REVIEW ARTICLE

Clinical Evaluation of the Cannabis-Using Patient: A Moving Target

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Abstract

The prevalence of cannabis use has been increasing among both adolescents and adults worldwide. New trends in cannabis legalization and enhanced social media marketing have led to the availability of multiple high-potency cannabis products with hundreds of new and powerful delivery systems. Over the last decade, there have been drastic changes in cannabis formulations, potency, routes of consumption, and device technology, with increased complexity and sophistication among growers, suppliers, and consumers. Patterns of cannabis use among patients can have important clinical implications, including acute neurocognitive effects, chronic multiorgan toxicity, psychiatric, behavioral, social, and economic impact. However, assessment of medical or surgical patients who use cannabis either recreationally or problematically has become challenging for the clinician due to the changing patterns of cannabis consumption. This review provides information on the clinical evaluation of patients who use cannabis in a problematic fashion, with the focus on tetrahydrocannabinol. It provides the clinician with knowledge regarding cannabis terminology, sources, pharmacology, routes of administration, formulations, dosing, and toxicities. Using these components, an assessment approach for diagnosing cannabis use disorder is synthesized at the conclusion of the article.

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Introduction

Cannabis is a generic term used to describe multiple psychoactive preparations of the plant *Cannabis sativa*. The plant contains > 400 active ingredients and > 60 various cannabinoid compounds, but the cannabinoid Δ9-tetrahydrocannabinol (delta-9-THC) is the major psychoactive constituent.[1] Marijuana refers to the parts of the plant that contain large amounts of THC. Cannabinoid is a term used to denote compounds that are structurally similar to THC. In this review, the terms THC and delta-9-THC are used interchangeably.

More than 147 million people, or 2.5% of the world's population, consume cannabis, making it the most cultivated, trafficked, and abused illicit drug.[2] THC use is especially popular among adolescent and young adults

because of its ability to alter sensory perception and cause euphoria and elation.

Approximately 7% to 10% of regular users develop physical and behavioral dependency on cannabis.[1] Several groups are at increased risk of harm from cannabis use, including children, adolescents, young adults, women who are pregnant or breastfeeding, and patients with personal or family history of psychotic disorders.[3]

The health benefits of cannabis have been the subject of much public controversy. Although more peer-reviewed research is needed, scientific studies have revealed potential benefits. There is conclusive evidence regarding therapeutic effects of cannabis in several conditions, including chronic pain in adults, chemotherapy-induced nausea and emesis, and spasticity symptoms due to multiple sclerosis.[4] There is also moderate evidence for the use of cannabis preparations in treating sleep disturbance associated with obstructive sleep apnea syndrome, fibromyalgia, and chronic pain.[4] The primary medical indications of marijuana are related to management of symptoms rather than disease modification or cure.

Recent agricultural modifications have led to an increase in the THC concentration in the plant from 7% to 14% (2003 to 2017) in the United States[5] and from 5% to 10% (2006 to 2016) in Europe.[6] In addition, due to the increase in demand, synthetic cannabinoids with much higher THC potency have entered the market. Cannabis use by oral ingestion and vaporization has gained popularity because these methods are perceived as "healthier" ways to consume the drug without smoke inhalation.[7] Numerous devices have emerged that can extract the active ingredients from dried cannabis, concentrated oils, or solid extracts and deliver the vapor to the user for inhalation.

Clinical evaluation of cannabis use has historically been neglected by health care practitioners who view it as insignificant in comparison to other drugs of abuse. However, legalization and social media marketing have given rise to extensive use of high-potency THC products, resulting in toxicity and adverse consequences on patients' physical and mental health. There is a growing need for clinicians to identify and assess the subgroup of patients whose use is problematic or those who present with adverse effects from THC.

In this review, cannabis terminology and sources used by sophisticated consumers are presented followed by a brief discussion of pharmacology, common formulations, routes of administration, dosing, and toxicities. At the end of the paper, an assessment method for patients using cannabis is briefly presented. The goal is to help the clinician become more knowledgeable and comfortable in assessing patients whose use of cannabis is problematic.

Please see the Supplemenary Appendix for a complete list of definitions and terminology.

Cannabinoid Types and Sources

PHYTOCANNABINOIDS

Phytocannabinoids are derived from plant sources. The most notorious cannabinoids include THC, the primary psychoactive compound, and cannabidiol (CBD), known for its analgesic, antianxiety, and anti-inflammatory properties. Sophisticated plant breeding and cultivation techniques have increased the potency of the cannabis plant in the last 2 decades.[8] Early classification of plant sources was historically based on morphology or cultivar and included *Cannabis sativa* and *Cannabis indica*. However, most of the commercially produced cannabis plants have become a crossbreed of *C. sativa* and *C. indica* or a hybrid cultivar, making this distinction no longer useful. A better classification system categorizes the cannabis plant based on chemovar or chemotype, which includes the prominent cannabinoid profiles (THC to CBD ratios) as well as the non-cannabinoid constituents, such as terpenes, flavonoids, phenols, and alkaloids.[9] The non-cannabinoid constituents represent minor components of phytocannabinoids, with secondary metabolites that can cause activation of anti-inflammatory pathways and suppression of pro-inflammatory cytokine systems, resulting in nociceptive transmission and analgesic effects.[9] When used in conjunction with the cannabinoids, these compounds work synergistically as a symphony of elements to create the final effect in the end user. This pharmacodynamic harmony has been termed the "entourage effect."[9]

SYNTHETIC CANNABINOIDS

The synthetic cannabinoids represent heterogeneous and diverse designer compounds that have become popular due to their ability to evade analytical detection in toxicology testing. They have high affinity and full agonist activity at the cannabinoid receptors with potencies of > 800 times the cannabis plant.[10] The compounds have a prolonged duration of action and can cause severe cardiac, respiratory, renal, and

neurologic toxicities.[10] The synthetic cannabinoids sold under such names as "Spice," "K2," or "Black Mamba" are typically dissolved in organic solvents and sprayed onto plant material or vaporized and inhaled in vaping devices.[10] In addition to cannabinoids, they contain toxic chemicals, such as linoleic acid, palmitic acid, vitamin E, benzyl benzoate, eugenol, oleamide, thymol, acetyl vanillin, and α-tocopherol.[10]

Cannabis Pharmacology

PHARMACOKINETICS

Absorption, bioavailability, excretion, and metabolism of THC is variable and depends on the product type and route of use (outlined below). Once THC reaches the serum via various routes, > 95% of it binds plasma proteins.[11] Less than 5% is unbound and capable of pharmacologic activity at the cannabinoid receptors.[11] THC is very lipophilic, readily crosses the blood–brain barrier, and accumulates in adipose tissue.[11] It has high tissue distribution, with a volume of distribution 3.4 L/kg.[11] THC is primarily metabolized in the liver via the cytochrome P450 isoenzymes CYP2C9, CYP2C19, and CYP3A4 to 11- hydroxy-delta-9-tetrahydrocannabinol (11-OH-THC), which has psychoactive activity.[11] This metabolite is further metabolized to 11-nor-9-carboxy - delta-9-tetrahydrocannabinol (THC-COOH), which has no psychoactive activity and is subsequently excreted in the feces (65%) and urine (25%) as conjugates.[11]THC has a fast initial elimination half-life (6 minutes)[12] but a long terminal elimination half-life (25–36 hours) because of its slow release and redistribution from lipid storage compartments and enterohepatic circulation.[2] The elimination half-life is even slower in regular cannabis users.[12]

Combustion

Following dry cannabis pyrolysis at high temperatures, the bioavailability or the fraction of THC that reaches the bloodstream is variable and is influenced by smoking topography, including inhalation volume, number of puffs, hold time, duration, and spacing of puffs.[13] Following combustion, 23% to 30% of THC is lost in pyrolysis, 40% to 50% is lost in sidestream smoke,[13] and 20% to 37% is delivered in mainstream smoke,[13] resulting in 25% maximum systemic THC absorption.[11] Inhalation has rapid onset (0–10 minutes) and short duration of action (2–4 hours).[14] Following absorption, THC quickly distributes from blood to body tissues within seconds, with a small amount remaining in the blood. Inhalation of cannabis avoids the extensive first-pass metabolism seen following oral administration, thus the breakdown to 11-OH-THC, which has psychoactive activity and does not significantly contribute to any pharmacologic activity.[15]

Vaporization

Vaporization has similar pharmacokinetics as combustion and is influenced by inhalation topography, with rapid onset (0–10 minutes), and short duration of action (2–4 hours).[14] Metabolism and excretion are also similar to combustion. However, vaporization is a more effective method of delivery, resulting in higher concentrations of THC in the serum compared to the combustion route. Bioavailability for cannabis by the vaporization route is ~ 10% to 35%, depending on inhalational characteristics, such as number and duration and interval of puffs, hold time for breaths, size of inhaled particles, and site of deposition in the pulmonary system.[12]

Oral Ingestion

Following oral ingestion, THC has a bioavailability of ~ 4% to 12%.[13] Several factors contribute to the low oral bioavailability, such as variability in absorption, gastric degradation by stomach acid, and considerable first-pass metabolism in the liver. Oral formulations have delayed absorption, with delayed onset of action (1–3 hours) and long duration of action (6–12 hours).[14] The oral THC formulations are extensively metabolized to 11-OH-THC in the liver before entering the circulation. The ratio of 11-OH-THC to THC is > 1:1 following oral ingestion compared to < 1:20 following inhalation.[15] Production of the hydroxy metabolite 11-OH-THC, which is approximately 10 times more potent than THC itself,[16] can cause psychogenic effects, including acute psychosis, especially in patients who take repeat doses because they do not feel the initial effects. Following the oral intake of cannabis, multiple pharmacokinetic parameters contribute to a delayed onset, lower peak concentrations, and an extended duration of pharmacodynamic effects. Delayed oral absorption often results in repeat dosing and difficulty in dose titration by patients, which in turn can cause unintentional intoxication or overdose.

Sublingual Route

The pharmacokinetics of oromucosal formulations have been studied via the commercially available standardized cannabis extract Sativex oromucosal spray, which contains THC and CBD in an approximately 1:1 ratio.[17] The bioavailability of the sublingual THC formulations is expected to be higher than oral formulations in theory if they bypass the first-pass metabolism by the liver. However the studies on Sativex have shown that the bioavailability of the sublingual formulations of THC is very similar to the oral formulations, with equivalent serum 11-OH-THC to THC ratios, indicating that at least part of the sublingual formulations may be swallowed, pass through the gastrointestinal tract, and undergo hepatic first-pass metabolism.[17] The relative bioavailability of the sublingual formulation of THC was slightly higher than the oral forms and was estimated to be 13% based on the study by Karschner et al.[17] Pharmacokinetics of the sublingual formulations of THC differ from oral formulations, with a faster onset of action (15–60 minutes), shorter time to reach peak effects (45 minutes), and a shorter duration of action (4–6 hours).[14]

PHARMACODYNAMICS

The mechanism of action of phytocannabinoids and synthetic cannabinoids involves activation and stimulation of the endocannabinoid system (ECS). The ECS includes 2 types of G-protein–coupled receptors, cannabinoid receptor type 1 (CB_1) and type 2 (CB_2).[18]

CB_1 receptors are widely distributed in the central and peripheral nervous system and are involved in neuroactive and psychoactive effects of cannabinoids.[18] They are also expressed in non-neuronal cells, such as hepatocytes, adipocytes, gonads, gastrointestinal, cardiac, and musculoskeletal tissues.[18] CB_2 is expressed peripherally in the immune system tissue and plays a role in regulating immune and inflammatory responses.[2]

THC acts as a partial agonist at the CB_1 and CB_2 receptors.[11] In addition, through CB_1 receptors, THC can initiate a second messenger signaling cascade, resulting in complex neuromodulatory effects on many neurotransmitter systems regulating their release and activity.[19] The interactions include both excitatory and inhibitory neurotransmitters, such as acetylcholine, glutamate, gamma aminobutyric acid (GABA), and opioid and monoamines (dopamine, serotonin, and norepinephrine).[19] Examples of crosstalk between the ECS and other neurotransmitter systems are listed below:

Dopamine interactions: CB_1 agonists through interactions with the acetylcholine system induce mesolimbic dopaminergic activity and increase dopamine release in striatal regions.[19] In addition, the CB_1-dependent inhibition of glutamate release onto the GABA neurons can increase dopamine release.[19] The effects on dopamine transmission play an important role in activating the reward pathway and abuse-related behavioral and neurochemical effects of cannabis.

Opioid interactions: Activation of CB_1 receptors can cause release of endogenous opioids, which in turn can modulate nociceptive signal transduction and pain perception.[19]

Serotonin interactions: Cannabis-agonists can affect serotonin release indirectly by CB_1-dependent inhibition of glutamate release onto GABA neurons in subcortical structures, such as the nucleus accumbens and the ventral tegmental regions.[19] The indirect impact of cannabinoids on the serotonin balance may contribute to the adverse effects of cannabis on mood and cognition.[19]

Noradrenergic interactions: CB_1 agonists can increase noradrenergic activity, in part through the stress-integrative locus coeruleus–norepinephrine system.[19] This interaction may play a role in cannabis' effects on the stress response regulation.[19]

Through these complex interactions, the ECS is responsible for mediating and modulating a wide array of physiologic functions, including learning, memory, cognition, motivation, reward, stress, emotions, neurogenesis, neurodegeneration, nociception, appetite, thermoregulation, immune modulation, lipid/glucose metabolism, cardiovascular, gastrointestinal, hepatic, and reproductive function.[18] Exogenous THC use can cause dysregulation or overstimulation of the ECS, leading to erratic neurotransmitter modulation and cannabis-induced multiorgan toxicities.[19]

Pharmacodynamic Tolerance

Studies in occasional THC users have shown clear dose-dependent reductions in neurocognitive and psychotomimetic function.[20] However, patients who consume high doses of THC continuously for prolonged periods of time, develop reduced responsiveness to the neurologic and

psychiatric effects due to neuroadaptive changes in the brain.[20] This is related to pharmacodynamic tolerance, with down-regulation of CB_1 receptors causing normalization of the dopaminergic output from the ventral tegmental area to the meso-limbic circuits following repeated exposure.[20] This phenomenon can have extreme importance in determining which cannabis-using patients may develop neurocognitive impairment in performing complex tasks such as driving a vehicle. For example, occasional cannabis users who do not have tolerance may show more impairment in driving than the experienced cannabis consumers. In addition, other studies show that neuroadaptive changes in the brain of chronic cannabis users may be unpredictable due to development of partial or incomplete tolerance.[20] The term "blunted highs" is used to define the uncertainty in neurocognitive deficits observed in the chronic cannabis users.[20]

Cannabis tolerance is reversible after prolonged abstinence in THC-dependent patients.[21] The mechanism for reversal of cannabis tolerance is related to the normalization of both number and function of CB_1 receptors.[20]

Common Cannabis Formulations, Routes of Administration, and Dosing

The increase in the prevalence of cannabis use warrants the need for clinicians to be knowledgeable regarding types of cannabis formulations, routes of use, and dosing among sophisticated consumers. This awareness would also improve identification of those patients with problematic use or at risk for side effects. Common cannabis administration, route of administration, and formulations are listed in Table 1.

Examples of dosing estimations for commonly used THC formulations are listed in Table 2.

Route of administration	Examples of formulations	Notes	Ref
Smoking / combustion	Dried flower, leaf, resin	Combustion at temperatures of 800–900 °C; exposure to pyrolytic compounds[a]	22
Vaporization			
Dry herb (vaping)	Dried flower, leaf, resin	Milled cannabis heated at temperatures of 60–190 °C to produce an aerosol; less exposure to pyrolytic compounds[a]	22
Liquid (vaping)	E-liquid concentrates (oils), distillate, CO_2, rosin	E-liquid concentrates prepared by various extraction techniques[b]; device atomizers use resistance heating to vaporize cannabis oil at temperatures of 160–230 °C; exposure to VCC emissions[c]	23
Solid (dabbing)	Solid concentrates, butane, hash oil, wax, shatter, budder, hash, kief	Solid concentrates prepared by various extraction techniques[d]; flash vaporization of concentrated extracts at temperatures of 200–400 °C; risk of overdose due to high THC concentrations; exposure to VCC emissions[c]	23
Liquid (direct dripping)	E-liquid concentrates (oils), distillate, CO_2, rosin	E-liquid is dripped onto the exposed atomizer coil at temperatures > 350 °C; excessive exposure to VCC emissions[c]	24
Oral	Brownies, cookies, candies	Titration difficult due to erratic absorption; risk of overdose with repeat dosing	14
Sublingual	Tinctures, lozenges, strips, wafer-thin tablets, sprays	Unpredictable absorption	14

Table 1: Common cannabis formulations and routes of administration

[a]Pyrolytic compounds and by-products include benzene, toluene, hydrocyanic acid, carbon monoxide, tar components, nitrosamines, acetaldehyde, ammonia, polycyclic aromatic hydrocarbons, and pesticides used during cultivation.[7,10,25]

[b]Common extraction techniques for e-liquid concentrates: Chemical extraction by hydrocarbons followed by vacuum distillation (distillate oil); decarboxylation, supercritical CO_2 extraction followed by solvent removal (CO_2 oil); and solventless extraction by pressure and heat (Rosinoil).[26]

[c]VCC emissions include volatile aromatic and carbonyl compounds, benzene, styrene, xylene, isoprene, carbon monoxide, VEA, residual solvents, and heavy metals from vaporizer heating elements.[27]

[d]Common extraction techniques for solid concentrates: Chemical techniques, such as hydrocarbon or supercritical CO_2 extraction (butane hash oil, wax, shatter, budder); physical extraction methods (hash, kief).[7]

CO_2 = carbon dioxide; Ref = reference; THC = delta-9-tetrahydrocannabinol; VCC = vaporizable cannabis concentrate; VEA = vitamin E acetate.

Cannabis Effects

CANNABIS TOXICITIES

THC affects multiple organ systems, and its toxic effects are related to overstimulation of the ECS, leading to erratic neurotransmitter modulation. The side effects and toxicities can be divided into acute effects (intoxication causing neurocognitive impairment), chronic effects (developmental, cardiovascular, pulmonary, gastrointestinal, reproductive, neurologic, and psychiatric toxicities), and social and economic effects (motor vehicle accidents, drug-related crimes, social/family problems, low achievement, and low education attainment).[31]

The list of organ toxicities from cannabis intoxication and withdrawal symptoms are listed in Table 3.

E-Cigarette or Vaping Associated Lung Injury

E-cigarette vaping associated lung injury (EVALI) presents as respiratory effects related to vitamin E acetate (VEA), which is a component found in cannabis oil used in vaping, and requires special attention. VEA or its degradation products can induce acute lung injury by triggering inflammatory reactions, causing diffuse alveolar damage, organizing pneumonia, or fibrinous pneumonitis.[34] This syndrome is more common in patients who use unregulated, black-market, or modified cannabis vape liquid concentrates.[34]

Cannabis Toxicities in Pregnancy and Breastfeeding

Cannabis use during pregnancy and breastfeeding also requires special attention because of its negative short-term effects on placental development, fetal growth, prepartum maturation, and the life-long postpartum effects on the offspring's neurocognitive, behavioral, emotional, and intellectual development. Cannabinoid compounds, such as THC, readily cross the placenta and are found in breast milk.[25] Research has shown that no amount of cannabis is considered safe during pregnancy or breastfeeding.[25] Use of THC during

Methods and materials used	Content	THC potency (%)	Maximum bioavailability (%)	Total absorbed THC dose (Mg)	Ref
Combustion					
Bowl/pipe (dried flower)	0.25 g	14	25	9 mg/bowl	5,11,28
Joint (dried flower)	0.58 g	14	25	20 mg/joint	5,11,28
Blunt (dried flower)	0.87 g	14	25	30 mg/blunt	5,11,29
Vaporization					
Dried herb vaping (dried flower)	0.3 g	14	35	15 mg/serving	5,12
Liquid vaping[a] (oil)	500 mg/mL e-liquid cartridge (100 puffs)	26[b]	35	46 mg/cartridge; 0.46 mg/puff[c]	12
Dabbing (wax)	76 mg/dab	76[d]	35	20 mg/dab	12,28
Direct dripping (oil)	4 drops (0.2 mL) of 500 mg/mL e-liquid	26[b]	35	9 mg/0.2 mL e-liquid	12
Oral					
Infused cookie	400 mg dried flower/cookie	14	12	6.7 mg/cookie	5,13
Sublingual					
THC tincture	10 mg THC/mL	1	13	1.3 mg/1 mL of tincture	17

Table 2: Examples of dosing estimations for commonly used THC formulations

[a]Dose delivered by the device aerosol is influenced by multiple factors: THC concentration, e-liquid composition, puffing behaviors (volume, duration, number, flow rate, interval), and device electric setting (voltage, power, coil temperature, airflow).[12,22]

[b]Proportion of THC-containing oil in the e-liquid is approximately one-third and the concentration of THC in the oil is 80%, resulting in an e-liquid THC potency of 26%.[22]

[c]Assuming each puff consumes 5 mg of e-liquid, and the psychoactive intravenous dose for THC is ~ 1.5 mg, it takes 4 puffs (1.8 mg of THC) to reach this threshold.[22]

[d]Even though advertised as > 90% potent, maximum THC potency in solid concentrates has been found to be up to 76%.[30]

Ref = reference; THC = delta-9-tetrahydrocannabinol.

System	Symptoms/toxicities	Notes	Ref
General	Sweating,[a] malaise,[a] chills,[a] fever,[a] increased appetite,[b] decreased appetite[a]	Increased appetite with intoxication, decreased appetite with withdrawals	21,32
Eyes	Conjunctival injection,[b] dilated pupils,[b] decreased intraocular pressure	Dilation of conjunctival vessels	25,31
Ear, nose, throat	Xerostomia,[b]	Decreased saliva production can cause halitosis, tooth decay, and periodontitis;	33
	Cannabis stomatitis	Gingival enlargement, erythroplakia, leukoplakia, possible transition to malignant neoplasm	33
Pulmonary	Asthma, fibrous pneumonitis, organizing pneumonia, diffuse alveolar damage, bronchitis, lung cancer, emphysema	Toxic exposure to pyrolytic compounds with combustion and VCC emissions with vaping; EVALI due to use of cannabis vaping products	25,31,34
Cardiovascular	Tachycardia,[b] hypertension,[b] postural hypotension[b]	Cannabis intoxication can cause hypertension by catecholamine release and/or postural hypotension by decrease in vascular resistance	25,31
Gastrointestinal	Abdominal pain,[a] nausea,[a] cannabinoid hyperemesis syndrome	Dysregulation and toxicity of central and enteric cannabinoid receptors	21
Reproductive	Decrease in sperm count, reduced libido, alterations in ovarian cycle, impairment of placental development	In utero exposure can cause life-long developmental effects	25,31
Neurologic	Headache,[a] tremor,[a] impaired psychomotor coordination,[b] impaired judgment,[b] impaired attention and concentration,[b] impaired learning, sedation, memory loss	Degree of long-term impairment in cognitive function depends on potency of cannabis and duration of use	21,31
Psychiatric	Irritability,[a] anger,[a] aggression,[a] nervousness,[a] anxiety,[a, b] sleep difficulty,[a] restlessness,[a] depressed mood,[a] hostility, euphoria,[b] psychosis,[b] lethargy,[b] sensation of slowed time,[b] amotivation, social withdrawal[b]	Psychotic symptoms may include paranoid thoughts, visual disturbances, hallucinations, and delusions	21,31,32

Table 3: Common cannabis toxicities, acute intoxication and withdrawal symptoms by organ system

[a]Associated with cannabis withdrawal.

[b]Associated with cannabis intoxication.

EVALI = e-cigarette vaping associated lung injury; Ref = reference; VCC = vaporizable cannabis concentrate.

pregnancy can cause fetal growth restriction, stillbirth, preterm labor, and low birth weight.[31] Cannabis exposure during pregnancy or through breast milk can affect brain development, leading to neuropsychiatric and neurocognitive disorders later in life.[25]

Cannabis Poisoning

In adults and adolescents, inhaled THC doses of 2–3 mg and ingested THC doses of 5–20 mg can cause psychoactive effects, such as impaired attention, concentration, short-term memory, and executive function.[2] Although THC poisoning or overdose can occur at higher doses, death due to overdose is extremely rare. The LD50 (lethal dose at which 50% of the sample population dies) for THC has not been determined in humans; however, it is estimated to be 40–130 mg/kg intravenously in animals.[25]

Following overdose, severe THC toxicity, especially in children, can occur and includes cardiac (bradycardia, tachycardia, hypotension), respiratory (apnea, respiratory failure), and neurologic (seizure, myoclonic jerks, unresponsiveness, coma) effects.[35] Severe toxicity from inhalation in adults can occur at doses > 7.5 mg/m^2 and from oral ingestion in children at doses > 1.7 mg THC/kg.[25,35]

CANNABIS WITHDRAWAL SYMPTOMS

In patients with prolonged heavy use (defined as daily or almost daily use for a few months), withdrawal symptoms usually start within 24–48 hours after abrupt cessation.[36] The symptoms are associated with a down-regulation and desensitization of cortical and subcortical CB_1 receptors.[21] The reversal occurs within 48 hours of abstinence and returns to normal within 4 weeks.[21] Cannabis

withdrawal symptoms peak on days 2–6 after cessation and can last for up to 3 weeks or longer in heavy users.[36] The typical symptoms of cannabis withdrawal symptoms by organ system are listed in Table 3.

Patient Assessment

Assessment of patients who abuse cannabis starts with patient observation followed by detailed history taking and physical examination. A stepwise method for assessment is included in Table 4.

Use of an assessment instrument is recommended to determine cannabis use disorder diagnosis, as well as severity. Diagnostic and Statistical Manual of Mental Disorders Fifth Edition, Text Revision (DSM-5-TR) criteria can be used to assess clinically significant impairments over a 12-month period in 11 domains. Positive responses to only 2 of the domains are needed to reach this diagnosis. The components of cannabis use disorder per DSM-5-TR[37] are listed below:

The patient 1) uses cannabis in larger amounts or for longer time than intended; 2) wants to cut down on cannabis use but has difficulty or has had multiple unsuccessful efforts with this task; 3) spends a lot of time obtaining cannabis, using it, or recovering from the effects; 4) has cravings or strong desire or urges to continue use of cannabis; 5) fails to carry out important tasks related to home, school, or work due to ongoing use of cannabis; 6) has recurrent use of cannabis despite social, interpersonal problems; 7) has given up important social, occupational, or recreational activities due to ongoing cannabis use; 8) continues cannabis consumption in situations where the use is physically hazardous; 9) continues cannabis use despite knowledge of persistent or recurrent physical and or psychologic problems; 10) has developed tolerance to cannabis (more of the substance is needed to get the same effects); and 11) exhibits withdrawal symptoms after stopping cannabis use.[37]

The number of positive responses to the above domains is used to determine the severity, with the presence of 2–3 symptoms indicating

Assessment component	Notes
Products used—formulations, brands, dosages, amounts, concentrations, and devices	Weight of dried flower or solid concentrates volume and THC concentration of e-liquids
Additives	Viscosity adjusters, flavorings, and residual solvents can increase risk of toxicity
Product source	Vape shop, online, homemade
Method of use	Combustion, vaporization, dabbing, direct dripping, ingestion, sublingual; participation in vaping tricks can increase toxic exposure
Frequency and duration of use	Occasional vs daily user, periods of abstinence
Age of initiation	Estimation of lifetime exposure
Changes over time	Estimation of tolerance level
Concurrent substances used	Alcohol, tobacco, or other drugs can have effects additive to cannabis' effects
Past attempts to discontinue or treatment participation	Assess ambivalence about ongoing use, readiness to change, or motivation to discontinue
External leverage to seek evaluation	Family conflicts, occupational maladjustment, legal issues
Psychiatric comorbidity	Baseline psychiatric disorder may be the reason for self-medication and may signal need for dual diagnosis treatment
Accidents or legal problems	May indicate impairment and poor judgment
Genetics and metabolism	Family history may be an indicator for substance use disorder severity
Assess for cannabis intoxication, withdrawals, and toxicities	Assess each organ system separately in review of systems and physical examination (see Table 3)
Assess for substance use disorder criteria and severity	Use DSM-5-TR criteria for cannabis use disorder (see text)

Table 4: Components of assessment for patients using cannabis

DSM-5-TR = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision; THC = delta-9-tetrahydrocannabinol.

mild, 4–5 symptoms indicating moderate, and ≥ 6 symptoms indicating severe cannabis use disorder.[37]

CANNABIS TOXICOLOGY TESTING

Cannabis toxicology testing is important in assessment of patients participating in substance abuse treatment. It is also useful in evaluating impaired drivers and workers in safety-sensitive occupational settings. Unlike alcohol, quantitative THC concentrations in whole blood following drug intake does not correlate with the degree of intoxication and or impairment and cannot distinguish between acute use vs residual THC that remains long into abstinence. The results are further confounded by the presence of incomplete tolerance in the chronic users.

Urine THC testing is most often used in clinical, employment, and legal settings. The test uses a cannabinoid immunoassay to screen for the urinary THC carboxy metabolite THC-COOH. The cutoff concentration threshold of 50 ng/mL is commonly used to identify positive test results. The window of detection of cannabis metabolites in urine is related to pharmacological variables affecting the rate of elimination from the body, including dose, route of administration, duration of use, percentage body fat, genetic factors, and rate of metabolism. Detection time is also dependent upon analytical factors, such as the sensitivity and specificity of the test. The window of detection for THC-COOH in urine following cessation of the drug is of interest in both clinical and forensic situations and is listed below[38]:

- Occasional or causal user (2–3 times per week): 3 days
- Moderate user (4 times per week): 5–7 days
- Chronic user (daily use < 30 days): 10–15 days
- Chronic heavy or long-term user (daily or multiple times per day for > 30 days): > 30 days.

Conclusion

The prevalence of cannabis use has shown a dramatic increase in the last decade, particularly in the younger generation. Legalization, exposure to cannabis-related content on social media, along with extensive marketing have led to an increase in the prevalence of problematic cannabis use and normalization of risky behaviors among many users. As the result of the availability of potent formulations, adverse consequences on physical and mental health, as well as social implications, are now common. Clinicians face a continually moving target as education and research has not kept up with the explosion of hundreds of new cannabis devices, formulations, and delivery routes. Enhancing clinician comfort in identification, diagnosis, and treatment of cannabis use disorder—especially in the high-risk groups such as adolescents, pregnant patients, or those with psychiatric comorbidities—can have considerable value in reducing or preventing cannabis-related health effects in these subgroups.

Supplementary Materials

Supplemental material is available at: https://www.thepermanentejournal.org/doi/10.7812/TPP/24.088#supplementary-materials.

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