Cannabis Provider Education Packet

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ESP Evidence Synthesis Program

Contents

Note: This packet was produced for the Veterans Health Administration by the Evidence Synthesis Program to help familiarize VHA clinicians with basic information about cannabis so that they might feel more comfortable engaging in discussions with their patients and answering questions. Current VHA policy stresses that clinicians should be prepared to engage in these discussions because cannabis is relevant to clinical practice, but the policy also stipulates that VHA providers cannot certify patients for, or recommend them to, state-approved medical cannabis pro-grams. We interviewed and surveyed VHA clinicians and prioritized issues for inclusion here that they had voiced as important. This is meant to be a very broad, high level evidence-based overview of a very complex topic. There are undoubtedly subtleties and nuances to the information presented that are not adequately captured in this overview. The information presented in this packet is based on our current understanding of a rapidly evolving body of evidence; readers are referred to the bibliography at the end for more details.

The cannabis plant contains over 140 compounds

Cannabinoids

The two best-studied cannabinoids are:

Delta-9-tetrahydrocannabinol (THC)
- Produces much of the intoxicating effect or "the high" associated with cannabis
- Popularly thought to contribute to various potential therapeutic benefits

Cannabidiol (CBD)
- No significant intoxicating effect
- Potential anxiolytic and therapeutic benefits, but not well-studied
- May decrease the intoxicating effects of THC

Terpenes

A largely unstudied group of compounds that produce the unique aroma and flavor of cannabis, and may influence the intoxicating effects of cannabinoids in whole-plant products. These may be part of the reason that different cannabis products with the same THC and CBD content might have differing effects.

Sativa or Indica?

These terms are used colloquially to characterize the expected effects of a given product: Sativa products are purported to have energizing, uplifting, and creative effects (a "mind high"), while Indica products tend to be sedating, and relaxing physically and mentally (a "body high"). While these terms are commonly used, they are not scientifically grounded.

The degree to which a product will have energizing, intoxicating, or relaxing effects is most likely determined by the relative amounts of THC and CBD in the product.

Dosing

The potency of a cannabis product is typically defined by the amount of THC in the product. There is no clear definition of a single "dose" of THC. A few states have defined a single dose as 5-10 mg of THC. However, cannabis dosing is complicated by the variation in bioavailability across formulations and across individuals, and by the complex interaction among the different compounds present in whole plant and plant extract products.

In studies

- Nabiximols is an oromucosal spray which has been effective in improving neuropathic pain in some studies. A single dose of nabiximols contains 2.5 mg THC and 2.5 mg CBD. Participants in these studies used, on average, 25 mg or less of THC over 24 hours.

- Dronabinol is a synthetic form of THC that has been FDA approved for treatment of AIDS-related cachexia, and refractory chemotherapy-induced nausea and vomiting. The recommended starting dose is 2.5-5 mg daily, with a maximum divided daily dose of 20 mg.

In dispensaries

- The concentration of THC in cannabis has been increasing over time and the amount of THC in dispensary products is much higher than the amount of THC in products studied in clinical trials.

- In one study, the median amount of THC in a 1.5 gram edible product in dispensaries was 54 mg

    - The median THC:CBD ratio was 36:1
    - Only 17% of product labels were accurate

Calculating the dose of THC

- Multiply the weight of the product by the percentage of THC in the product

- According to estimates, the average joint weighs about 0.32 to 0.66 grams. A high-potency cannabis product might contain 20% THC
Joint is 320 mg x 0.20 = 64 mg THC/high-potency joint
Joint is 660 mg x 0.20 = 132 mg THC/high-potency joint

Cannabis formulations

| Form	Other Terms	Development	Route of Administration
Plant	Flower, bud	The highest concentration of cannabinoids are found in the flower, not the leaf, of the female plant; topical preparations and rectal suppositories can be made with dried flower or plant extract	Smoking Vaporization Topical Rectal
Edibles	Brownies, cookies, candy	Typically butter or oil used to extract cannabinoids and put into a variety of edible products	Oral
Tincture	Golden dragon, green dragon	Alcohol or glycerin used to extract active ingredients	Oral Sublingual Oromucosal
Oil	Rick Simpson oil	Alcohol used to make highly viscous concentrated extract	Oral Topical
Resin	Hash, dry sift, kief	Concentrate made by mechanically separating trichromes (hair like protrusions on flower with high concentration of cannabinoids) from the plant	Smoking Vaporization
Nabiximols	Sativex™	Pharmaceutically prepared whole plant extract in spray form; 1:1 THC:CBD concentration; approved for prescription use in many countries outside the US	Oromucosal
Dab	Wax, shatter	Ultraconcentrated extract made with solvents such as butane; very high levels of THC; risk of overdose and acute psychosis	Dabbing (concentrate placed on very hot metal rod and inhaled)
Pharmaceutical cannabinoids	Dronabinol™, Nabilone™, Epidiolex™	Dronabinol and nabilone are FDA approved synthetic THC (chemotherapy induced nausea/ vomiting; AIDS related cachexia); Epidiolex is a highly purified CBD plant extract and is FDA approved for the treatment of two rare epilepsy syndromes	Oral

Routes of administration: compare & contrast

Route	Smoking	Vaporization ("Vaping"*)	Oral/Edibles	Topical
Notes	Combustion of dried cannabis flower using several methods: cigarettes (joints, spliffs), pipes, water pipes (bongs)	Vaporizer is used to heat dried flower or concentrated extract (oil, resin) and the resultant vapor is inhaled	Variety of edibles available; often dose/single serving is a fraction of the product (*ie,* one part of a cookie or brownie)	Many forms available: creams, ointments, patches, poultices, oils
Pharmacology	Rapid onset and peak	Rapid onset and peak similar to smoking	No inhalation; broad range of products; slower onset and longer duration of action	None of the pulmonary effects associated with inhalation; probably much less intoxicating
Cautions	Bronchial irritation; cough; sputum; production contains carcinogens; potential for adverse effects on lung function with heavy use over many years	Substantially higher blood THC concentrations achieved at a given dose than with smoking; higher risk of adverse effects in novice users; long term lung safety is unknown; need for potentially costly equipment; potentially fatal vaping-related pulmonary illness	Onset and peak are delayed and effects can last many hours which makes it more difficult to titrate dose; oral metabolite of THC (11-OH-THC) may have four-fold more powerful psychoactive effect; risk of overdose; caution especially in novice users	Very little is known about topical preparations; unknown systemic absorption

*At this time, providers should caution patients against vaping given the lack of certainty regarding the cause and scope of the recently described series of severe vaping-related pulmonary illness cases.

The pharmacology of cannabis

Pharmacokinetics

THC concentration in blood / Time (hours)

Legend:
- Smoking/vaping
- Sublingual/oromucosal
- Oral
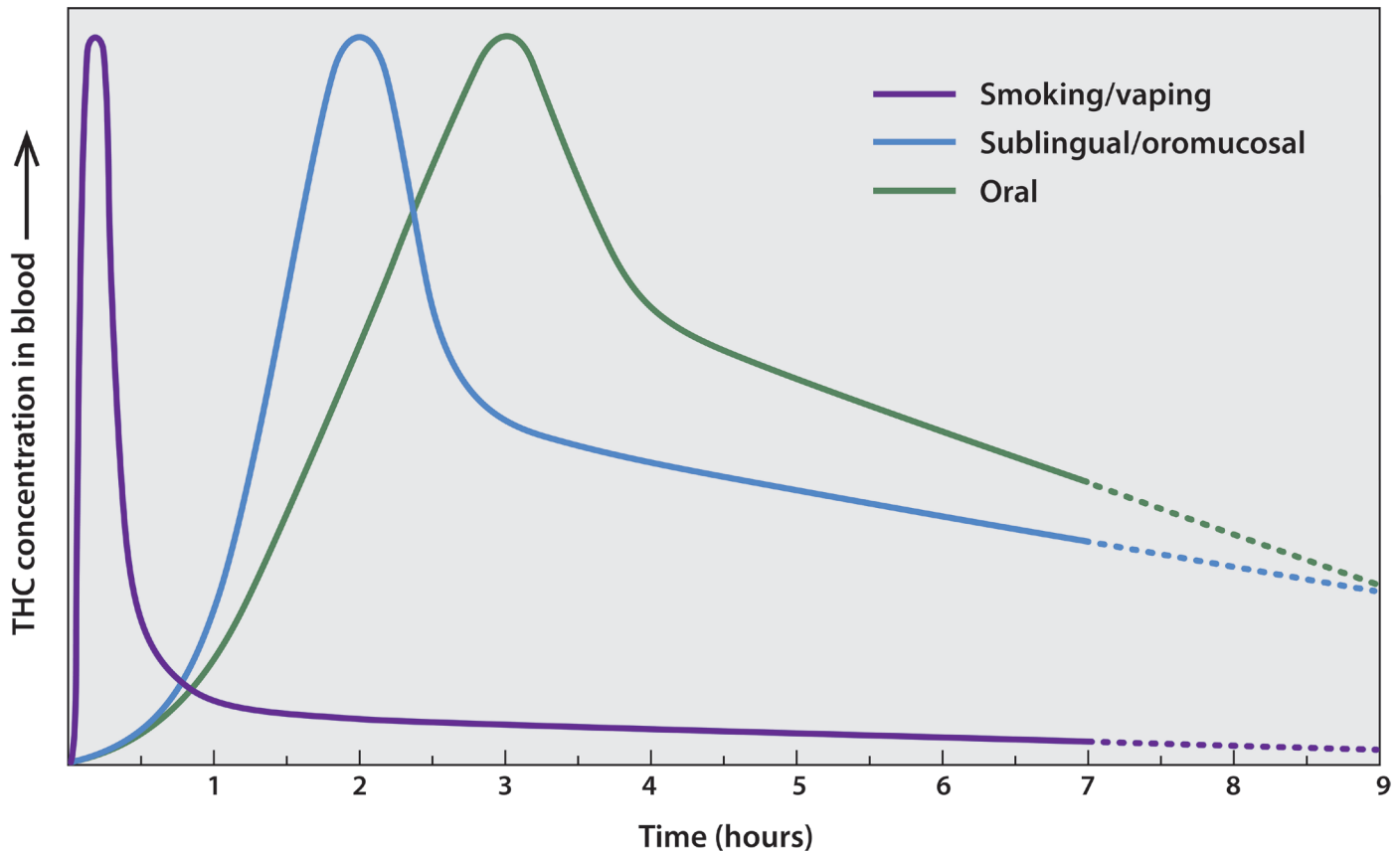
Note: The graph is meant to illustrate relative differences in time to peak concentration. The actual concentration of THC at different time points varies markedly across individuals and is influenced by patient characteristics, dose, and frequency of use. Low levels can persist for days to weeks in frequent users.

Cannabis-drug interactions

Cannabis has the potential to compound the **sedative effects** of different drug classes, including **anticholinergics and CNS depressants**. The sedative effect of cannabis combined with **antidepressants or lithium is unpredictable**.

Cannabinoids can induce or inhibit CYP enzymes and can, therefore, decrease or increase the levels of pharmacologic drugs. For example:

- THC may reduce levels of the following drugs: **aminophylline/theophylline, clozapine, ropinirole**
- CBD may increase levels of the following drugs: **clobazepam, diazepam, proton pump inhibitors, phenytoin/fosphenytoin**

Since THC and CBD are substrates of different CYP enzymes, their levels can also be increased by certain drugs. For example:

- Boceprevir, Ritonavir, Clarithromycin, Conivaptan, Ketoconazole, Posaconazole, and Voriconazole can **increase levels of CBD**
- Carbamazapine, Phenobarbitol, Phenytoin, Rifampin, and St. Johns Wort can **increase levels of THC**

Cannabis & chronic pain
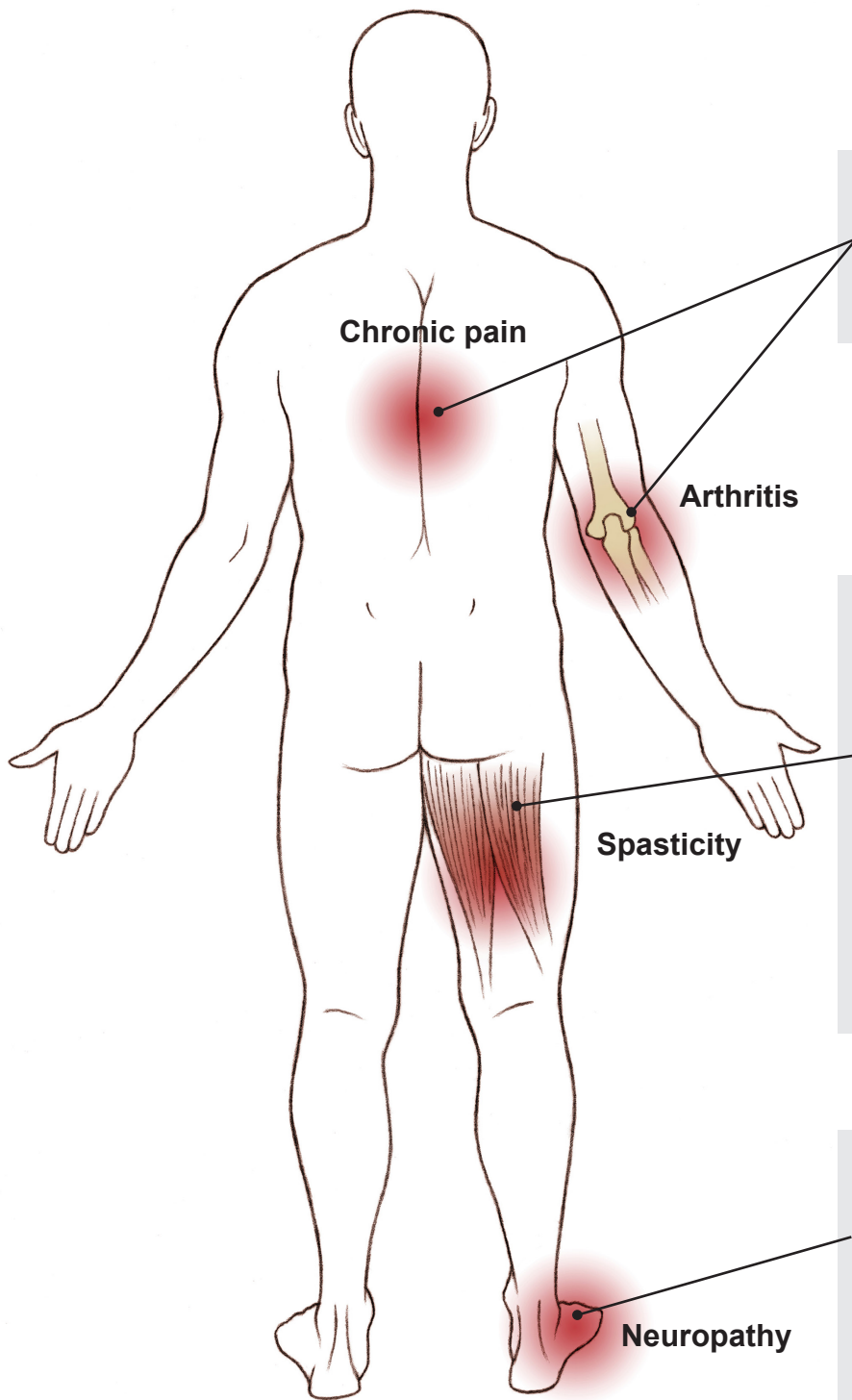
Chronic musculoskeletal pain
- Insufficient information because these populations have largely not been included in well-done studies

Spasticity in multiple sclerosis
- Products with precisely defined amounts (in a 2:1 or 1:1 ratio) of THC and CBD were associated with improved spasticity and pain in MS patients at up to 15 weeks
- Longer-term effects have not been studied
- The formulations that have been effective are different from what is often available in dispensaries

Neuropathic pain
- Products with precisely defined amounts of THC and CBD were associated with clinically important effects on neuropathic pain in a small subset of patients over hours to a few weeks
- Longer-term effects are unknown
- The formulations that have been effective are different from what is often available in dispensaries

Harms

Cognition
- Active, regular cannabis use is associated with negative effects on cognition
- Particular concern in the developing brain (adolescents and young adults), and possible risk of neuropsychiatric symptoms later in adulthood
- Effects of past use are unclear

Cannabis Use Disorder (CUD)/Substance Use Disorder (SUD)
One in three cannabis users meets criteria for a CUD. See page 10 for details.

Lung function
- Light smoking (weekly or less) has not been associated with a decline in lung function over 20 years in younger individuals
- Daily use over many years may reduce lung function
- The impact of smoking in older patients or those with multiple medical comorbidities is unknown
- Smoking is also associated with bronchitis symptoms

Mental health
- Increased risk of acute psychosis, especially with high-THC products
- Long-term cannabis use has been linked to an increased risk and earlier onset of chronic psychotic symptoms, especially in at-risk individuals (*eg*, those with a family history of psychotic illness)
- May increase the risk of mania

Motor vehicle accidents
- Acute intoxication has been associated with a 35% increased risk

Cannabis withdrawal syndrome
- Can present up to a week after discontinuation and persist for several weeks
- Symptoms include dysphoria or depression, anxiety, insomnia, chills, and restlessness

Cardiovascular
- Impact on risk of MI and stroke are unknown
- Associated with tachycardia, hypertension, and hypotension

Cannabis hyperemesis syndrome
- Increasingly recognized form of cyclic vomiting syndrome seen in those using cannabis on a regular basis
- Hallmark is improved symptoms with hot showers, though this symptom is not present in all individuals
- Treatment is discontinuation of cannabis (may take weeks)
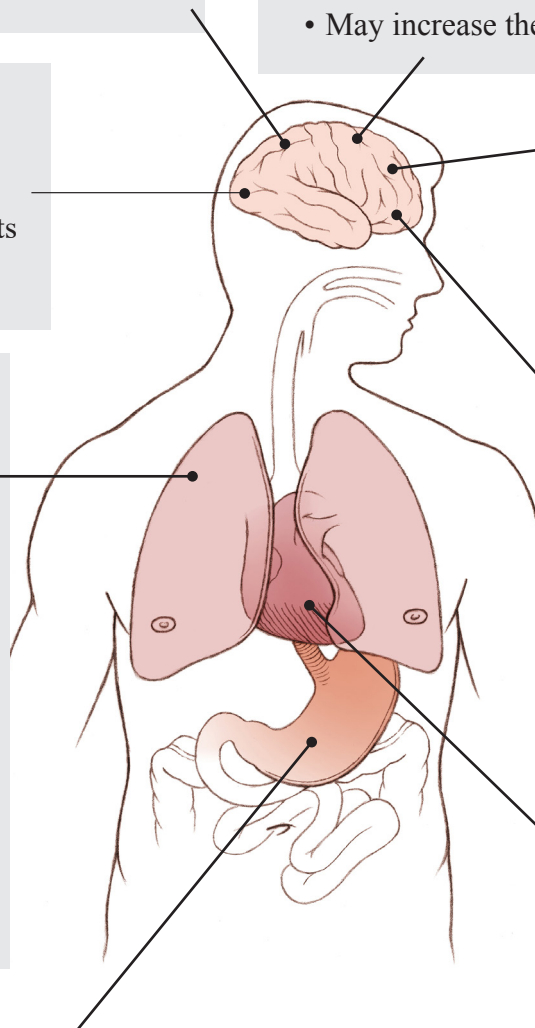
Cannabis & overdose

- While cannabis has not been associated with death from overdose, intake of a high amount of THC can cause symptomatic overdose often manifesting as acute psychosis. There have also been recently described fatalities associated with vaping cannabis.

- Acute psychosis from THC overdose has been reported, particularly with edible cannabis
    - Patients can inadvertently take too high a dose because the peak effect of edible cannabis is delayed (usually about 1-3 hours), and they may take more than the recommended dose after feeling nothing initially
    - Oral ingestion produces a particularly potent metabolite of THC

- In a case series of patients hospitalized for cannabis-induced psychosis, patients had ingested 100 mg or more of THC

Non-prescription synthetic cannabinoids: *BEWARE*

There have been several large overdose outbreaks associated with non-prescription synthetic cannabinoids.

- Products go by the name of "K2" or "Spice" and can be purchased on the street, or at convenience stores and gas stations

- In one large outbreak, cannabinoids were adulterated with brodifacoum, which potentiates cannabis effects and is a coumarin derivative
    - Numerous hospitalizations and several deaths related to bleeding complications

- Two "zombie" outbreaks associated with ultrapotent street cannabinoid AMB-FUBINACA

- These compounds are not detectable on urine drug screen

Cannabis Use Disorder (CUD)/Substance Use Disorder (SUD)

- The prevalence of CUD among those reporting cannabis use in the past year is about 1 in 3
- Cannabis use is associated with a two-fold increased risk of future alcohol use disorder or any SUD

Assessing for Cannabis Use Disorder

There are a variety of CUD assessment tools, although they have not been as broadly tested in clinical practice as tools for other substance use disorders. The following short screener is one option.

Stepwise assessment of cannabis use disorder

Step 1. Do you currently use cannabis?   Yes No

Step 2. If yes:

1. How often during the past 6 months did you find that you were not able to stop using cannabis once you had started?
   - (1) Never
   - (2) Less than monthly
   - (3) Monthly
   - (4) Weekly
   - (5) Daily or almost daily

2. How often in the past 6 months have you devoted a great deal of your time to getting, using, or recovering from cannabis?
   - (1) Never
   - (2) Less than monthly
   - (3) Monthly
   - (4) Weekly
   - (5) Daily or almost daily

3. How often in the past 6 months have you had a problem with your memory or concentration after using cannabis?
   - (1) Never
   - (2) Less than monthly
   - (3) Monthly
   - (4) Weekly
   - (5) Daily or almost daily

   Total score _____

   Positive screen = 2 or higher

Step 3. Confirm with DSM5 criteria for cannabis use disorder

- Using a larger quantity or over a longer duration than intended
- Unsuccessful attempts to limit/quit
- Significant amount of time spent obtaining cannabis
- Cravings
- School/occupational impairment
- Social/interpersonal impairment
- Reduction of social/occupational/recreational activities
- Recurrent use in physically harmful situations
- Continued use despite recurrent physical or psychological harms
- Tolerance
- Withdrawal

Mild	**2-3 criteria**
Moderate	**4-5 criteria**
Severe	**6 or more criteria**

Cannabis use disorder is an increasingly recognized harm. Daily users, young adults, and men are at higher risk. The risk of frequent non-medical cannabis use and the risk of cannabis use disorder is also higher among patients with chronic pain.

% with any past year cannabis use who met criteria for CUD	36
% of those with prior cannabis use who develop CUD (incidence)	25
Odds of developing any other substance use disorder	2.1
Odds of developing alcohol use disorder	2.0

Treatment of Cannabis Use Disorder

A number of medications have been tested, but there are none with adequate evidence to support routine use in treating CUD yet.

The mainstay of treatment is psychological: cognitive behavorial therapy, motivational enhancement therapy, and contingency management. These are accessed through specialty substance use disorder treatment programs.

Harm reduction strategies

While VA providers may not provide medical recommendations for cannabis use, in many states patients have ready access to cannabis through medical and/or recreational dispensaries. For patients who are using cannabis, there are several strategies that may help mitigate potential harms:

- Ask patients about cannabis use: formulation, dose, frequency, route

- Consider assessing for cannabis use disorder (see previous section)

- Keep cannabis out of reach of children and adolescents

- Educate patients about:

  o Cannabis withdrawal syndrome and that the symptoms of withdrawal are similar to some of the symptoms patients may be using cannabis to help treat

  o Avoiding prolonged, daily use

  o Avoiding products with high levels of THC

  o Cannabis-naïve individuals should be especially cautious starting use of edible products, use low doses, and avoid rapid dose escalation

  o Dabbing is best avoided by everyone

  o Advise patients at risk for psychotic spectrum disorders and severe anxiety to avoid cannabis, especially high-THC products

  o Vaping has been associated with severe, life-threatening pulmonary illness, and should be avoided

  o Avoid products sold outside of state-licensed dispensaries given the greater potential for unknown content including synthetic cannabinoids

Cannabis policy

Veterans Health Administration
VHA policy is that:
- Providers discuss cannabis use with Veterans due to its clinical relevance
- Providers make individualized decisions about modifying treatment plans based on cannabis use
- There is no policy mandating specific action for those being prescribed opioids who are also using cannabis.
- Providers document discussions regarding cannabis in the medical record
- Providers cannot recommend, refer to, or complete forms related to state-approved medical cannabis programs.
- Veterans must not be denied VHA services solely because they are participating in state-approved cannabis programs. However, an individual's treatment plan may be modified as clinically indicated due to cannabis use.

Federal law
- Cannabis remains a Schedule 1 substance under the Controlled Substance Act, which means that the federal government classifies it as a substance with high potential for dependence or addiction and no accepted medical use.
- Research on cannabis in the US is very challenging because of the scheduling of cannabis.

State policy
- In 2019, cannabis is legal for medical purposes in 33 states and the District of Columbia (see https://medicalmarijuana.procon.org/view.resource.php?resourceID=000881).
- It is legal for recreational purposes as well in 10 of those states and DC.
- Monitoring, labeling, and quality control requirements vary substantially across states.
- Chronic pain is the most commonly approved medical indication for cannabis.

Cannabis policy & opioids
- Widely publicized ecological studies in the US initially suggested that states with medical cannabis legalization saw an accompanying decrease in opioid prescription and overdose deaths. However, the same analyses extended through 2017 actually found a reversal of that trend, and suggest caution in applying the results of these ecological studies.
- Data from individual patient-level studies are mixed, but have not shown a consistent decrease in opioid use among chronic pain patients using cannabis. Some studies show that cannabis has no impact on opioid use, while others show higher opioid use in those using cannabis.
- The use of cannabis as an opioid substitute has garnered interest, but there has been little evidence examining this practice.

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