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Clinical approaches to cannabis: a narrative review

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Introduction

Over the past decade, cannabis use in the United States (U.S.) experienced an unprecedented increase in public acceptance. As of Spring 2021, 37 states (including the District of Columbia) legalized medical cannabis use, 22 of which passed laws in the last ten years, and 18 states (including the District of Columbia) legalized adult-use (recreational) cannabis, 16 of which passed laws in the last five years.[1–3] Despite this, the federal legal status of cannabis use remains heavily restricted. The U.S. Controlled Substance Act classifies cannabis as a Schedule I substance with no currently accepted medical use and a high potential for misuse, categorizing it with other substances like heroin.[4] Regardless of its legal status, cannabis use is growing in social acceptability in the U.S.,[5] almost ensuring that medical providers will increasingly encounter patients who use cannabis, whether under the guidance of a health care provider or not.

This review provides a brief history of cannabis use in the U.S., followed by epidemiology, pharmacology, and neurobiology of cannabis, use of cannabis for therapeutic purposes, and finally, complications of cannabis use. Table 1 lists definitions of common terms used when discussing cannabis.

Background

In the late nineteenth- and early twentieth- centuries, cannabis in the U.S. was mostly restricted to medical use, including for the management of pain, migraines, and seizures. Adult-use cannabis was seen more often in Mexico, starting in the 1880s and onward. Laws regulating and restricting the use of cannabis first arose in 1914, when the border-town,

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El Paso, Texas, banned the sale and possession of cannabis due to the prevailing ideology that cannabis use causes violent behavior and was limited to use among racial and ethnic minorities and people of low socioeconomic status (The Criminality Theory). These laws gained more prominence federally with the passage of the Narcotic Import and Export Act in 1922, which effectively outlawed the use of cannabis. In the following decades, in the setting of increasing anti-Mexican bias, more laws, particularly the Marihuana Tax Act, were passed that restricted use of cannabis and limited the ability to conduct medical research on cannabis.[6,7]

By the 1950s, The Criminality Theory had fallen out of favor, and the concept of cannabis as a gateway drug to other substances such as heroin or cocaine, became more popular. In the following two decades, adult-use cannabis became more popular, and was widely accepted, particularly among antiwar protestors and other counter-cultures. In this context, cannabis was categorized as a Schedule I substance by the U.S. Controlled Substances Act in 1973. By some accounts, the drive to categorize cannabis as Schedule I, or a "drug or other substance with high potential for abuse… with no currently accepted medical use… and a lack of accepted safety for use of the drug" was driven by a desire to criminalize communities of color and antiwar groups.[6,7] Cannabis remains classified as a Schedule I substance; however, since 1996, states began legalizing cannabis use for medical purposes.[1–3]

Criminalization of cannabis use and possession disproportionately impacts Black and Hispanic people.[8,9] Arrest rates for cannabis possession in the U.S. are 3.6 times higher for Black people than White people, despite similar rates of cannabis use in both groups, and laws in many states decriminalizing medical cannabis use.[8,10] Medical cannabis laws provide access to medical cannabis with lower risk of legal ramifications; however, barriers remain to providing equitable access to communities affected by the criminalization of cannabis.[11,12]

Medical cannabis laws vary greatly between states, including but not limited to differences in active ingredients, route of administration, types of products allowed (e.g., whole plant, oil-based, capsules, edible), medical conditions for which patients are allowed to use medical cannabis, and pathways to obtaining medical cannabis.[7] Further, medical cannabis is unique from other medical therapies in that health care providers may make recommendations on dose, frequency, or route of administration; however, in practice, medical cannabis dosing and route of administration are primarily titrated by patients based on their own symptoms.

Epidemiology

Cannabis use in the U.S.

Trends of cannabis use in the U.S. have changed with policy and public opinion. In 2019 17.5% of the population over age 12 (or 48.2 million people) reported having used cannabis in the past year, compared to 11.0% of the population (or 25.8 million) in 2002.[13] Among adults 26 years of age or older, reported cannabis use rose from 7.0% to 15.2% in the same time period.[13] Perception of risk of harm from smoking cannabis declined from 38.7% to

30.8% from 2015 to 2019 among adults 26 years of age and older and from 19.1% to 15% among adolescents ages 18–25.

Variation by state

Unsurprisingly, rates of cannabis use are higher in states in which medical or adult-use cannabis is legal, while the rates of perceiving that it has a high risk of harm are lower. For instance, in 2013 in Washington (where medical and adult use cannabis is legal), 12.7% of people 12 years old and older reported cannabis use in the past month, while in Utah (where cannabis use was illegal), 5.4% reported use in the past month.[14] States with higher rates of use also had lower perception of risk of harm from smoked cannabis. In the same report 18.8% of those surveyed in Washington reported perceiving great risk of harm from smoking cannabis while in Utah 32.8% perceived a great risk of harm.[14] Thus, it's likely that rates of use and perception of harm from cannabis use will continue to change as state and federal laws shift.

Demographic characteristics of people who use cannabis

Rates of cannabis use vary by gender and race. Among adults 26 years of age and older in 2019, rate of cannabis use was similar in White people (16.4%), Black people (16.9%), and Native Americans (18.0%), and less common among Asian Americans (5.6%) and Pacific Islanders (12.2%). Rate of cannabis use was higher among those who are not Hispanic or Latino (15.9%) compared with Hispanics and Latinos (11.5%). Rates of cannabis use in the past year were higher in males (18.7%) than in females (12.1%).[13]

Demographic characteristics of people who use medical cannabis

While medical cannabis use also varies by gender and race, these variations are different than those observed among all cannabis users. Patients who are White, male, and earn over $60,000 dollars per year are more likely to obtain medical cannabis.[15] For instance, in a study in Florida in 2019, while census data revealed Floridians were 53.2% White, 26.4% Hispanic, and 16.9% Black, those who used medical cannabis were 83.4% White, 7.6% Hispanic, and 1.9% Black.[16] In a study of Californians who used medical cannabis, 64.8% were employed and 73.4% had private health insurance.[12] These variations likely reflect barriers to accessing medical cannabis that exist due to issues of cost, health care provider preference, stigma among both patients and health care providers, and racism in the health care system.

Cannabis pharmacology and neurobiology

The endocannabinoid system

Cannabis pharmacology was relatively recently discovered, with cannabinoids (Table 1) being characterized first in the 1960s and further research developing in the following decades.[17] There is much to be discovered about the endocannabinoid system and it is like that there will be more developments in upcoming years. To date, we know that cannabinoids act on an endogenous system of receptors in the human body called the endocannabinoid system.[18] The system contains two receptors, cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2).[18] CB1 is located primarily in the

central and peripheral nervous system, though it is also located in other tissues including the gastrointestinal tract, endocrine glands including the pituitary and thyroid, and the reproductive system.[19] Activation of the CB1 receptor is involved in regulation of pain, fear, sleep, appetite, memory and motor responses, as well as psychoactive effects.[19] CB2 is located primarily in the immune system including the lymphoid tissues and on immune cells such as B and T cells, macrophages and monocytes, as well as on immune regulatory cells in the brain (glia), the peripheral nervous system, and the gastrointestinal system.[19] Activation of the CB2 receptor is involved in up or down regulation of the inflammatory response.[19] The endocannabinoid receptors are stimulated by endogenously produced lipophilic cannabinoid receptor ligands (endocannabinoids). Two of these endocannabinoids are Anandamide, a potent CB1 agonist named after the Sanskrit word Ananda which means 'bliss,' and 2-Arachidonoylglycerol (2-AG), which acts as a full agonist for both CB1 and CB2.

Phytocannabinoids

Phytocannabinoids are cannabinoids produced by the cannabis plants, *Cannabis indica* and *Cannabis sativa*.[20] Phytocannabinoids act as ligands on either or both CB1 and CB2, and sometimes on other receptors as well .[20] There are over 100 known phytocannabinoids, but the most frequently studied are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is a partial agonist for both CB1 and CB2.[20] The activity of THC on CB1 is primarily responsible for the psychoactive effects of cannabis.[21] CBD has low affinity for CB1 and CB2, and can act as an antagonist to the binding of other cannabinoids to these receptors.[21] CBD is nonpsychoactive and much of its activity is due to its effect as a ligand on other non-cannabinoid receptors.[21] The remaining phytocannabinoids contribute to the therapeutic effect of cannabis,[22] and terpenes (e.g., limonene, myrcene) produce the smell, taste, and appearance of the plant.

Some phytocannabinoids have been formulated as pharmaceuticals for medicinal purposes. Epidiolex is a CBD-containing liquid solution taken orally which has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of rare seizure disorders in children.[23] In the United Kingdom Nabiximols, an oral mucosal spraying containing plant-derived THC and CBD, has been approved for the treatment of spasticity and pain.[24]

Synthetic cannabinoids

Synthetic versions of cannabinoids have been created both for medicinal and recreational purposes. The U.S. FDA has approved the use of two synthetic cannabinoids. Dronabinol is a capsule taken orally which contains THC and is approved for the treatment of nausea, vomiting, and cachexia.[23] There are other synthetic versions of cannabinoids which are used at medical cannabis dispensaries and illicitly. One of the most notorious of these is a CBR1 super-agonist called K2 or Spice which is associated with psychosis.[25]

Pharmacokinetics/Pharmacodynamics

The effects of cannabis vary based on the content of the cannabinoids within and the amount of each cannabinoid present.[26] Potency, duration, and time to onset of effects also vary based on the mode of delivery. Both adult-use and medical cannabis are used in a variety of

modes including inhaled (smoking or vaping), oral ingestion, absorption in the oral mucosa, and topical.[26] For example, in studies of THC use, THC levels peak at 30 minutes and subside within 1–3.5 hours when cannabis is smoked. When ingested, peak levels are not reached until 30 minutes to 2 hours and do not subside for 5 to 8 hours, due to the first pass mechanism.[26] The effects of a cannabis product are based not only on its content but also on its mode of use. Table 2 describes pharmacokinetics and pharmacodynamics of various administration methods of cannabis.

Medical cannabis

Interpreting the literature on medical cannabis can be challenging. As referenced previously, medical cannabis regulations vary by state, and there is no standardization of products from one state to the other. A detailed and comprehensive review of the clinical efficacy of cannabis was published in 2017 but the National Academies of Sciences, Engineering and Medicine.[7] They found that there is conclusive or substantial evidence that cannabis is effective in the management of chronic pain in adults, chemotherapy-induced nausea and vomiting, and improving patient-reported multiple sclerosis spasticity. Below, we briefly discuss the evidence for the use of cannabis for the management of qualifying conditions for medical cannabis use in most states.

Common conditions for which medical cannabis is used.

Chronic or severe pain—The most common condition for which patients are certified to take medical cannabis is chronic or severe pain.[27,28] A systematic review of randomized controlled trials (RCTs) found that, compared with placebo, cannabinoids are more likely to result in a reduction in pain scores.[29] Of the 28 RCTs reviewed, 22 evaluated plant-derived cannabinoids, and most used a placebo control condition. Most studies used a plant-derived medical cannabis product developed for medical use outside of the U.S. The remainder evaluated cannabis in flower form, which can be obtained for research studies from the National Institute on Drug Abuse. To our knowledge, RCTs testing legal medical cannabis products used by patients in the U.S. for the management of pain have not been published.[30]

Severe or persistent muscle spasms—Cannabinoid use for management of spasticity has been studied primarily in people with multiple sclerosis (MS). One systematic review identified 27 studies (8 RCTs) examining spasticity in adults;[31] 21 of these studies included adults with MS. Spasticity improved in all 8 RCTs, although improvement was sometimes measured subjectively through self-report. Many studies used an outdated measure of spasticity that is now considered unreliable, the Modified Ashworth Scale.[31,32] In another meta-analysis, investigators conducted a pooled analysis of data from 3 studies investigating the efficacy of cannabinoids for spasticity in MS.[29] Formulations of cannabis with THC and CBD were associated with improved spasticity on a patient-reported rating scale compared with placebo and improvements in patient-reported symptoms were greater with formulations containing both THC and CBD than those containing THC alone. As with the research on chronic pain, these studies were all conducted with forms of medical cannabis that are not the same as those used by patients receiving medical cannabis in the U.S.

However, the cannabis products included in the studies contained the same main active ingredients (THC and CBD).

Severe nausea—Few studies have examined the effect of cannabis on severe nausea.[30] Oral synthetic THC (nabilone or dronabinol) has been used for chemotherapy-induced nausea for decades. It is superior to placebo and equally efficacious to comparator antiemetics [33]. In human studies, CBD is less well studied than THC for management of nausea. In animal studies, CBD alone was an effective antinausea agent [34].

Cachexia or wasting—The use of cannabis for cachexia or wasting has been studied primarily in either AIDS wasting syndrome or cancer-associated cachexia. In an article summarizing 4 RCTs that investigated the effect of cannabis in patients with AIDS wasting syndrome, the author concluded that these trials had a high risk of bias, but there is some evidence that cannabis is effective for weight gain in individuals with HIV.[29] All 4 of these studies compared dronabinol (synthetic THC) with placebo or megestrol acetate. For cancer-associated cachexia, a phase III multicenter RCT compared cannabis extract (THC and CBD), THC alone, and placebo for 6 weeks. Participants were monitored for appetite, mood, and nausea. Of 243 participants enrolled, 164 completed the study, and no difference was found between groups. Recruitment was terminated early because the data review board determined that it was unlikely that differences between groups would emerge.[35] In a more recent pilot study, 17 patients with cancer-associated cachexia were enrolled and received high THC: low CBD cannabis capsules for 6 months. Only 6 participants completed the study, 3 of whom had weight gain of at least10% from baseline; weight remained stable in the other participants.[36] There is very limited rigorous evidence that cannabis is effective in the management of cachexia or wasting.

Seizures—In June 2018, CBD was approved by the U.S. FDA to treat two forms of childhood epilepsy: Dravet syndrome and Lennox-Gastaut syndrome.[37] Dravet syndrome is a complex childhood epilepsy disorder associated with treatment-resistant seizures and a high mortality rate. In a double-blind RCT, daily oral CBD reduced the frequency of convulsive seizures from 12.4 to 5.9 per month. There was a change in frequency from 14.9 to 14.1 seizures per month in the control group.[38] In another childhood syndrome with treatment-resistant seizures, Lennox-Gastaut, CBD use resulted in a 41% reduction in seizure frequency. Reduction in seizure frequency was dose-dependent.[39]

The use of cannabinoids for management of seizures in adults is not as well studied. In an open-label study of CBD in 132 adults and children with treatment-resistant epilepsy, 64% experienced at least a 50% reduction in seizure frequency. Participants also experienced reduced severity of seizures and fewer adverse events.[40] A smaller open-label study including 21 adult participants with treatment-resistant seizures receiving CBD found a 71% reduction in seizure frequency, an 80% reduction in seizure severity, and improved mood.[41] These outcomes are very encouraging but were achieved with doses of CBD alone that exceed the doses usually provided in state-run medical cannabis programs. There is little evidence for the use of other cannabinoids to manage seizures [42].

Post-Traumatic Stress Disorder—The efficacy of cannabis for managing PTSD is not well studied [43]. Several small studies have examined the effect of THC on nightmares and global functioning in patients with PTSD, most of whom were combat veterans.[44–47] In all of these studies, participants experienced improved sleep. Concern remains that cannabis use in people with PTSD may result in adverse outcomes, such as cannabis use disorder; however, this is also not well studied.[43]

Opioid use—Medical cannabis treatment has emerged as a potential strategy for addressing the opioid epidemic; however, the evidence to support its use is mixed. In most ecological studies, legal medical cannabis laws are associated with a reduction in opioid-related deaths, opioid prescribing, and opioid use.[48–52] As the opioid epidemic has changed from opioid analgesics for pain to heroin and fentanyl indicative of opioid use disorder, more recent studies found conflicting results, with opioid overdose mortality increasing in some analyses.[53,54] As discussed earlier, cannabis has analgesic effects, which may explain why medical cannabis legalization was associated with decreased opioid overdose deaths when the opioid epidemic was fueled by opioid analgesics prescribed for pain. Because there is very limited data to support the use of cannabis for opioid use disorder, it is not surprising that when the opioid epidemic changed to one driven by heroin and fentanyl,[55] the association between legalized cannabis and opioid overdose changed. In all retrospective and observational studies, it is impossible to eliminate all possible confounders. While these studies help us understand how the opioid epidemic and co-occurring availability of medical cannabis may contribute to population level outcomes, they cannot determine causality. More rigorous studies at the individual patient level are needed, such as RCTs to truly understand the relationship between medical cannabis use and opioid use.

Assessing patients for medical cannabis use.

In the authors' combined experience of over 10 years of certifying patients for medical cannabis use, we developed certain tenets for our patient assessments; these are presented below. In all patients being evaluated for medical cannabis certification, it is important to take a thorough history. Typically, this includes patient's presenting symptoms, as well as a comprehensive history of co-morbidities. Psychiatric and substance use histories are included in this assessment, including history of psychosis, hallucinations, or schizophrenia. A detailed history of prior and current cannabis use is also important, including the frequency, administration, and amount of cannabis use (Table 1).

Assessing for absolute and relative contraindications to medical cannabis use is also important. Few states define clear contraindications to medical cannabis certification. THC exposure has been associated with tachycardia and development of worsening psychosis.[56–58] Additionally, chronic THC exposure during pregnancy has been associated with preterm labor and intrauterine growth retardation.[59] Therefore, it is important to be cautious when determining whether to certify a patient for medical cannabis use who has unstable cardiac disease, risk factors for cardiac disease, a history of psychosis or hallucinations, or pregnancy. A harm reduction approach is an important guiding principal when assessing the patient for contraindications to medical cannabis use, especially in patients whose situation is complex and not straight forward. For example, if a patient

is pregnant and is currently using non-medical cannabis, medical cannabis could be used to reduce overall THC exposure during the course of the pregnancy as a harm reduction strategy.

Initiating medical cannabis

When giving recommendations for medical cannabis dosing and administration method, there are many reasons to discourage patients from using smoked forms of cannabis, including combustible cannabis and vaped. These reasons include concerns for chronic bronchitis and airway inflammation with prolonged use,[60] risk of vape-related lung injury,[61] and risk of respiratory infection.[62] When advising patients on different administration methods, it is important to provide education on expected time of onset and duration of effect. For example, the onset of effect when cannabis is orally ingested is much longer than when it is inhaled (Table 2).[63–67] It is recommended that patients refrain from taking additional doses of orally ingested cannabis products while awaiting the onset of effect of their first dose (e.g., dose stacking, which can lead to adverse events).[68,69]

Similar to when patients initiate new medications, when initiating medical cannabis, it is reasonable for patients to start with the lowest possible dose of THC available to them. In addition, starting the first dose before bedtime may reduce the risk of adverse events. Maintaining the initial dose for 2–3 days is warranted prior to increasing the dose in the smallest possible increment. Overall, this strategy is consistent with other published recommendations to “start low and go slow.”[70]

Patients who are already using non-medical cannabis may need to start at a higher dose to avoid potential THC withdrawal. In addition, it is important for these patients to abstain from non-medical cannabis use 48–72 hours prior to starting medical cannabis so that they can attribute the effects of the medical cannabis (and not non-medical cannabis) to their signs and symptoms.

Cost of medical cannabis

Due to the Schedule I status of cannabis, medical cannabis is not covered by private insurance. Further, it must be paid for with cash or a debit card, which may pose a significant barrier to its use. Depending upon the state, medical cannabis products could cost over $150/month. Patients and providers must weigh the risks and benefits of using medical cannabis, particularly if it poses risk of financial hardship.

Potential complications of medical cannabis

Medication Interactions—The effects of cannabis may be additive with other agents used targeting similar areas of effect, including analgesic, sedative, and psychotropic effects. The cannabinoids THC and CBD are metabolized by the cytochrome P450 (CYP450) system and so may inhibit metabolism of other agents also metabolized by this system.[26] Further research and data on the potential medication interactions between medical cannabis and other medications are sorely needed.

Psychiatric symptoms—Few high quality studies have been published examining how cannabis affects psychiatric symptoms, and few examined the specific effects of THC and CBD on psychiatric symptoms. In studies of adolescents and young adults using street cannabis, chronic cannabis use is associated with psychiatric symptoms, including anxiety,[71] depression,[71] and psychosis, and has been linked to worsening schizophrenia in those with a preexisting genetic vulnerability.[72,73] However, a direct causal relationship is difficult to establish as a multitude of confounding factors blur the relationship between cannabis use and psychiatric illness. For example, people with symptoms such as anxiety or stress may be more likely to use cannabis.[74] Additionally, preclinical and clinical studies show that CBD improves social anxiety, while THC worsens it.[75–77] It is reasonable to monitor for new or worsening psychiatric symptoms in patients new to medical cannabis, and to recommend termination of medical cannabis if new psychiatric symptoms are identified.

Cannabis hyperemesis syndrome—The most common severe gastrointestinal adverse effect of cannabis use, cannabis hyperemesis syndrome,[78] presents as cyclical nausea and vomiting and abdominal pain in patients with chronic cannabis use. A recent study reported that gastrointestinal symptoms were the most common cause for emergency room visits related to cannabis use.[68] Symptoms may improve with hot showers or baths and resolve after cessation of cannabis use.[79]

Pulmonary effects—Chronic inhaled cannabis use can lead to chronic bronchitis symptoms, including cough, sputum production, and wheezing.[80,81] Cannabis use may result in pulmonary function test changes, but, unlike tobacco, cannabis has not been associated with chronic obstructive lung disease.[80,81] The mode of consumption could be related to specific types of respiratory syndromes.

A new lung disease associated with heavy vaping, vaping-related lung injury, emerged in late 2019.[82,83] To date, it remains unclear whether the risk is limited to specific types of vaping products or oils or with specific use patterns. It is suspected that vaping lung injury is caused by a severe inflammatory response to vitamin E acetate, an oil included in some formulations of vaporized products (including nicotine and cannabinoids). However, more studies are needed to confirm that vitamin E acetate is directly responsible for vaping lung injury.[84]

For patients who choose to vape, using products from registered facilities reduces the risk that patients are exposed to toxins.[70] Cannabis smoking may predispose individuals to pneumonia through damage of central airways and local immune response changes.[85–87]

Smoked cannabis contains carcinogens, raising concerns about lung cancer. Observational studies have had inconsistent findings—one reported increased risk of lung cancer in all users,[88] another reported increased risk only among heavy users,[89] and another showed no increased risk.[89] These studies included potential confounders (e.g., tobacco use, environmental exposures) that may have affected results. Further research is needed to understand how people using cannabis should be monitored for cancer.

Cannabis Use Disorder—Cannabis use disorder (CUD) is a potential complication of both adult-use and medical cannabis. An estimated 8 to 12% of people who use cannabis regularly will develop CUD over time.[90,91] Globally, CUD has been found to contribute to substantial disability[92] and is responsible for up 15% of all admissions into substance use treatment programs in the U.S.[93]

Several psychotherapies have been studied for the management of CUD and have been shown to reduce frequency and quantity of cannabis use. These include motivational enhancement treatment, cognitive behavioral therapy, and contingency management.[94] Unfortunately, access to evidence based psychotherapies are limited for many due to geographic and structural barriers.[95] Due to these limitations, there is an increasing interest in identifying pharmacologic treatments to supplement psychotherapies.[95] These are primarily used to address symptoms of cannabis withdrawal. For example, there is evidence that zolpidem and benzodiazepines may be useful for sleep disturbance due to cannabis withdrawal. Cannabinoids such as dronabinol and nabilone have also been studied and show promise in reducing cravings and withdrawal-related sleep disturbance.[95] Medical cannabis for the management of CUD has not been explored.

Conclusions

This review can help clinicians better understand how to approach cannabis use in the clinical setting. Cannabis policy is rapidly changing in the U.S., including its legal status, availability to patients, and acceptability in medical communities and among the general public. High quality research on medical cannabis has been difficult to complete due to federal restrictions. Nevertheless, clinicians will encounter patients using cannabis and should be familiar with the existing evidence for the management of common indications with cannabis, cannabis pharmacology, and potential complications of its use. By understanding these fundamental aspects of cannabis, clinicians can make informed recommendations to patients who use or have questions regarding use of cannabis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key points:

- Cannabis use is rapidly growing in social acceptability and use.
- Black and Hispanic Americans have been disproportionately affected by the criminalization of cannabis.
- Cannabis and its cannabinoid constituents interact with the endocannabinoid system, located in the central and peripheral nervous system, endocrine system, gastrointestinal system, and inflammatory cells.
- Evidence for the use of medical cannabis for certain conditions is growing.
- Clinicians should be aware of potential complications of cannabis use.

Synopsis

Cannabis use in the United States (U.S.) is growing at an unprecedented pace. Most states in the U.S. have legalized medical cannabis use, and many have legalized adult-use (recreational) cannabis use. In this setting, health care providers will increasingly see more patients who have questions about cannabis use, its utility for medical conditions, and the risks of its use. This review article provides an overview of the background, pharmacology, therapeutic use, and potential complications of cannabis.

Table 1:

Relevant terms

Term	Definition
Cannabis	A broad term describing various products and chemical compounds derived from the *Cannabis sativa* or *Cannabis indica* species [30]
Marijuana	Leaves, stems, seeds, and flower buds derived from the *Cannabis sativa* plant [30]
Hemp	*Cannabis sativa* plant with very low levels of THC (<0.3%) [96]
Street cannabis	Cannabis that is not obtained from a licensed cannabis dispensary and not recommended by a medical care provider
Dronabinol	An orally administered medication approved by the U.S. Food and Drug Administration to treat anorexia associated with weight loss in patients with HIV or nausea/vomiting associated with cancer chemotherapy who have not responded adequately to conventional antiemetic treatments. The active ingredient is synthetic THC [97]
Cannabinoid	One of a group of over 100 biologically active chemicals found in the *Cannabis* plant
delta-9-tetrahydrocannabinol (THC)	The main psychoactive constituent of cannabis [30]
Cannabidiol (CBD)	A constituent of cannabis traditionally considered nonpsychoactive [30]
THC:CBD ratio	The ratio of THC and CBD in a medical cannabis product
Administration method	In NYS, the administration methods for medical cannabis are inhaled, oral, sublingual, topical, and suppository. Edible products, such as candies, gummies, or baked goods, are not currently available in NYS.
Dispensary	A retail site of an organization that NYS has registered to dispense medical cannabis to patients with medical cannabis certification
Less frequent or no cannabis use	Cannabis use on *less than 20 days* in a month [98]
Near-daily cannabis use	Cannabis use on *at least 20 days* of the month [98]
Harm reduction	In the clinical context, an approach and practical strategies are targeted to reduce the negative consequences of substance use. It is founded on respect for the rights of individuals who use drugs.

Table 2:

Cannabis Administration Methods and Their Effects

Product, Method of Use, and Bioavailability	Onset and Duration of Effect	Advantages	Disadvantages
Combustible flower: usually smoked rolled in paper or in a pipe. • **Bioavailability:** Varies between10–35% due to difference in number of breaths, duration of puff, breath holding, inhalation volume.[26]	• **Onset:** 3–10 minutes[26] • **Duration:** ≤2 hours[99]	• Quick onset of action	Potential for adverse effects (short- and long-term): • Intoxication[68] • Chronic bronchitis[60]
Vaped oil: Inhaled using a battery-operated portable pen-like device • **Bioavailability:** Varies between 2% to 56% due to difference in smoking dynamics (number of puffs, spacing of puffs, hold time, inhalation time, etc.) [99]	• **Peak:** 9 minutes[99] • **Duration:** ≤2 hours[99]	• Quick onset of action	Potential for adverse effects (short- and long-term): • Intoxication[68] • Chronic bronchitis[60] • Vaping lung injury (vitamin E acetate additive) [84]
Vaped ground flower pods: Inhaled using a unique table-top device that creates vapor from plant material • **Bioavailability:** Varies between 2% to 56% due to difference in smoking dynamics (number of puffs, spacing of puffs, hold time, inhalation time, etc.) [99]	• **Peak:** 9 minutes[99] • **Duration:** ≤2 hours[99]	• Quick onset of action	Potential for adverse effects (short- and long-term): • Intoxication[68] • Chronic bronchitis[60]
Capsule: Oral ingestion • **Bioavailability:** 4% to 25% depending upon the study. [63–67] Variable due to drug degradation in stomach, variable absorption in the stomach, and first-pass metabolism	• **Peak:** 1–5 hours[63–67] • **Duration:** ≤25 hours[63–67]	• Slow onset of action, low bioavailability • Avoid adverse effects of smoking	• Risk of dose stacking—repeating doses before an effect is felt by the patient. Usually attributable to a long period before onset of effect. Results in unanticipated intoxication and adverse effects[68,69]
Tincture and spray: Sublingual/oral • **Bioavailability:** 87.5% to 90%[100,101]	• **Onset:** As early as 10 min[100–102] • **Duration:** ≤10 hours[100,101]	• Fast onset of action • Avoid adverse effects of smoking	• Taste • Potential for user error
Suppository: Rectal • **Bioavailability:** 14% to 67% [22,103]	• **Onset:** 1–2 hours[104] • **Duration:** ≤8 hours[104]	• Avoid first-pass effect[104] • Avoid adverse effects of smoking	• Undesirable dosing method • Very little supporting data for the use of suppositories
Lotions, gels: Transdermal • **Bioavailability:** Dependent upon how it is formulated, only studied in animal models[22]	• **Onset:** 2 hours[105] • **Duration:** ≤48 hours[105]	• Avoid adverse effects of smoking • Helpful in patients unable to adhere to other formulations (terminal illness, etc.)	• Variability of bioavailability depending on how it is formulated[105]