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Cannabis and Cannabis Use Disorder Cannabis/marijuana is used by more than >150 million people world wide. The 2023 United States National Survey on Drug Use and Health, estimated that 42 million people used “marijuana” over the last month, while 62 million people used nicotine and 136 million drank alcohol (https://www.samhsa.gov/data/release/2023-national-survey-drug-useand-health-nsduh-releases). Notably in 2023, 10 million younger people (12-25 year olds) consumed marijuana each month, while 12 million used tobacco products. For reference, nearly 19 million 12-25 year olds used alcohol on a monthly basis. Since the Agriculture Improvement Act of 2018 (AIA; Public Law 115-334) amended the Controlled Substance Act, products made from Cannabis sativa species have been defined as marijuana when the plant or finished product contains >0.3% Δ-9-tetrahydrocannabinol (D9THC) by dry weight. Conversely, cannabis plant material, extracts, and derivatives that contain no more than 0.3% D9THC by dry weight are defined as “hemp.” We will be using the terms marijuana and can nabis interchangeably in this report since marijuana is the term used in multiple surveys, and in state and Federal laws. Marijuana is primarily grown for its euphoric and medicinal properties, which are principally mediated by D9THC acting on neuronal type 1 cannabinoid receptors (CB1R). The contribution of minor cannabinoids (including cannabi diol [CBD]) or terpenes is limited and largely unproven to be clinically relevant at concentrations found in marijuana. Marijuana remains federally illegal as of May 2024, but 24 states, 3 U.S. territories, and Washington, DC, have passed measures to legalize nonmedicinal (adult) use, whereas 38 states, 4 U.S. territories, and Washington, DC, have legalized medicinal cannabis use.

Hemp varietals are federally legal to grow and manufacture into seed/oil products, fiber, or CBD extracts. Some varietals can contain >12% (w/w) of the nonintoxicat ing CBD, while the D9THC level remains within the definition of “hemp” (0.3%). High CBD hemp was first envisaged as a source for the treatment of childhood seizure disorders (Federal bill H.R. 5226, 2014). However, after hemp legalization, processors began to derivatize hemp into Δ-8-tetrahydrocannabinol (D8THC) and other intoxicat ing hemp products (IHPs). According to one recent survey, people who use D8THC report it to be milder than D9THC and perceive it to be legal. Pharmacologic studies support lower potency of D8THC than D9THC, but other IHPs such as tetrahydrocannabiphorol can be considerably more potent (20–30×). It is worth noting that the 2023

Monitoring the Future national survey found that 11% of 12th-grade U.S. students reported past-year D8THC use. Marijuana legalization has increased the demand for, and supply of, increasingly high D9THC-containing cannabis strains. Can nabis flower products now range from <0.3% in hemp to 20–30% in legal dispensary products. Further, extracts used as liquids in “vape pens” purportedly contain up to 75% D9THC, while adver tisements of solid extracts (e.g., “shatter”) containing up to 95% D9THC are not uncommon, although most of these claims appear to be exaggerated. Solid high-D9THC preparations are used for high-temperature vaporization (“dabbing”). Inhalation is a highly bioavailable (efficient) and rapid route of absorption for D9THC, so vaping products deliver high D9THC doses with rapid effect onset, conditions linked to increased risk of addiction. In contrast, edible D9THC-infused products (e.g., candies, cookies, and drinks) have slower rates of onset and are perceived to be associated with reduced harm. Edible products are less bioavailable than inhaled D9THC, but absorption can vary depending on the presence and nature of food in the stomach. Notably, “edibles” are favored by younger users and are associated with a higher probability of accidental dosing than inhaled products. PHARMACOLOGIC EFFECTS Cannabis is used recreationally because it enhances the subjective sense of well-being, provides rewarding sensations, and can dampen stress responses. However, consumption of high doses of D9THC can induce anxiety, paranoia, and panic. D9THC is primarily a par tial agonist (activator) of G protein–coupled cannabinoid receptors (CB1R and CB2R), with the euphorigenic effects mediated through CB1Rs primarily located on excitatory glutamatergic and inhibitory γ-aminobutyric acid (GABA)-ergic interneurons and glial cells in brain regions that process stress, mood, and reward. These receptors are the effectors of the endocannabinoid system (ECS), which is physi ologically activated by the endogenous ligands 2-arachidonoylglycerol (2-AG; a full agonist), and anandamide (a partial agonist). According to current understanding, 2-AG modulates synaptic signaling by inhib iting overstimulated synapses. Endocannabinoids are synthesized and eliminated on demand and thus provide a temporally and regionally specific modulatory signal. In contrast, the effect of intoxicating can nabinoids are defined by dose and their period of effect, not subtle “just in time” synaptic synthesis. Consequently exogenous cannabinoids disrupt important ECS neuroregulatory processes. The rewarding effects of D9THC are thought to be mediated by modulating glutamatergic and GABAergic activity in the midbrain ventral tegmental area (VTA), from where dopaminergic neurons project into the nucleus accumbens (NAc). In the NAc, rewarding experiences are reinforced (learned) by glutamatergic and dopaminer gic signal interactions. The anxiolytic effects of D9THC are mediated by its effects on the amygdala, a region critical for threat perception and emotional reactivity. CANNABIS PHARMACOKINETICS Smoking (e.g., joints and water pipes) remains the most common route of cannabis administration, but e-cigarette–type “vape pens” are increasingly being used. Vape pens use “e-liquid” concentrates, and the plasma concentrations achieved following their use depend on the e-liquid D9THC concentration and the

“puffing profile.” The ability to take a single puff from a vape pen offers easier dose control than smoking. Vaping is perceived to be less harmful than smoking, but the long-term toxicology of e-liquids in humans is not yet clear. The subjective effects of cannabis are affected by dose, route of administration, (smoked, vaped, or ingested), and the subject’s prior experience (which also modulates expectation). Smoked D9THC exhib its a bioavailability of 10–35%, with interindividual differences stem ming from variations in the capacity to hold smoke in the lungs. The pharmacokinetics of heated (not burnt) cannabis flower and vaporized ethanolic extracts are similar to those of smoked flower, but no data are available to compare pharmacokinetics of smoked flower and commer cial e-liquids or solid concentrates. When cannabis is smoked, plasma

D9THC concentrations become maximal within 5–10 min. After this time, plasma levels decrease with two phases governed by different elimination exponentials. There is an initial distribution phase with an (alpha) half-life (t1/2) of ~6 min, governed by absorption into lipophilic tissues (e.g., brain). During this alpha phase, brain concentrations continue to increase even as plasma levels fall, resulting in a hysteresis (lag) between changes in plasma concentration and pharmacodynamic effects. Subjective effects tend to be maximal at 20–30 min after smoking. The plasma beta t1/2 is approximately 1–2 h, and the total period of phar macodynamic effect ranges from 4 to 8 h. Elimination of D9THC occurs by conversion to 11-hydroxy-THC (pharmacologically active) and subsequent conversion to a long-lasting, but pharmacologically inactive, 11-norcarboxy THC metabolite (11-COOH-THC). It is this analyte that is detected during marijuana urinalysis. Terminal elimina tion of 11-norcarboxy-THC exhibits a t1/2 ranging from 20 to 35+ h, so THC use remains detectable for days in those who use occasionally and for weeks in those who use frequently and with saturated fat stores. Regular D9THC use results in tolerance to its pharmacologic effects, so a given D9THC plasma concentration may not correlate to similar impairment levels in those using occasionally versus regularly. This chal lenge in correlating D9THC levels in biological matrices with behavioral effects has hampered efforts to regulate marijuana-impaired driving. Orally consumed cannabis products (edibles and drinks) typically exhibit slower effect onset than smoked/vaped D9THC. This is partly due to stomach residence time but mainly because lipophilic cannabinoids are poorly absorbed through the water/mucus-rich layer of the intestine. The comparatively slower rate of oral cannabinoid absorption means that no hysteresis is observed, unlike after inhalation. Orally administered D9THC is extensively metabolized by intestinal and hepatic cytochromes (first-pass metabolism), so bioavailability ranges from 5 to 6% (compared to 30+% when smoked). However, when consumed with fatty foods, can nabinoids can exhibit 200–400% increased bioavailability because fatty foods (or pharmaceutical triglyceride vehicles) stimulate bile release. This emulsifies fat-associated cannabinoids, thus increasing the surface area for absorption into portal blood and stimulating absorption by enterocytes, which secrete into lymphatic lacteals. This allows a portion of fat-dissolved cannabinoids to bypass hepatic elimination, increasing bio availability. However, lymphatic flow is slower than blood, so while lym phatically transported D9THC exhibits higher bioavailability, it also has a slower effect onset. In summary, depending on the edible product design or the consumer’s feeding status, D9THC bioavailability and onset time can vary greatly. This unpredictability can complicate efforts to determine a precise dose and presents a potential overdose risk for the unwary. HARMFUL EFFECTS The frequency and severity of cannabis adverse effects are influenced by dose, frequency of use, route of administration, and the individual’s health, age, and genetic background. Especially concerning are the potential negative effects of cannabis on the brain during early life stages. Perturbation of ECS signaling during early fetal development affects neuronal development, migration, and connectivity. A recent

animal study found that deficiencies in vital fatty acids like docosa hexaenoic acid could help explain the association between intrauterine exposure to D9THC and lifelong health disturbances in the offspring, including cognitive and memory impairments. The relevant human studies, which are few and confounded by the frequent use of other drugs, provide substantial evidence of lower birth weight and suggest an association between maternal marijuana use and fetal growth and preterm delivery. In addition, early results from the Adolescent Brain and Child Development (ABCD) study, a longitudinal neuroim aging, behavioral, and genetic study of close to 12,000 children in the United States, provide some evidence that exposure to cannabis during pregnancy can increase intracranial volumes and blunt development of visuospatial processing. Another analysis of the same cohort also found small but significant effects on white matter integrity during childhood, especially in the fornix, which has been implicated in the processing of emotions and memory. Not surprisingly, the American College of Obstetricians and Gynecologists recommends discouraging use of marijuana by women who are pregnant or planning a pregnancy.

Children and adolescents are also more vulnerable to the harmful effects of cannabis, the use of which increases markedly during adoles cence and has been associated with lower grades, lower IQ, and higher risk of dropping out of school, although a causal relationship cannot yet be established. Brain imaging studies have revealed that use of cannabis at this stage is associated with structural and functional brain changes (not always replicated) often in the form of reduced brain connectivity and cortical thickness. Though it is not clear whether these are caused by early exposure to cannabis, research in 799 adolescents in Europe found a negative, dose-dependent correlation between self-reported cannabis use at age 14 and prefrontal cortex thickness at age 19, sug gesting that cannabis use in middle to late adolescence may alter corti cal development. Moreover, recent results from the ABCD study are consistent with the notion that preadolescence exposure to cannabis may contribute to lower scores on an episodic memory task and that more cannabis use may lead to poorer performances on verbal, inhibi tory, working memory, and episodic memory tasks.

CHAPTER 466 In 2019–2020, a syndrome known as e-cigarette or vaping product use-associated lung injury (EVALI) was observed. It became associated with vitamin E acetate, a thickening agent used to dilute black-market marijuana e-liquids. Once known, EVALI incidents diminished as this unapproved agent disappeared from use. Cannabis and Cannabis Use Disorder CANNABIS USE DISORDER Repeated cannabis use, especially during adolescence, can result in can nabis use disorder (CUD), which the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, defines as “a problematic pattern of cannabis use leading to clinically significant impairment or distress.” The diagnostic criteria for a use disorder include drug craving, toler ance to effects, a withdrawal syndrome, and failure to fulfill role obliga tions due to recurrent use and drug seeking. The risk of CUD increases with earlier age of initiation, frequency of use, and exposure to canna bis with high THC content. Several studies have found a broad reduc tion in cannabinoid receptors in the brains of people who use cannabis when compared to control participants who do not use cannabis, but receptor density recovers rapidly, returning to values similar to those of control participants within 28 days of abstinence. In people who use cannabis regularly, abstinence results in a withdrawal syndrome that peaks within 1–3 days of drug discontinuation and manifests as anxiety, restlessness, insomnia, depression, and reduced appetite. Many of these symptoms resolve within approximately 2 weeks of discontinu ation. Insomnia often persists longer and may contribute to relapse, although the degree to which this represents withdrawal rather than cannabis use to self-medicate disordered sleep is unclear. ■ ■PREVENTION Preventing cannabis

use during adolescence reduces the risk for CUD and the risk of other substance use disorders. There are several evidencebased prevention strategies focused on children and adolescents that have shown benefits in decreasing cannabis use during adolescence or in delaying its age of initiation. Such prevention interventions can target the individual (e.g., Keepin’ It Real, Life Skills, InShape), the family (e.g., Brief Strategic Family Therapy, Coping Power Program [CPP], Familia Adelante), or the community (e.g., The Abecedarian Project, Midwest ern Prevention Project, Caring School Community). School-based prevention programs are the most widely implemented. Evidence from randomized controlled trials, prospective cohort trials, and longitudinal studies all demonstrate that comprehensive interventions that include antidrug information with refusal skills, self-management skills, and social skills training provide the most effective approaches for long-term reduction of cannabis (and alcohol) use in adolescents. ■ ■TREATMENT The treatment of CUD involves tapering cannabis use and providing psychosocial support to alleviate withdrawal symptoms. There are cur rently no U.S. Food and Drug Administration (FDA)-approved medi cations for CUD. There is evidence of effectiveness of several behavioral interventions as CUD treatments. Contingency management is an effective therapeutic and combined motivational enhancement, and

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Revision #1
Created 2026-01-06 16:35:58 UTC by Omar Ayman
Updated 2026-01-06 16:35:58 UTC by Omar Ayman