13.1%), France (17%), Spain (17.3%), United Kingdom (20%), and Switzerland (22.1%). It is interesting to note that residents of European countries generally reported less lifetime cannabis use than the United States, despite many of them having less strict laws regarding possession of cannabis for personal use.

Laws governing cannabis use

Many countries (and states in the USA) have considered whether it would be prudent to modify the current statutes governing cannabis use. A number of factors underlie this consideration, including the high prevalence of use, the cost of enforcing prohibition, and the growing body of scientific evidence suggesting that controlled cannabis use provides therapeutic benefits with a tolerable margin of safety. In the USA, the government considers cannabis to have a strong potential for abuse and no accepted medical value, hence it is classified as a Schedule I drug by Title II of the Comprehensive Drug Abuse Prevention and Control Act of 1970. Cannabis receives the same classification status as heroin and LSD, whereas cocaine and methamphetamine receive less stringent regulations (Schedule II). Twelve states in the USA have passed laws to lessen criminal penalties for the possession or use of cannabis under various circumstances, but the federal government does not recognize these laws and retains the right to prosecute. Similarly, the European Union and United Nations classify cannabis as a controlled narcotic drug, but specific laws regarding use and possession differ across member nations. The general trend in many European countries has been to focus on "harm reduction" rather than criminalization. Alternative methods to prosecution include campaigns to discourage individuals from using cannabis, educating them about its potential dangers, and providing treatment for those with problems. Individuals distributing large amount of cannabis are more likely to be prosecuted, whereas those with small amounts for personal use may be reprimanded or left alone. Canada has been moving toward a position on cannabis that more resembles that of many European countries rather than the approach employed in the United States. Although the current public sentiment suggests a movement toward more lenient cannabis possession laws, the legal status of cannabis use remains an issue of intense dispute.

A brief introduction to cannabis neuropharmacology

Cannabinoid receptors and endogenous agonists in the brain

Increased interest in cannabis is evident in the scientific, sociopolitical, and legal realms. Published investigations on the central nervous system (CNS) and behavioral effects of cannabis increased by 100% from the 1980s to the 1990s. Further, the number of studies between 2000 and mid-2005 (at the time this chapter was written) already exceeds the total number published during the 1990s. Cannabis research increased significantly following the discovery and cloning of cannabinoid receptors CB_1 in mammalian brain (Devane, Dysarz, Johnson, Melvin, & Howlett, 1988; Howlett, Johnson, Melvin, & Milne, 1988; Matsuda, Lolait, Brownstein, Young, & Bonner, 1990) and CB_2 outside of the CNS (Munro, Thomas, & Abu-Shaar, 1993).

The cannabinoid (CB) receptors are in the family of G-protein-coupled receptors. Such proteins are involved in second messenger signaling, and modulate chemical reactions inside cells. The CB_1 receptors are diversely distributed in human brain tissue, where it is thought to be the most plentiful G-protein-coupled receptor (Biegon & Kerman, 2001; Herkenham et al., 1990; Herkenham, Lynn, de Costa, & Richfield, 1991). Highest concentrations of CB_1 are reported in basal ganglia, cerebellum, hippocampus, and amygdala, with lower concentrations in thalamus and brainstem (Abood & Martin, 1996; Breivogel & Childers, 1998; Glass, Dragunow, & Faull, 1997; Pertwee, 1997). The CB_1 receptors are also found peripherally in humans, but in much lower concentrations. The CB_2 receptors, on the other hand, are present mainly in immune tissues and cells (Galiegue et al., 1995; Munro et al., 1993). To date, CB_1 is thought to be the only cannabinoid receptor found in brain. More recent evidence, however, suggests the possibility of a third cannabinoid receptor (CB_3) in the brain (Breivogel, Griffin, Di Marzo, & Martin, 2001; Di Marzo et al., 2000; Fride et al., 2003).

The discovery of cannabinoid receptors in mammals prompted the search for naturally occurring ligands in the brain. Several endogenous metabolites of arachidonic acid (an essential fatty acid found in cell membranes and the brain) that are active at cannabinoid receptors have been identified (reviewed in De Petrocellis, Cascio, & Di Marzo, 2004; Freund, Katona, & Piomelli, 2003; Martin, Mechoulam, & Razdan, 1999; Piomelli, 2003). Anandamide (*N*-arachidonoyl-ethanolamine: Devane et al., 1992) and 2-AG (2-arachidonoyl-glycerol: Mechoulam et al., 1995; Sugiura et al., 1995) were the first endogenous cannabinoid receptor agonists with similar binding activity to THC to be identified and have been the most frequently studied. Several additional endogenous compounds reputedly bind with cannabinoid receptors; these include noladin ether (2-arachidonoyl-glyceryl ether: Hanus et al., 2001), virhodamine (*O*-arachidonoyl-ethanolamine: Porter et al., 2002), and NADA (*N*-arachidonoyl-dopamine: Bisogno et al., 2000; Huang et al., 2002).

Functioning of the cannabinoid signaling system in the CNS

The endocannabinoid system exerts its effects on the brain by regulating neurotransmission. Cannabinoid receptors in brain inhibit adenylyl cyclase and affect second messenger signaling through cAMP – they can decrease Ca^{2+} influx and increase K^+ conductance (reviewed in Pertwee, 1997; McAllister & Glass, 2002). Modulation of signaling by activity at CB_1 receptors has been implicated in many neurotransmitter systems, but is well understood to produce both inhibitory and excitatory signals by affecting GABAergic and glutamatergic systems (reviewed in Freund et al., 2003; Piomelli, 2003).

Several mechanisms for cannabinoid receptor function have been proposed. The CB_1 receptors in hippocampus are thought to be important in a critical process of GABAergic retrograde (postsynaptic to presynaptic) rapid signaling, termed depolarization-induced suppression of inhibition (DSI: reviewed in Davies, Pertwee, & Riedel, 2002; Maejima, Ohno-Shosaku, & Kano, 2001). A similar process, depolarization-induced suppression of excitation (DSE), may be mediated by cannabinoid receptors on glutamatergic neurons (reviewed in Maejima et al., 2001). Cannabis is thought to exert effects on cognition and behavior via signal modulation in structures that have the greatest level of CB_1 receptor density – the cognitive and behavioral functions associated with such brain structures would theoretically be most affected (reviewed in Freund et al., 2003; Iversen, 2000; Piomelli, 2003).

Interestingly, not all the mechanisms by which cannabis affects brain function are thought to be potentially harmful. Indeed, under specific circumstances cannabinoids are neuroprotective (Grundy, 2002; Guzman, Sanchez, & Galve-Roperh, 2001; Marsicano, Moosmann, Hermann, Lutz, & Behl, 2002; Mechoulam, 2002; Mechoulam, Panikashvili, & Shohami, 2002). For example, cannabinoids can inhibit the release of the excitatory neurotransmitter glutamate and production of reactive oxygen species (ROS), both of which are damaging to neurons in excess. Moreover, several cannabinoids, including THC, dampen experimentally induced excitotoxic injury in rodent brain tissue (reviewed in van der Stelt et al., 2002). Cannabinoids reduce damaging ROS through their powerful antioxidant properties, which have been demonstrated with cannabidiol, THC, and synthetic cannabinoids (reviewed in Hampson et al., 2000). Some cannabinoids have attenuated brain injury in several animal models of ischemia and show promise for management of traumatic brain injury in humans (reviewed in Biegon, 2004). The CB_1 receptors on sympathetic terminals inhibit norepinephrine release and may be involved in control of blood pressure (Pacher, Batkai, & Kunos, 2005).

Cannabis-associated mental health symptomatology

Mental health symptoms associated with acute intoxication

The acute effects of cannabis ingestion on mood, perception, and overall mental state have been well described. The majority of individuals report pleasant subjective characteristics of the cannabis "high," including euphoria, relaxation, heightened sensory experiences, and a proclivity for laughter. Common additional effects are light-headedness, rapid pulse, sedation, and psychomotor slowing. However, acute intoxication of cannabis has also been associated with more severe undesirable effects, including hypotension, paranoid thinking, anxiety, panic attacks, unpleasant feelings of depersonalization, and undesirable hallucinations. A recent comprehensive review of naturalistic and laboratory studies of cannabis intoxication concluded that subjective effects and behavioral features of cannabis intoxication vary considerably both within and across individuals (Green, Kavanagh, & Young, 2003) and are influenced by set (a person's expectations and psychic state) and setting. The review found that the majority of individuals in most studies reported pleasant effects, though multiple individual and environmental factors likely affect whether a person judges their subjective experience to be pleasant or not. After smoking a single cannabis cigarette initial psychophysiological effects are experienced within minutes, peak in the first hour, and dissipate several hours later.

The cannabis "withdrawal syndrome"

At present, it is unclear as to the presence and severity of mood and/or cognitive disturbance(s) emerging after cessation from cannabis use. "Cannabis withdrawal" is recognized formally in the most recent versions of the International Classification of Diseases (ICD-10), but not in the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-IV-TR). The putative effects of ceasing cannabis use have been studied extensively in both humans and animals, however the result of these studies is inconsistent with respect to the identification of a pattern of symptoms that occurs consistently following the cessation of cannabis abstinence. The disparities in the findings across studies often occur as a result of variability in the methods used by investigators to induce and measure "withdrawal." Furthermore, the relatively lengthy half-life of THC and its slow systemic elimination may attenuate withdrawal, thereby complicating findings.

There is substantial consensus that an acute withdrawal syndrome can be induced in animals receiving cannabis by administration of a potent CB_1 antagonist (SR 141716A); in contrast, the findings of studies in which animals undergo natural discontinuation from cannabis have yielded inconsistent results. Recent reviews of animal studies that utilized experimentally-induced withdrawal reported that findings depend on multiple factors, including the specific species examined, cannabinoid agonists used, and dosing schedules (Maldonado, 2002; Tanda & Goldberg, 2003).

Both reviews present evidence for cannabis tolerance and withdrawal. Maldonado (2002) tempers this conclusion by noting a lack of proof for strong reinforcing effects of cannabis, whereas Tanda and Goldberg (2003)

report that new studies with squirrel monkeys demonstrate THC's reinforcing properties through self-administration. Nevertheless, the high doses and treatment schedules of animal studies may not generalize to humans (Maldonado, 2002).

There is extensive debate regarding the presence, onset, course, and character of symptoms that potentially emerge with cessation of cannabis use by humans. A review by Smith (2002) presents evidence from several outpatient and residential laboratory studies that show undesirable emotional and physical symptoms among cannabis users, but finds the data suspect based on its methodological failings. Limitations observed included disparate methods of cannabis administration, lack of suitable control groups, absence of an *a priori* definition for cannabis withdrawal, inconsistent reports of the symptoms characteristic of withdrawal, poor quantification of symptom severity, and cannabis using groups not thought to be representative of the general population of cannabis users. Smith concluded that further examination is warranted to determine if the unpleasant effects many users seemingly experience when abstaining from cannabis constitute a withdrawal syndrome.

In light of new evidence, Budney and colleagues (2004) have reexamined the conclusions of Smith (2002). Both reviews agree that early studies of cannabis withdrawal produced inconsistent findings of indeterminate significance; however, if the findings from several well-controlled inpatient laboratory and outpatient studies are considered separately, it was consistently observed that chronic daily cannabis smokers reliably display unfavorable symptoms upon abstinence that emerge by 48 hours after cessation of use, peak between 2 and 6 days, remit within 1–2 weeks, and are corroborated by family and friends.

Based on the results of these studies, Budney and others (2004) proposed criteria for a cannabis withdrawal syndrome. According to Budney et al., individuals meet the diagnostic criteria for cannabis withdrawal when they experience the following symptoms: "significant distress or dysfunction" from at least four symptoms classified as common (i.e., anger and aggression, decreased appetite or weight loss, irritability, nervousness/anxiety, restlessness, sleep difficulties) or uncommon (i.e., chills, depressed mood, stomach pain, shakiness, and sweating). The authors report that the criteria were formulated on the basis of investigations in which the samples were comprised of chronic daily cannabis smokers. They emphasize the need for more research to determine the quantity, frequency, and duration of cannabis use that is necessary to elicit a withdrawal syndrome.

Cannabis addiction: Potential for abuse and dependence

The issue of a cannabis withdrawal syndrome has often been used to guide sociopolitical arguments regarding the dangers and legal status of the drug; in particular, the presence of withdrawal symptoms is utilized as evidence of

cannabis "addiction." It is noteworthy that current scientific and diagnostic practices no longer view tolerance and withdrawal as necessary for establishing a substance "addiction." The common feature of addiction as proposed by Dr Alan I. Leshner, former director of the National Institute on Drug Abuse, is an "uncontrollable, compulsive drug seeking and use, even in the face of negative health and social consequences." Such behaviors are the hallmark features used to diagnose "abuse" and "dependence" in commonly used classification systems. "Cannabis abuse" and "cannabis dependence" are treated as mental health diagnoses in the ICD-10 and DSM-IV-TR. Both classification systems require individuals to meet minimal criteria marking continued substance use despite causing specific adverse effects in a person's functioning.

The National Survey on Drug Use and Health (NSDUH, formerly NHSDA) during 2003 found that 2.5 million Americans aged 12 and over met the DSM-IV criteria for cannabis dependence and another 2.5 million met the criteria for cannabis abuse. When taken together, these numbers indicate that of all Americans that reported using cannabis in their lifetime, 5% met the criteria for cannabis abuse or dependence during 2003 compared to 4% for cocaine, 5% for heroin, and 12% for alcohol. Others have found that the risk of developing cannabis dependence among those who have tried the drug (conditional dependence) is 9%, but 32% for tobacco, 23% for heroin, 17% for cocaine, and 15% for alcohol. Thus, current evidence suggests that a sizable minority of all cannabis users is at significant risk for cannabis dependence or abuse, but the vast majority of cannabis users never meet such criteria. Future studies need to be conducted in order to identify risk factors for the onset of cannabis dependence and whether such vulnerabilities are specific to cannabis or any number of substances.

Associations between cannabis use and other mental health conditions

During 2003, the NSDUH reported that 17.2% of American adults using cannabis in the past year had a serious mental illness, compared to 7.8% of those who did not report using illegal drugs (Substance Abuse and Mental Health Services Administration, 2003). Estimates such as these provide valuable information, but they do not prove direct mental health consequences from cannabis use. Several fairly recent review articles have qualitatively summarized findings from the published scientific literature examining associations between cannabis and mental health conditions (Degenhardt, Hall, & Lynskey, 2003; Johns, 2001; Leweke, Gerth, & Klosterkotter, 2004; Macleod et al., 2004). Although cannabis use and psychopathology are often correlated, there appears to be no conclusive evidence to suggest that cannabis use can cause mental health problems in the absence of other confounding problems. Below we discuss conclusions from these reviews and methodological challenges that have made it difficult to make causal inferences regarding cannabis use and psychopathology.

Many investigators have examined links between cannabis use and psychotic symptoms or schizophrenia. Evidence exists to suggest that some individuals with no prior history of mental illness can develop transient psychotic episodes after very high doses of cannabis ingestion (Johns, 2001; Leweke et al., 2004). However such investigations have been deemed to suffer for numerous methodological weaknesses, including a lack of urine toxicology testing to rule out the presence of other drugs (Johns, 2001; Leweke et al., 2004). Further, Leweke et al. (2004) find no conclusive evidence for a distinct mental health entity called "cannabis psychosis" that produces symptoms specific to cannabis use. Johns (2001) concluded that studies of how cannabis modulates symptoms of individuals with schizophrenia have produced mixed and often contradictory results and no strong evidence implicates cannabis as a cause of schizophrenia. Leweke et al. (2004), however, note that cannabis might affect the symptomatology and course of schizophrenia, but further studies are needed to obtain more definitive findings.

The possibility that cannabis might cause or affect symptoms of depression has been extensively examined and recently reviewed (Degenhardt et al., 2003). As previously noted, cannabis use is correlated with psychopathology – the same observation has been made concerning depression. In their review of cross-sectional and longitudinal investigations of depression and cannabis use, Degenhardt and colleagues (2003) report that cannabis use was often found to be associated with a greater risk of depression later in life, particularly when use begins in adolescence. Longitudinal evidence did not support a "self-medication" hypothesis, where depression predicted later cannabis use. However, the authors conclude that when findings from all investigations are taken together, the evidence for cannabis to cause depression remains mixed due to many confounding variables. If a causal relationship exists, the authors thought it likely to be seen when individuals use cannabis heavily at an early age, but note that it probably, "makes, at most, a modest contribution to the population prevalence of depression."

The results of many investigations examining connections between cannabis use and psychopathology have been difficult to interpret due to several common limitations (Degenhardt et al., 2003; Macleod et al., 2004). Use of alcohol and other illegal psychoactive substances is often reported among cannabis users, but many investigations have failed to employ urine toxicology testing. Further complicating interpretation, many studies use participant samples seeking treatment for their cannabis use, because it has become problematic in their lives. Such samples are not thought to be representative of the vast majority of cannabis users. Establishing strong evidence of causation has also been hindered by reliance on cross-sectional designs. Many studies linking cannabis use with mental health problems have often poorly examined or controlled for factors that may differ between cannabis users and controls, which may account for differences in mental health symptoms. Such factors include economic disadvantage, low education, other substance use, parental level of education, family history of psychopathology, and mental health symptoms present prior to onset of cannabis use.

Not all investigations on this topic are hindered by these limitations. Macleod and colleagues (2004) reviewed only longitudinal studies with individuals 25 years old and younger in the general population. Causation can be more readily inferred from such investigations and confounds are more adequately controlled, thus they are more likely to clarify and address adequately the role of cannabis use in causing mental health problems. Unfortunately, only 16 of the 48 studies they recovered met their criteria for a "high quality" investigation (e.g., low chance of selection bias, adjustments for confounds, assessment of drug exposure using validated instruments). Equivocal findings were observed among studies implicating cannabis use with psychological problems and antisocial behavior. However, cannabis use was associated with lower educational attainment and more prevalent use of other drugs. The authors concluded that an association likely exists between cannabis use and poorer psychosocial outcomes, but found no clear evidence to suggest that it is causal or of a large magnitude.

The impact of cannabis use on neurocognitive functioning

Considerations in neurocognitive studies of cannabis use

The effects of cannabis use on neurocognitive functioning have been studied with various methods, such as examining brain activity, either at rest or when undergoing a cognitive challenge, using electroencephalography (EEG), positron emission tomography (PET), single photon emission computed tomography (SPECT), or functional magnetic resonance imaging (fMRI). Investigators have also relied on the results obtained by individuals on neuropsychological measures of various mental abilities, which include tests of processing speed, motor functions, attention, reaction time, visuospatial abilities, and executive and verbal functions. Below, we discuss findings of neuroimaging and neuropsychological studies of cannabis users, but first we present important methodological considerations that must be considered when interpreting the results of these investigations.

Regardless of the specific methods employed, to discuss the findings and relevance of neurocognitive studies, one must consider the length of abstinence from cannabis among participants in the study at the time the study is conducted. In their review, Pope et al. (1995) present a classification scheme that divides the effects of cannabis on neurocognition into two types: acute effects and residual effects. *Acute effects* on neurocognitive functions refer to the time when an individual is intoxicated with cannabis and several hours thereafter; that is, when a person is "high" and experiencing the psychoactive, intoxicating effects of the drug. *Residual effects* of cannabis use refer to changes in neurocognitive functioning that persists after cessation of cannabis use and after acute intoxication has subsided. Pope and others (1995)

make a distinction between two types of residual effects. The first is referred to as a "*drug residue effect*," which is used to describe cognitive changes that are apparent after acute effects have abated but cannabis products (i.e., THC and other cannabinoids) are still detectable in the individual. During this time, a cannabis withdrawal may be experienced, as we discussed in the previous section of this chapter. The second type of residual effect consists of changes in neurocognitive functioning as a result of cannabis use that persist despite no traces of cannabis in a person's system (i.e., after the drug has been completely eliminated). Pope et al. refer to this as a "*CNS alteration.*" Others have referred to these stages as *acute, subacute*, and *chronic* effects of cannabis use, respectively (e.g., Solowij, 1999).

Because the term subacute can refer to severity of symptoms, their duration, or both in medical practice, we prefer the designation *intermediate duration disorder*. First proposed by Grant and Judd (1976), intermediate duration refers to neurobehavioral changes that slowly improve over many months. Such slow resolution of symptoms most likely reflects gradual processes of metabolic recalibration (e.g., changes in concentrations, conformation, or activity of proteins involved in receptor function, ligand turnover, or cellular metabolism) that occur after pressure from an exogenous psychoactive substance is released. If neurobehavioral deficits improve, but ultimately some abnormality persists indefinitely, then the term *persistent disorder* is appropriate (Reed & Grant, 1990).

To establish residual neurocognitive effects of cannabis, it is critical to rule out multiple potential confounds. These include, but are not limited to, acute effects, effects from other substances, preexisting differences between heavy or light cannabis users (i.e., premorbid differences), or other risk factors that differ between the population of heavy versus light or noncannabis users (e.g., academic achievement, occupational achievement, impoverished home environment). Later, we will discuss the methodological limitations of the existing literature in more detail.

Acute effects

As previously discussed, individuals experience a variety of subjective acute effects from cannabis use, which are due to seemingly transient changes in brain functioning from the actions of THC and possibly other cannabinoids on cannabinoid receptors in the brain. EEG, PET, SPECT, and fMRI have been used to study these acute changes, and the findings have been reviewed by others (Loeber & Yurgelun-Todd, 1999). Most studies conducted to date have examined regional cerebral blood flow (rCBF) or metabolism using radiolabeled molecules (usually oxygen or glucose). Nearly all of the studies reported increased rCBF among experienced cannabis users when challenged with intravenous THC or smoked marijuana compared to their drug-free baseline, when administered a placebo, or when compared to participants with no cannabis use. This effect is consistent with known vasodilatory effects

of cannabinoids and contrasts with reduced regional flow associated with many other drugs of abuse, including cocaine, methamphetamine, and alcohol. Increased rCBF is most often seen in frontal, limbic, and cerebellar regions. Similarly, relative to controls, more rCBF primarily in "paralimbic" brain regions (i.e., orbital and mesial frontal lobes, insula, temporal poles, anterior cingulate, and cerebellum) have been observed when participants performed a task of attention after smoking cannabis, despite no significant differences on task performance compared to controls (O'Leary et al., 2002). Several studies have found correlations between rCBF and subjective feelings of intoxication, but the specific feeling reported and the specific region to which it is correlated have been inconsistent (Mathew, Wilson, Turkington, & Coleman, 1998; Mathew et al., 1999). Increased rCBF has been observed 30 minutes after a low-dose intravenous infusion of THC and found to persist beyond 120 minutes (Mathew et al., 2002). Results of EEG studies with humans intoxicated with cannabis are less consistent and sometimes yield contradictory findings, but most suggest changes in brain wave activity that are consistent with drowsiness (reviewed in Solowij, 1999).

Iverson (2000) provides a brief overview of studies that have specifically examined cognitive functioning during acute intoxication with cannabis. The subjective effects that individuals report when intoxicated include a distorted sense of time, perceptual changes, depersonalization, and psychomotor slowing, all of which could conceivably affect performance on neuropsychological measures administered during intoxication. However, Iverson indicated that individuals' subjective reports during intoxication do not generally correlate with their objective neuropsychological performance. For example, despite subjective reports of changes in cognition, intoxicated persons tend to perform fairly well on simple tests of attention. The ability to remember overlearned facts or autobiographical information (i.e., well-established memories) does not appear to be affected. Performance deficits are often noted on measures of declarative memory (e.g., hearing and then immediately repeating a list of words) and short-term recollection of recently presented information (e.g., a digit span test). The most consistent impairments, however, are reported to occur on measures that require sustained attention or on those that require active maintenance and mental manipulation of information (i.e., working memory). Intoxicated individuals will perform even more poorly on these measures of complex attention when presented with additional distracting stimuli.

In summary, studies of acute cannabis intoxication show that participants experience subjective changes in their cognition. Brain imaging studies generally demonstrate increased blood flow and metabolic rate in multiple brain regions (see Loeber & Yurgelun-Todd, 1999). On measures of neuropsychological performance, intoxicated cannabis users often show deficits in learning and remembering newly presented information, sustained attention, and on tasks of working memory. However, a consistent correspondence between functional neuroimaging results and neuropsychological functioning

has not been established among acutely intoxicated cannabis users. Further, most of these investigations have examined individuals several hours to days after their last cannabis use, rather than during acute intoxication.

As it happens, few studies have examined neurocognitive functioning in acutely intoxicated cannabis users. These studies essentially addressed the following question: Do individuals that are acutely intoxicated with cannabis show differences in brain function? Most researchers agree that cannabis intoxication results in neurobiological changes that affect cognition, mood, and behavior. From a public-health standpoint, these investigations have also not been deemed as pertinent as those examining residual effects, which have been researched intensely and their methodologies and findings scrutinized and debated.

Residual (nonacute) effects

Neuroimaging and brain function

Loeber and Yurgelun-Todd (1999) also reviewed nine imaging studies (i.e., Mathew, Tant, & Burger, 1986; Mathew, Wilson, Coleman, Turkington, & Degrado, 1997; Mathew & Wilson, 1993; Mathew, Wilson, Humphreys, Lowe, & Wiethe, 1992; Mathew, Wilson, & Tant, 1989; Tunving, Thulin, Risberg, & Warkentin, 1986; Volkow et al., 1991, 1996; Solowij, Michie, & Fox, 1991) of brain function among abstinent cannabis users and concluded that findings were inconsistent (see also Crippa et al., 2005). Interpretation of the findings was constrained by disparate imaging methodologies, differences in cannabis use histories among participants, rigor with which abstinence has been ensured, the degree to which investigators controlled for other drug or alcohol use, demographic differences among participants, and varying length of abstinence among participants that have ranged from 12 hours to 3 months. These caveats notwithstanding, three of the four investigations that examined resting rCBF among abstinent users of cannabis relative to controls reported lower resting rCBF among the cannabis users, which contrasts with the increases in blood flow typically observed among acutely intoxicated individuals. These conclusions have been substantiated by a more recent study (Block et al., 2000), which reports that frequent cannabis users exhibit a relatively circumscribed decrease in cerebellar CBF relative to controls after approximately 27 hours of supervised abstinence. However, most studies report that rCBF differences are no longer present after approximately 2 weeks of abstinence, which supports the notion of a time-limited change in brain functioning (i.e., CBF and metabolism). Such findings suggest a residual (or drug residue) effect from cannabis use, but no permanent "CNS alterations." At present, however, the association between these functional changes and neurocognition is unclear.

More recent studies have investigated changes in cerebral metabolism in response to a cognitive challenge. Consistent with the findings reported on

acute cannabis intoxication, these studies often find group differences in brain functioning despite no differences on task performance compared to controls. Block et al. (2002) examined brain metabolism and verbal memory, using O^{15}-labeled water, among frequent cannabis users abstinent for 16–28 hours. Relative to demographically matched controls, cannabis users required more presentations to learn a word-list during the first testing session (approximately 16 hours after last cannabis use) and demonstrated poorer recollection of word-list items during the second testing session (approximately 28 hours after the previous testing session). On the other hand, they remembered the same number of items as controls when tested with a new word-list during the second testing session. However, when recalling word-list items during the second testing session, cannabis users demonstrated decreased metabolism in prefrontal cortical regions, increased metabolism in cerebellum, and a different lateralization pattern of hippocampal metabolism relative to controls. An additional study compared oxygen metabolism among 11 frequent cannabis users abstinent at testing and matched controls while performing a modified version of the Stroop Color Word Task that requires inhibiting an automatic, dominant but inappropriate response (Eldreth, Matochik, Cadet, & Bolla, 2004). Although no between-group differences were observed on task performance, cannabis users showed decreased metabolism in left prefrontal regions and increased metabolism in hippocampus, bilaterally, after 25 days of verified abstinence – suggesting that cannabis users needed to recruit a more extensive neural network to achieve comparable performances to controls.

Findings from fMRI studies similarly report discordance between changes in function and neurocognitive performance. Kanayama, Rogowska, Pope, Gruber, and Yurgelun-Todd (2004) reported that a group of 12 frequent heavy cannabis users with recent abstinence from cannabis (between 6 and 36 hours) generally showed more widespread activation involving prefrontal, striatal, and temporal brain regions during a working memory task than a group of ten matched controls. Groups showed a similar level of task performance. In another investigation by this group, decreased activation in supplementary motor cortex and anterior cingulate was observed among nine recently abstinent (4–36 hours) heavy cannabis users during a finger tapping task relative to 16 controls despite no differences between groups on task performance (Pillay et al., 2004). Further, brain activation did not correlate with levels of THC metabolites in urine. Gruber and Yurgelun-Todd (2005) measured brain activation using fMRI with nine heavy cannabis users who tested positive for cannabinoids in urine and with nine controls who completed a modified version of the Stroop Color Word paradigm. Groups showed normal levels of performance and did not differ significantly on any task parameters, though cannabis users tended to make more errors during the most demanding task condition. However, pattern of activation in prefrontal regions differed between groups. Participants in this study were very heavy users that approximately consumed, on average, 39 cannabis joints a