Origin

Cannabis resin is secreted specifically by glandular hair structures, or trichomes, most thickly clustered on the surfaces of flowering heads and adjacent grey-green leaves of the hemp plant. The plant’s resin content depends on several variables: growing conditions, time of harvest, plant sex (female plants have more resin than male), and genetics. Samples of wild cannabis strains have traditionally contained low to moderate THC concentrations, but improved cultivation techniques and plant selection have led to significant increases. For example, it has been reported that the mean THC content in seized US cannabis specimens increased nearly three-fold during the decades of the 1980s and 1990s, such that whereas an average 1970’s “joint” contained only about 10 mg of THC, its late 1990’s counterpart may frequently have contained six-to10-fold more. The three main types of cannabis sold at street level are marijuana, hashish, and hash oil. Marijuana (or marihuana) refers to the dried and crushed flower heads and small leaves of the cannabis plant, but it is also sometimes used to refer to the cannabis plant itself (as is the term hash plant). Slang synonyms include grass, dope, blow, skunk, weed, pot, hemp, bhang, and ganja, among many others. Marijuana typically contains up to 5% THC. Hashish (derived from the Arabic hashish al kief [dried herb of pleasure], otherwise known as hash) refers to the cannabis resin alone, sans plant. Pure hashish is typically a brown malleable semisolid, but depending on its origin and purity, it can vary from soft and gooey to brittle or hard, and its color varies from brown to black, red, or yellow. Hash oil can contain up to 20% THC (sinsemilla, made from unfertilized female plants, being the strongest variety). Hash oil, the most potent form of cannabis, is a concentrated, greenish-black, viscous liquid extract of the resin that may contain greater than 60% THC.

Descriptive Chemistry

Cannabis refers to the flowering tops of the hemp plant, Cannabis sativa, which originated on the Indian subcontinent but is now widely cultivated. Hemp is composed of many different compounds. Cannabis resin contains more than 60 pharmacologically active derivatives of 2-(2-isopropyl-5-methylphenyl)-5-pentylresorcinol, known collectively as cannabinoids. The most abundant cannabinoids are (-)-trans-Δ⁹-tetrahydrocannabinol (Δ⁹-THC, Δ¹-THC), (-)-trans-Δ⁸-tetrahydrocannabinol (Δ⁸-THC [Δ¹-6-THC]), cannabinol (CBN), cannabidiol (CBD), and Δ⁹-tetrahydrocannabinolic acid.* Of these, Δ⁹-tetrahydrocannabinol has the most psychoactive potency, nearly 20-fold greater than that of Δ⁸-THC. Cannabinol and cannabidiol, although present in large amounts, likewise have low activity. Δ⁹-tetrahydrocannabinolic acid is inactive but is converted by smoking into active Δ⁹-THC.

Δ⁹-tetrahydrocannabinol

Synonyms: (-)-trans-Δ⁹-tetrahydrocannabinol; Δ¹-THC; Δ⁹-THC

Formula: C₂₁H₃₀O₂

Molecular mass = 314.4617 Daltons

CAS-1972-08-3

Δ⁸-tetrahydrocannabinol

Synonyms: (-)-trans-Δ⁸-tetrahydrocannabinol; Δ¹-6-THC; Δ⁸-THC

Formula: C₂₁H₃₀O₂

Molecular mass = 314.4617 Daltons

CAS-5957-75-5

* Note that cannabinoid nomenclature is complicated by the fact that cannabinoids can be described as either substituted monoterpene (Δ¹) or dibenzopyran (Δ⁹) compounds, giving rise to two different molecular numbering systems. We will conform to the dibenzopyran (Δ⁹) system here.
Cannabinol

*Synonym:* CBN; 6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol

*Formula:* C_{21}H_{26}O_{2}

*Molecular mass* = 310.4299 Daltons

CAS-521-35-7

![Cannabis molecule](image)

Cannabidiol

*Synonym:* CBD; 2-[3-methyl-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-pentyl-1,3-benzenediol

*Formula:* C_{21}H_{30}O_{2}

*Molecular mass* = 314.4617 Daltons

CAS-13956-29-1

![Cannabis molecule](image)

$\Delta^9$-tetrahydrocannabinolic acid

*Formula:* C_{22}H_{30}O_{4}

*Molecular mass* = 358.4712 Daltons

CAS-23978-85-0

![Cannabis molecule](image)

Pharmacology

**Intended Use/Medical Use**

Hemp was known and used by the Chinese, Egyptians, Greeks, and Romans from ancient times as a source of fiber in rope and textiles, seeds in lamp oil and food, and resin as a medicinal. These cultures are not known to have developed a tradition of using it for intoxication, whereas India, the Middle East, and Eastern Europe did use it as an intoxicant. Although the recreational use of cannabis in Western Europe and the United States is said to date from the mid-19th century, it achieved real popularity beginning in the 1960s. Today, cannabis is the most common, most widely cultivated, and most broadly distributed illicit substance worldwide; it was used, according to United Nations estimates, by as many as 192 million people in the year 2016. Marijuana has been characterized as “the number one cash crop in the US,” with earnings estimated at more than $500 billion a year. Cannabis has potential medical uses, including as an appetite stimulant in, for example, anorexia related to AIDS or cancer; as an antiemetic treatment for vomiting associated with cancer chemotherapy; and in the treatment of glaucoma and multiple sclerosis. Table 18-1 lists various formulations of medical cannabis.

Two cannabis pharmaceutical preparations in capsule form (2.5-10 mg; daily adult oral doses ranging from 2.5 to 20 mg) are dronabinol (Marinol), which is identical to natural THC (synthetic $\Delta^9$-tetrahydrocannabinol in sesame oil), and nabilone (Cesamet), which is a synthetic analog similar to $\Delta^9$-tetrahydrocannabinol. Another standardized cannabis pharmaceutical preparation, Sativex (THC plus CBD in approximately equal ratios), is a mouth spray used to treat neuropathic pain in patients with multiple sclerosis. (Each spray delivers a fixed dose of 2.7 mg THC and 2.5 mg CBD.) Under federal workplace drug testing regulations, the use of one of these approved pharmaceutical forms of cannabis is an acceptable alternative medical explanation for a finding of positive THC in a preemployment or “for cause” urine drug screen, whereas use of “medical marijuana” is not.

At the time of this writing, 29 states, the District of Columbia, Guam, and Puerto Rico have all enacted laws that permit the use of medical cannabis. With the exception of the District of Columbia, each state has limited the conditions for which cannabis can be prescribed. Examples of acceptable medical indications for cannabis include chronic pain, nausea, seizures, epilepsy, muscle spasms, cachexia, cancer, glaucoma, and anorexia in AIDS patients. However, broader use is allowed in some states for other “debilitating medical conditions” of the same kind or class as those listed previously where the potential benefits outweigh the health risks. In order to prescribe medical cannabis, states typically require physicians to have an established relationship with the patient, register with the state, and possibly complete a medical education program. The prescribed cannabis can then be obtained at specified state dispensaries.

Despite many states decriminalizing the use of medical marijuana and some even decriminalizing the possession of small amounts of the drug, marijuana remains listed as a Schedule I drug under the...
Cannabis, though often characterized as a depressant, is hard to classify pharmacologically because it causes a variety of effects. Both endogenous and exogenous cannabinoids act on G-protein–coupled cannabinoid binding receptors (CB) known as CB1 and CB2. CB1 receptors are primarily concentrated in the basal ganglia, cerebellum, hippocampus, association cortices, spinal cord, and peripheral nerves, while CB2 receptors are mainly found on the cells (e.g., leukocytes) in the immune system. Depending on the location of the CB and the specific G-protein involved, the stimulation of CB1 may result in the inhibition or stimulation of various neurotransmitters (e.g., acetylcholine, L-glutamate, dopamine, norepinephrine, and 5-hydroxytryptamine), which contributes to the central and peripheral effects observed. THC is only a partial agonist and binds to brain anandamide receptors causing dose-dependent and time-dependent stimulant, sedative/hypnotic, or hallucinogenic central nervous system (CNS) effects, accompanied by peripheral catecholamine release, tachycardia and/or sympathetic antagonism, and orthostatic hypotension. Other side effects include analgesia, muscle relaxation, antiemesis, appetite stimulation, and the reduction of intraocular pressure. On the other hand, synthetic cannabinoids are full agonists and have a much higher affinity for the CB receptors, thus increasing the physiological and toxicological effects.

Pharmacokinetics

Route of drug administration and drug formulation determine the rate of drug absorption. Smoking or vaporization provides extremely rapid absorption of THC, dissolving rapidly in pulmonary surfactant upon entering the lungs, entering the bloodstream in seconds, and achieving peak CNS levels within...
a few minutes because of high lipid solubility (the high THC octanol/water coefficient being variously estimated in the range of $6 \times 10^3$ to $9 \times 10^6$). Only a relatively small proportion of the dose crosses the blood-brain barrier, because blood THC is so lipophilic that it is 95% to 99% bound to plasma lipoproteins. Bioavailability of smoked drug ranges from 2% to 56% because of variability in smoking technique, which allows the user to effectively titrate the dose. More recently, the vaporization (ie, vaping) as route of cannabis administration has grown in both medical and recreational users. The duration of action lasts approximately 2 to 3 hours. Another alternative method of cannabis use growing in popularity is the inhalation of highly concentrated THC extract known as “dabbing.” Butane hash oil “dabs” may contain THC concentrations of 70% to 90% compared to traditional flower concentrations of 3% to 6%. The creation of the extract and process of inhalation involves using a solvent (eg, butane), resulting in a sticky oil which is then placed on the end of a hot surface (eg, nail), typically heated with a blow torch, and inhaled through a dab rig. While producing rapid effects, the higher THC concentrations and risk of burns leads to more toxicity and drug dependence.

THC can also be ingested. It is absorbed from the gastrointestinal tract more slowly and irregularly, with oral bioavailability estimated at 4% to 20% (10-20% for ingested dronabinol). Onset of effects may take 30 to 60 minutes, with peak THC absorption at 2 to 4 hours, and lower peak concentrations than when cannabis is inhaled. Among factors accounting for these differences between the smoked route and the oral route are marked effects of drug dose and vehicle on absorption rate, as well as gastric degradation of ingested drug.

After absorption by either route, THC blood levels quickly decline because of rapid redistribution from blood to tissues and subsequent extensive first-pass liver metabolism. Drug is initially taken up by highly vascular tissues, such as brain, lung, heart, and liver; it builds up more slowly during redistribution in tissues with lower rates of perfusion, such as fat. It has been estimated that a pseudo-equilibrium between plasma and tissue drug levels occurs approximately 6 hours after intravenous dose. The rate-limiting step in the overall metabolism of THC appears to be its redistribution from fat into the blood, and after longer periods of exposure, the drug is concentrated in fat, where its retention may be lengthy, possibly caused by formation of fatty acid conjugates of THC and 11-OH-THC, increasing their fat stability. Chronic cannabis use does not appear to cause major alterations in its initial pharmacokinetics, suggesting that the observed tolerance seen with such use is more likely due to altered pharmacodynamics.

Metabolism

The principal routes of THC metabolism are shown in Figure 18-1. THC is metabolized in the liver via oxidation by the cytochrome P450 system (principally by CYP2C9, CYP2C19, and CYP3A4) to many different compounds (more than 100 minor oxidative metabolites have been identified, including hydroxyl derivatives, ketones, aldehydes, and carboxylic acids). The principal route of metabolism, however, appears to be via hydroxylation by CYP2C9 to 11-OH-THC, which is pharmacologically active, and to a lesser extent to the less active 8Δ- and 8Δ-OH-THC. These three compounds, in turn, are subject to further hydroxylation to 8,11-diOH-THC. Route of drug administration has a major impact on the rate of these reactions, such that 10 to 15 minutes after the onset of smoking cannabis, plasma 11-OH-THC levels peak at only about 10% of THC concentration, which is much lower than after cannabis ingestion. 11-OH-THC is also majorly subject to oxidation to the inactive metabolite 11-nor-9-carboxy-Δ9-THC (THCCOOH), levels of which increase steadily and exceed those of THC by 30 minutes or so after smoking. The final phase of THC metabolism involves derivatization of the hydroxyl groups of THCCOOH, 11-OH-THC, and 8,11-diOH-THC, principally by glucuronidation, making them more water soluble, although they remain extensively protein bound in plasma. Enterohepatic circulation of metabolites may occur.

(It should be noted that drug-drug interactions between THC and other legal or illicit drugs may
affect its metabolism and those of the other agents. Such interactions have been described for atropine, barbiturates, cocaine, disulfiram, fluoxetine, HIV medications, lithium, neuroleptics, opioids, sildenafile, theophylline, and tricyclic antidepressants, among others. For more details on this topic, see Drugs of Abuse by Wills.1)

Excretion12,4,15
The principal routes of excretion for the broad range of cannabinoid metabolites are feces (60-70%) and urine (30-40%). The primary fecal THC excretion product is conjugated 11-OH-THC, and the predominant urinary THC metabolite is conjugated THCCOOH (conjugated parent drug and 11-OH-THC are only minor constituents of urine, typically undetectable; note that there is significant renal tubular reabsorption of THC and its metabolites). Altogether, anywhere from 70% to 90% of a THC dose is normally excreted within 3 to 5 days by both routes, but the terminal elimination half-life may be significantly prolonged in chronic users, due to prolonged redistribution of cannabinoids stored in body fat. In one reported case in an individual who had used cannabis for more than 10 years, the urine was positive by immunoassay (at >20 ng/mL) for 67 days after drug exposure.16

Volume of Distribution2,4,15
The standard volume of distribution (Vd) for THC is reported at about 10 L/kg (range 4-14 L/kg) in spite of the fact that the drug is heavily protein bound. Taking this into account, dynamic estimates of the steady-state Vd are in the range of 3 L/kg to 4 L/kg.17

Half-Life2,4,6
Plasma half-lives (t1/2) for THC have been estimated at 1.5 hours in occasional users and 2 hours in chronic users, and for THCCOOH, 120 hours and 144 hours, respectively. Estimates of THCCOOH urinary excretion half-lives range from 9 to 27 hours, whereas terminal urinary THCCOOH elimination t1/2 estimates have ranged from 3 to 4 days in occasional users to 12 days or more in frequent users. Detection of cannabinoids in urine is indicative of prior cannabis exposure, but the long excretion half-life of THCCOOH in the body, especially in chronic cannabis users, makes it difficult to predict the timing of past drug use.

Abuse Potential and Characteristics13,4,6
As with most other drugs of abuse, the recreational experience with cannabis is partly conditioned by surroundings, mood, and prior expectations of the user. First-time users sometimes report little or no effect, possibly because of inadequate dosage but also possibly attributable to lack of a placebo effect (experienced users frequently asserting that one must have some familiarity with the cannabis “high” in order to enjoy it fully). This high typically consists of initial elation, followed by relaxation, social disinhibition, heightened imagination, increased sensory awareness of colors, textures, and sounds, and increased appetite (the “munchies”). There may also be a pleasant perception of time passing more slowly. At high doses, illusions or hallucinations may appear. As users “come down” from the high, they not infrequently become drowsy and sleep. Smoking, the principal route of administration, delivers drug rapidly and efficiently from the lungs to the brain, contributing to the abuse potential of cannabis, with the strong reinforcement produced by the almost immediate drug exposure to the CNS. In spite of reports of chronic cannabis use leading to tolerance and psychological dependence, major degrees of physical dependence have not definitively been shown to occur. Withdrawal symptoms that have been described are nonspecific and may include such things as anorexia, anxiety, insomnia, irritability, restlessness, sweating, headache, and mild gastrointestinal upsets.

Analysis

Analytical Parameters2
Dissociation constant: Δ9-THC: pKα 10.6.

Specimen Types, Requirements, and Characteristics2,4,15
Cannabinoids and metabolites have been reported as measured in many specimens such as urine, whole blood, serum, plasma, hair, sweat, meconium, umbilical cord tissue, breast milk, and postmortem tissues.

Plasma THC specimens collected in glass are reportedly stable for 4 to 6 months at 5°C or -20°C, but whole blood specimens are said to be stable for only 2 weeks at -20°C, requiring lower freezer temperatures for longer periods. Specimens should never be collected or stored in plastic or at room temperature because THC binds readily to plastic, reducing recoveries during analytical procedures. This THC adsorption can be reduced by storing the compound in organic solvents or in basic solution in amber silylated glassware.

Urine specimens for THCCOOH are not stable, even when frozen, for periods beyond 4 weeks, especially if pipetted or stored in plastic. Urine specimens reportedly lost 11% of their original THCCOOH content after 45 days at -18°C.18 The effects of potassium nitrite used as a urine
adulterant can reportedly be countered by the addition of bisulfite or sulfamic acid to the specimen. Specimen preparation for confirmatory cannabinoid testing often includes hydrolysis (either enzymatic using β-glucuronidase or alkaline with sodium hydroxide [NaOH]) to remove glucuronide conjugates.

**Modes of Analysis**

A number of immunoassays are available for detection of cannabinoids in body fluids, and a variety of chemical methods are used for confirmation, including separation and identification methods. Given the range of compounds encountered both in cannabis drug specimens and in vivo, high degrees of analytical specificity are required.

**Known Analytical Issues and Problems**

Over the years, cannabinoid immunoassays have been optimized for the detection of THCCOOH, the principal urinary THC metabolite, at the expense of decreasing cross-reactivity with other cannabinoid metabolites. This has necessarily represented a trade-off between analytical specificity and overall clinical sensitivity, but it has increased the reliability (eg, likelihood of confirmation) of positive THCCOOH screens. Cannabinoid immunoassays have been reported to be subject to analytical interferences from prescription drugs. For a period of time, the Syva EMIT assay for THCCOOH was subject to false-positive interference by the nonsteroidal anti-inflammatory drug ibuprofen (Advil), but this was corrected in a reformulation of the kit by the manufacturer some years ago. No other immunoassays have shown this problem. In 2002, the antacid pantoprazole (Protonix), a proton pump inhibitor, was found to cause false-positive immunoassay results for marijuana metabolites; however, these screening results do not confirm with gas chromatography/mass spectrometry confirmatory testing. Another common inquiry from patients is regarding the ability of passive cannabinoid smoke inhalation to give a “positive” immunoassay result for THC. However, passive exposure has not been demonstrated to reliably produce concentrations high enough (eg, >50 ng/mL; common immunoassay cutoff) to be detected in most urine drug screens.

**Clinical Issues**

**Clinical Interpretation of Analytical Findings**

For medicolegal (workplace or forensic) purposes, administrative regulatory cutoffs have been established by the Department of Health and Human Services for declaring positivity of urine screening immunoassays (50 ng/mL) and gas chromatography/mass spectrometry confirmatory assays (15 ng/mL). These cutoffs do not challenge the limits of detection of most assay methodologies and differ from one another because of the analytical difference between quantitating THCCOOH glucuronide and other cross-reacting cannabinoids and metabolites in the screen versus a single analyte-free THCCOOH posthydrolysis—in the confirmation. Historically, a number of considerations entered into the federal government’s determination of these cutoffs, including the necessity for the cutoffs to be applicable across multiple different immunoassay platforms with different specificities and cross-reactivities, the desire to eliminate potential false-positives due to passive inhalation of sidestream marijuana smoke, and so forth. Studies comparing clinical sensitivity, specificity, and efficiency of a variety of commercial immunoassays at 20, 50, and 100 ng/mL urinary cutoff levels in experimental subjects after exposure to measured inhaled doses of cannabis showed that lowering the cutoff concentration to 50 ng/mL increased sensitivity in all immunoassays (range, 57.0-79.5%), while specificity decreased slightly (with false-positive results increasing 1.0-2.6%), with all assays being highly efficient (increasing from 91.4% to 94.7%) at both cutoff concentrations. At this cutoff, a naïve or infrequent user smoking a single joint may test positive for 1 to 3 days, whereas a frequent, chronic user’s urine may continue at detectable levels below the cutoff values for a month or longer (estimates ranging from 3 to 8 weeks). In addition, there is considerable interindividual variation in mean detection times in urine after smoking, even in controlled-dose studies. Given all of this, a positive urine cannabinoid test can really only be interpreted as indicating the occurrence of drug exposure and does not provide information about how much, when, how, if significant impairment resulted, or whether the urine positivity was due to residual excretion of drug redistributed from body fat or from new drug use. In drug treatment settings, this latter issue may be important to differentiate; some have utilized urine creatinine normalization of THCCOOH concentrations to address this. Others have suggested that urinary THC parent drug and 11-OH-THC, although present as alkaline-resistant glucuronides in low concentrations, might nonetheless be useful as biomarkers of recent cannabis use, but this has been shown not to be the case. In this study, the authors showed extended urinary excretion of both THC and 11-OH-THC for at least 24 days, which
demonstrated it couldn’t be used as a biomarker for recent cannabis exposure.23

Cannabinoid testing in alternative matrix specimens (oral fluid, sweat, and hair) is also being continuously developed and is in used in a variety of settings. In 2015, the Substance Abuse and Mental Health Services Administration introduced guidelines for oral fluid testing for workplace testing, with initial THC screening cutoffs of 4 ng/mL and confirmatory testing cutoffs of 2 ng/mL. Lastly, as the legalizing and decriminalization of recreational cannabis and approval of medical cannabis continues, a single blood THC laboratory-based concentration for a legal per se limit or zero tolerance concentration that is always associated with impairment in all users (eg, occasional or frequent) is desired but very unlikely to exist.24 While studies continue, the reality of a single cannabinoid concentration that would consistently indicate impairment fades.

Overdose and Toxicity23,25
Severe cannabis intoxication may result in confusion, dizziness, weakness, malaise, visual impairment, short-term memory deficit, depersonalization, visual hallucinations, and occasional episodes of acute paranoid psychosis or panic reaction. Nausea and vomiting may be seen with oral use of cannabis. The manufacturers’ warnings for Marinol include not engaging in any hazardous activity until tolerance is established and avoiding use of alcohol or other CNS depressants, which could potentially cause additive effects with THC (Physicians’ Desk Reference, 1997). On physical examination, patients with THC intoxication may exhibit tachycardia, orthostatic hypotension, conjunctival injection, incoordination, dry mouth, slurred speech, ataxia, fine tremor, and stupor. THC intoxication has been reported to result in coma in children. In adults, the principal risk of fatality relates to impaired judgment and motor incoordination in driving or operating machinery while under the influence; however, there are rare reports of loss of consciousness or even death directly from cannabis, such as in very infrequent instances of intravenous injections of marijuana extract or hash oil causing dyspnea, abdominal pain, fever, shock, disseminated intravascular coagulation, acute renal failure, and death. Cannabis may also be used in combination with other drugs that increase the risk of lethality, for example, phencyclidine (PCP) combined with marijuana in so-called “superweed” or “wicky stick” to obtain a more intense high. Cannabis toxicity is typically diagnosed on the basis of history of use accompanied by altered mood or cognitive function and typical physical findings, such as tachycardia and conjunctival injection. Useful routine laboratory results may include electrolytes and glucose.

Adverse Effects and Complications

Central Nervous System1
Effects of chronic cannabis use on the CNS are poorly understood. Early reports of CNS structural changes have not been confirmed, and reported associations with chronic schizophrenia remain unproven. Flashbacks (eg, reruns of the intoxication experience) have been reported with cannabis, but they are both milder and less frequent than with the major hallucinogens like lysergic acid diethylamide (LSD). Findings regarding increased incidence of anxiety, depression, and deficits in learning and short-term memory are conflicting. Chronic drug abuse in general often coincides with tendencies toward social isolation and poor personal performance. In the case of heavy chronic cannabis use, this has been characterized as the so-called amotivational syndrome, in which users seem deficient in goal-oriented behavior, have short attention spans, and have increased tendencies toward introversion and apathy. To what extent such tendencies may result from any CNS changes due specifically to cannabis use is unclear.

Cardiovascular1,26
Activation of CB1 by endocannabinoids or synthetic ligands mediates acute hemodynamic effects and might contribute to pathology in cardiovascular disease. Cannabis use is associated acutely with increased cardiac output and decreased oxygen-carrying capacity of the blood, in turn associated with tachycardia. This may increase the frequency of angina on exertion in patients with ischemic heart disease, but the incidence of myocardial infarction does not appear to be increased. Although cardiac palpitations are sometimes reported, they are not generally accompanied by arrhythmias. Dilation of peripheral veins associated with local impairment of cerebral blood flow results in postural hypotension, with dizziness and fainting upon standing. Desensitization or tachyphylaxis may lead to both orthostatic hypotension and tachycardia in frequent users.

Respiratory1,5
It may be useful to compare the smoking of cannabis to tobacco cigarette smoking. Marijuana joints are homemade, loosely wrapped cylinders, without filters, that are usually smoked down to the very end, with the final draws being of smoke that is hotter and denser with particulates, tar, and carbon
monoxide than those of a cigarette, and they are inhaled much more deeply, with the breath commonly being held for a few seconds after inhaling (unlike with cigarettes). All of this, plus the higher tar content of cannabis smoke, puts the airways at greater risk of damage and allows cannabis particulates to permeate the lower airways more completely and deposit more tar than tobacco smoke typically does. Acute inhalation of cannabis smoke causes bronchodilation in normal individuals, but the irritant smoke stimulates bronchoconstriction in people with asthma, and chronic use increases large-airway resistance, unlike tobacco. On the other hand, cannabis smoking, like tobacco, commonly causes chronic productive cough and/or sore throat and inhibits pulmonary defense mechanisms, increasing the risk of infection or allergy. Fungal spores (typically Aspergillus) often found in dried cannabis have been reported to cause infection (in immunocompromised persons) or hypersensitivity pneumonitis (in people who are allergic to the fungus). Likewise, cannabis pollen may be allergenic. Rare instances of pneumomediastinum, secondary to alveolar overdistention and rupture associated with deep inhalation, have been described during marijuana smoking. Chronic cannabis smoking has not been definitively associated with lung cancer, primarily because studies of its epidemiology have been confounded by the frequency with which chronic cannabis smokers also use tobacco. Nonetheless, expert consensus remains that such a link is likely. Although risk might be thought to be mitigated among chronic cannabis smokers (who usually smoke less often than do tobacco smokers), studies of the prevalence of precancerous airway lesions have shown higher rates in exclusive cannabis smokers than in exclusive tobacco smokers, and the highest rates in those who smoke both. Anecdotal reports of cancer of the head, neck, mouth, jaw, and tongue in young adults have been attributed to chronic cannabis use.

Reproductive

Reported associations between chronic cannabis use and gynecomastia, oligospermia, decreased testosterone in males, and decreased libido in both sexes are unconfirmed, and no effect on fertility has ever been described. The US National Birth Defects Prevention Study found that fetuses with marijuana exposure within their first month of gestation were at significant risk for anencephaly. Reports of behavioral alterations among the infants of women who smoked marijuana during pregnancy are inconclusive, and most epidemiological studies of infants from cannabis-exposed pregnancies are confounded by alcohol and tobacco use, race, and socioeconomic status. THC and metabolites are excreted in breast milk, but the few studies of its effects on breastfed infants are inconclusive; nonetheless, the American Academy of Pediatrics regards marijuana use as contraindicated in breastfeeding mothers (Committee on Drugs, American Academy of Pediatrics, 1994).

Toxic Dose

No toxic dose has been generally established for THC, given the rarity of cannabis dosage fatalities. Toxicity is dose related but subject to much interindividual variability. An admission radioimmunoassay cannabinoid blood level of 180 ng/mL was reported in a comatose 19-year-old user of cannabis who recovered. Postmortem THC blood levels ranging from 3 ng/mL to 22 ng/mL were recorded in six cases of presumed fatal cardiovascular drug toxicity; postmortem THC tissue concentrations in another presumed THC fatality were 3.75 µg/100 g in liver, 4.2 µg/100 g in kidney, and 1.2 µg/100 g in spleen. Treatment and Rehabilitation for Overdose and Toxicity

Treatment of toxicity includes the following emergency and supportive measures. Psychological disturbances—such as anxiety or panic reactions or transient psychosis—may be managed by a combination of reassurance and benzodiazepines. Sinus tachycardia is usually self limited but may require beta blockers. Orthostatic hypotension usually responds to the head-down position plus fluids (intravenous, if necessary). If stat detoxification is necessary after a large oral ingestion, for example by children in the home, ipecac-induced vomiting may be of benefit if instituted immediately; otherwise, prompt administration of activated charcoal without gastric emptying is the treatment of choice. The Vd of cannabinoids is so large that enhanced elimination is ineffective in dealing with acute oral overdose.

References


