Marijuana
Everyone Is Using It, So We Better Know About It

Learning Objectives

- Discuss the legal status of cannabis use in your community
- Identify when medical marijuana might be an appropriate therapeutic option and educate your patients
- Explain to patients how to safely use marijuana
- Recognize the risks associated with acute and chronic cannabis use and educate patients about those risks
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Marijuana Uses in History

- Marijuana is the most used illicit substance in the world
- Evidence points to the botanical origins of cannabis in Western and Central Asia and has been cultivated in Asia and Europe
  - Cannabis sativa - cultivated in Central Asia; used in folk medicine and as a source of textile fiber since ancient times
- Had prominent uses in medicine as transmitted through ancient Hindu texts
- Important medicinal benefits have been described in Chinese medicine since 2000 BC
  - Used as a balm or smoked Analgesic, anesthetic, antibiotic, antidepressant, sedative, antibiotic
- In the 1600s, cultivation of hemp was encouraged by British colonies to produce rope, sails, cloths and paper, and the Virginia colonies issued laws requiring farmers to produce it

Baron, EP. A comprehensive review of medicinal marijuana, cannabinoids, and therapeutic implications in medicine and headache: what a long strange trip it has been. Head Curr. 2015; 885-916.

Marijuana Uses in History

- Marijuana or Cannabis is also known as pot, tea, grass, and weed
  - Marijuana is the drug extracted from cannabis. The active ingredient is delta-9 tetrahydrocannabinol (THC) concentrated in the resin or flowering parts of the plant
  - Hashish is the more potent form (8 times more potent) and obtained through drying of the resin and is smoked
- Cannabis fibers in the form of hemp had industrial uses throughout history
- Industrial hemp had applications in the textile industry for clothing, manufacturing, building materials, oil plants, solvents, fuel, paper, plastic, wood and cellulose fibers, soaps, shampoos, cosmetics, food, medicinal purposes, phytochemicals
  - Recent renewed interest in hemp; important applications in the pharmaceutical industry including cannabinoids, terpenes and phenolic compounds. Applications in the construction industry as its stems can be used for concrete-like material and bioplastics

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History of Marijuana Legislation

- In the 1920’s and 30’s, marijuana was associated with the Great Depression, the influx of migration workers from Mexico and Africa, increased crime, ultimately leading to the Marijuana Tax Act of 1937
  - Cannabis referred to as “national menace”
  - Anti marijuana sentiment further expanded in the propaganda movie series Reefer Madness of the 1930’s purporting marijuana as a drug that led to criminality, suicide, rape, hallucinations and descent into madness
  - The Marijuana tax Act of 1937 prohibited possession and cultivation of cannabis
- The 1960’s
  - Negative association of marijuana perpetuated with the hippie and psychedelic movement of the 1960’s and the counterculture and anti-establishment movement
  - In the 1960’s most countries placed restrictions on possession of marijuana and hashish, sale and supply, to restrict trafficking
  - Controlled Substance Act of 1970 classified marijuana as controlled substance. Schedule I classification as a controlled substance with the highest potential for dependence and abuse and no acceptable medicinal use
  - Restricts access to scientific research and seriously limits investigation of the substance, restricts funding
  - Medical organizations are calling for reclassification of the substance and increased research of cannabis in medicine


THC was isolated in the 1960’s and therapeutic uses started to emerge in the 20th century

Decriminalization efforts in the 1990’s in the US led several states to legalize marijuana for medical purpose

Proposition 215 led to the breakthrough Compassionate Use Act (CUA) in 1996 in California. Allowing the use of medical marijuana for medicinal purposes

- CUA of 1996 allowed patients and caregivers to use medical marijuana for conditions such as anorexia, cancer, AIDS, spasticity, chronic pain, arthritis, migraine, nausea, glaucoma

Marijuana Legal Status in the United States

- Farm Bill of 2018 signed into law in Dec. 2018, defined hemp as the *C. Sativa* including all parts of the plant, with THC content of no more than 0.3% of dry weight. This bill practically removed hemp from CSA

- The 2018 Farm Bill places hemp under the regulation of Food Drug and Cosmetic Act (FD&C) like all other products regulated under the FDA

**CSA = Controlled Substances Act**


Status of Cannabis Research

- Physicians are hesitant to recommend medical marijuana because of federal restrictions and classification as Schedule I, its association with controlled substances and potential for addiction and dependence

- The National Institute of Drug Addiction (NIDA) through the National Institutes of Health (NIH) can approve research applications of cannabis in the context of addiction only

  - Researchers must register with DEA, obtain cannabis through NIDA, submit an investigational new drug (IND) application for review by FDA. Cannabis for research is provided through University of Mississippi Marijuana Research Facility, the only facility allowed to manufacture cannabis for research

  - Funding is directed towards research of harm and abuse related to cannabis use rather than therapeutic benefits resulting in bias

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### Epidemiology Trends in Cannabis Use

- Epidemiological studies from domestic and international surveys show that the perceived harmfulness of cannabis is inversely related to its use among adolescents, and that negative perception is decreasing (from 50% to 33% between 2012 to 2014)

- Prenatal and childhood exposure in <6 years old are on the rise (4.2 million in 2000 to 10.4 million in 2013)

- Medical and recreational users have similar profiles (race, education, depression, cannabis use disorder (CUD)) in states with non-restrictive medical marijuana laws (MMLs), only 17% used cannabis medically

- Another national study showed that medical cannabis users were 9.8% of all cannabis users. 21% of medical users came from non MML states suggesting that physicians are recommending cannabis use in non MML states


### Trends in marijuana use patterns, marijuana use disorders, and perceived risk of harm in US

[Graph showing trends in marijuana use, use disorders, and perceived risk of harm from 2002 to 2014.]

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**Recreational Marijuana Laws (RMLs)**

- Allow the use of recreational marijuana without a medical justification or authorization
- Reduced biased enforcement of law and arrest of minorities in relation to illicit cannabis possession
- Increase availability and access to cannabis and may increase the risk of adverse events and access to other substances
- Little is known on the impact of RML on public health, on CUD, outcomes


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**Recreational Marijuana Laws (RMLs)**

- THC potency in legally marketed cannabis is increasing and can reach 28%-32% in Colorado
- **Cannabis potency** has doubled worldwide average. THC content is now 6% from 3.7% in 1990s. This change is relevant to public health
- Smoking is the most common form of administration, newer forms offer higher THC levels (edibles, vaping)

Evidence from Epidemiological Studies

- **Childhood exposure**
  - Symptoms: lethargy, ataxia, dizziness, respiratory depression
  - There might be an increased risk of pediatric exposure in states where cannabis use is legal

- **Adolescent exposure**
  - Early-onset (adolescence), prevalence of use was 5.4% among 13-14 years or 8th graders
  - May impact the development of the adolescent brain, poor educational outcome, school dropout, cognitive impairment, lower life satisfaction, addiction


Epidemiology of Cannabis Use on Motor and Cognitive Function

- THC impairs motor and cognitive functions needed for safe driving
- Consuming THC during driving increases the risk of vehicle crashes and fatal injuries

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Epidemiology of Cannabis Withdrawal Syndrome

- Cannabis withdrawal syndrome has been reported after cessation of use, in the first week and may persist for one month
  - In 1/3 of chronic users and 50%-80% of heavy users
  - Characterized by 3 or more symptoms of anxiety, restlessness; depression, irritability; insomnia or odd dreams; physical symptoms like tremor; decreased appetite
  - May be confused with psychiatric disorders, and limit prescribing cannabis for mood/anxiety disorders


Epidemiology of Cannabis Use and Psychiatric Comorbidities

- Cannabis use disorder (CUD) strongly linked to mood and anxiety disorders
  - Co-morbidities of major depression and psychiatric disorders, or causal associations
  - CUD shares genetic risk with major depression, or causal effect of CUD on major depression
  - Cannabis use is linked to increased psychosis risk, and increasing levels of use further increases risk (NAS 2017)
  - Cannabis is a modifiable risk factor for developing psychotic disorder, children with a risk should be counseled against its use
  - Nicotine use disorders: nicotine and cannabis co-use can intensify respiratory distress than each substance alone

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**Epidemiology of Cannabis Use in Mood and Anxiety Disorders**

- Many patients self medicate with marijuana to treat symptoms of anxiety and depression in states that legalize medical marijuana, and reduced anti-depressant use in those states have been reported.
- Medical marijuana is authorized for PTSD in 21 states and may be used for anxiety and depression.
- Return of symptoms may happen on cessation of use and may be due to cannabis withdrawal.
- Synthetic cannabinoids theoretically may be effective in aspects of PTSD but the clinical evidence shows cannabinoids worsen PTSD.


**Epidemiology of Cannabis Use**

- Substitute for opioids in chronic pain
  - Less risks than opioids in relation to risks of overdose, physical dependence, addiction, transition to heroin
  - Lack of fatal overdose, transition to heroin, side effects of cognitive and motor impairment
  - Suggests substitution of medical marijuana to opioids
  - Medical marijuana laws (MMLs) led to lower rates of opioid use and misuse, lower prescriptions, less hospitalizations for opioid use disorder (OUD) and require more studies
  - Nationwide studies showed a decrease in opioid overdose deaths, hospitalizations and prescriptions in MML states
- CUD as classified by DSM-IV remains undertreated in the US
  - Physicians should screen patients with substance use disorder (SUD) for cannabis use and whether cannabis use/withdrawal might be causing a cycle of anxiety/depressive disorder

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Legal Status

33 legal medical marijuana states and DC
11 legal and recreational marijuana states and DC


Legal Status of Medical Marijuana

- Medical marijuana is legal in 33 states, the District of Columbia, Guam and Puerto Rico
- The remaining 17 states passed laws legalizing CBD oil with no or minimal psychoactive THC component (Alabama, Georgia, Indiana, Iowa, Kansas, Kentucky, Mississippi, North Carolina, Oklahoma, South Carolina, South Dakota, Tennessee, Texas, Utah, Virginia, Wisconsin, Wyoming)
- Recreational marijuana is legal in 11 states and the District of Columbia (Alaska, California, Colorado, Illinois, Maine, Massachusetts, Michigan, DC, Nevada, Oregon, Vermont, Washington)

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Legal Status of CBD Oil in the United States

- CBD oil contains trace amounts of THC (<3%) and are rich in CBD. They are processed from hemp
- CBD oil is legal and readily obtainable in all 50 states

Can Doctors Recommend Cannabis?

Physicians can recommend cannabis but...

- Cannabis is a Schedule I substance that is illegal for physicians to prescribe including states where medical marijuana is legal
  - In MML states, doctors can write a "recommendation" for cannabis plant for a patient suffering from a qualifying condition approved by the state
  - This physician recommendation is protected by the first amendment
  - After physician writes a recommendation for medical marijuana, patient must register in the state database and obtain a marijuana ID card and obtain from a marijuana dispensary
  - Having a marijuana ID card allows patients to obtain, grow, possess marijuana but does not shield patients from the federal legislation
  - Doctors are hesitant to recommend a product which form, strength, type is not defined and recommendations for delivery and type of product is made by dispensary personnel
  - Patient can generally not travel across state lines or internationally with prescribed MM


Which Cannabis Formulation to Recommend?

- Cannabis may contain contaminants such as pesticides and molds
- Some states require that doctors who recommend marijuana have an existing bona fide relationship with their patients to counter the increase in doctors recommending marijuana, or “pot docs” phenomenon in MML states
- There are no trusted resources such as package inserts for medical marijuana, states have no requirements for clinical training for doctors who write recommendations for marijuana

Patient License to Obtain Cannabis

Qualifying conditions approved for patients to obtain cannabis

- Patients must have a doctor certify that they have a qualifying condition then apply for a license from the state
- The National Academies of Science and Engineering (NAS) 2017 published report about therapeutic benefits and risks of cannabis and found conclusive evidence of benefit in:
  - Chronic pain, MS associated spasticity, nausea and vomiting due to chemotherapy
  - Considered as qualifying conditions by MML states, in addition to other conditions where there are mixed evidence of efficacy (anxiety or depression)
  - Chronic pain has been historically the most reported patient qualifying condition, followed by muscle spasms for multiple sclerosis, PTSD, and cancer
  - Qualifying conditions and symptoms may differ by state and be more stringent than others


Marijuana Products: The Cannabis Genus

- The three species Cannabis Sativa, Cannabis Indica, Cannabis ruderalis contain variable amounts of THC and different ratios of THC to CBD
- THC and CBD exist in various concentrations according to the cannabis plant source. Cannabis Sativa has the highest amount of THC, especially in the flowers or buds
- Delta 9-tetrahydrocannabinol (THC) is the most studied compound and responsible for the physical and psychotropic effects of cannabis
- Cannabidiol or CBD is the non psychoactive cannabinoid
- Cannabis containing high levels of delta-9 THC, the psychoactive cannabinoid, and low levels of CBD is referred to as marijuana
- Cannabis with high levels of CBD and very low levels of THC is referred to as industrial hemp
Active Compounds in Cannabis

- The most studied compounds of the plant are THC, CBD, and cannabinol (CBN), canabigerol (CBG)
- Delta 9 THC exerts psychotropic effects of cannabis through suppression of glutamate and GABA release
- There are 400 components in the cannabis plant, including terpenes, flavonoids, phenols, amino acids, vitamins, proteins, steroids, and many other substances
- Terpenes possess a range of properties including anti-inflammatory, anti-anxiety, anti-oxidant, anti-neoplastic, anti-bacterial, anti-malarial properties

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Marijuana Products
Cannabis Sativa

- Routes of Administration
  - Smoking or inhalation
  - Oil for sublingual administration
  - Oral or edible products
  - Topical
Endogenous Cannabinoids

The Endocannabinoid System

▪ Is an old evolutionary system from vertebrates with important physiological functions in the body and is widely distributed throughout the brain and spinal cord

▪ Modulates physiological processes including inflammation, appetite regulation and metabolism, immunity, memory, pain perception, psychiatric disease, psychomotor behavior, stress and emotion, sleep/wake cycles

▪ Endogenous cannabinoid receptor ligands (endogenous cannabinoids)
  ▪ Arachidonylethanolamine (anandamide or AEA)
  ▪ 2-arachidonoylglycerol (2-AG)

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Phytocannabinoids

CDB versus THC

▪ CBD does not bind to CB1 and CB2 receptors but interacts with different receptors, enzymes and channels that ultimately exert analgesic, anti-epileptic, anti-emetic, anxiolytic, anti-inflammatory, anti-psychotic effects

▪ CBD and THC are strong anti-oxidants and reduce neurotoxicities

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**Cannabinoid Receptors CB1 and CB2**

- CB1 and CB2 are located presynaptically and modulate neurotransmitter release (peripheral and central nerve terminals)
  - CB1 is located on presynaptic on peripheral and central nerve terminals, CB2 in peripheral tissues
  - CB2 is concentrated in peripheral tissues and immune cells influence cytokine release and cell migration, and to a lesser extent in brain regions in PAG and neuronal subtypes (astrocytes microglia and oligodendrocytes)
- Endocannabinoids are arachidonic acid derivatives produced on demand in the post-synaptic terminals in response to cellular needs, and simultaneous cross talk with other pathways also occurs

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**The Endocannabinoid System**

- Endocannabinoids AEA and 2-AG are produced in the postsynaptic cells.
  - They bind and activate CB1 receptors located on the pre-synaptic neurons in the brain and nervous system.
  - Activation of the CB1 receptors leads to suppression of neurotransmitter release from intracellular presynaptic vesicles.
  - Neurotransmitter modulation by AEA and 2-AG is thought to produce physiologic responses in the body.
  - Cannabidiol (CBD), from the Cannabis plant, influences CB1 receptors without binding to or activating them.
  - CBD may raise the synaptic levels of endocannabinoids, and hence increase their physiologic actions, by inhibiting their breakdown.

Modulation of the CB1 and CB2 Receptor Pathways

- CB1 activation in the CNS inhibits neurotransmitter release of GABA, serotonin, dopamine, acetylcholine, noradrenaline, and other substances at synapses (inhibitory and excitatory)
- CB1 receptor is most abundant G-protein coupled receptors in the peripheral and central nervous systems
- CB1 receptors are 10 times more concentrated and co-located with opioid receptors, and augment opioid effect synergistically and potential opioid dose sparing
- Cannabinoid receptor agonist leads to endogenous peptide release
  - Chronic delta 9-THC leads to increase endogenous opioid peptide release in spinal and supraspinal structures involved in pain perception
  - In the cardiopulmonary centers of the brain, CB1 receptors are less concentrated than opiate receptors, that is why respiratory depression is less likely than with opioids

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Therapeutic Properties of the Endocannabinoid System

**Analgesic properties through CB1 receptors**

- Cannabinoids including THC anti-nociceptive effects in the PAG gray matter, the main area in the brain responsible for migraine generation, and in ascending and descending pain generation
- Cannabinoid analgesic properties are transmitted through the CB1 receptors in the brain, spinal cord, and peripheral nerves, and in areas of the brain involved in pathophysiology of migraine (PAG, RM, nucleus trigeminal caudalis, trigeminal ganglia)
- Endogenous cannabinoid AEA modulate pain signaling in CNS, inhibits vasodilation from via modulation of effects of CGRP, nitric oxide, capsaicin, these effects are reversed by cannabinoid antagonism
- AEA have inhibitory effects on serotonin typ3 (5HT3), suggesting a role in emesis and analgesia
- Endogenous cannabinoids anti-nociceptive effects happen in isolation or through simultaneous stimulation of opioid receptors

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# Conclusions of the Institute of Medicine 2017 Report

<table>
<thead>
<tr>
<th>Conclusive or substantial evidence for the benefits of use of cannabis</th>
<th>Conclusive or substantial evidence for the risks of use of cannabis</th>
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<tbody>
<tr>
<td>Treatment of chronic pain in adults (cannabis)</td>
<td>Worsening of respiratory symptoms with long term cannabis smoking</td>
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<td>Antiemetics in CINV (oral cannabinoids)</td>
<td>Increased risk of motor vehicle crashes</td>
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<td>Patient reported MS related spasticity symptoms (oral cannabinoids)</td>
<td>Prenatal cannabis use results in lower birth weight</td>
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<td>)</td>
<td>Development of schizophrenia and other psychoses, highest risk among heavy users</td>
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<td>)</td>
<td>Being male and smoking cigarettes lead to progression of cannabis use and problem cannabis use later, initiating cannabis use early onset lead to cannabis problem use</td>
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**Conclusions of the Institute of Medicine 2017 Report**

- The National Academies of Sciences, Engineering and Medicine (previously IOM) in its 2017 published report stated
  - **Moderate evidence**
    - Improves sleep outcomes in patients with chronic pain, fibromyalgia, obstructive sleep apnea, MS
    - Impaired cognitive domains of learning, memory, attention with acute cannabis use
    - Increases symptoms of mania in patients with bipolar, increased risk of depressive disorders, increased risk of suicidal ideation (heavy users)
  - **Limited evidence of association between cannabis use**
    - Triggering of acute myocardial infarction, ischemic stroke, subarachnoid hemorrhage, decreased risk of metabolic syndrome and diabetes
    - Progression of liver fibrosis or hepatic disease in HCV
    - Pregnancy complications and admission to NICU

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Health Canada Report on Cannabis Therapeutic Uses

- Palliative Care: use of cannabis in CINV, anorexia/cachexia, severe intractable pain, severe depressed mood and anxiety, insomnia
  - Prescription cannabinoids (dronabinol, nabinol, nabiximols) and cannabis may alleviate symptoms in palliative care settings and allow reduced dosing of other medications used for the relief of these symptoms

- Wasting syndrome (cachexia from tumor or infection) and loss of appetite (anorexia) AIDS and cancer, anorexia nervosa
  - Cannabis and dronabinol increase appetite and caloric intake and promote weight gain in AIDS. Modest effects in patients with cancer and weak in patients with anorexia nervosa


Health Canada Report on Cannabis Therapeutic Uses

- Multiple sclerosis, amyotrophic lateral sclerosis (ALS), spinal cord injury
  - THC, CBD, nabiximols improve symptoms of tremor, spasticity, inflammation
  - Cannabis and cannabinoids THC, CBD, nabiximols and dronabinol result in improvement in symptoms of MS and spinal cord injury (SCI) such as pain, spasticity, spasms, sleep, bladder dysfunction
  - Evidence from pre-clinical studies in ALS that cannabis delay disease progression and prolong survival, and mixed results from clinical studies

- Epilepsy
  - Oral CBD (epidiolex) efficacious and tolerable in drug resistant epilepsy in Dravet and Lennox Gastraut syndrome. FDA approved for this indication in children >2 years
  - CBD oil and herbal supplements associated with reduced frequency of seizures and increase in QOL in adolescents with drug resistant epilepsy

Health Canada Report on Cannabis Therapeutic Uses

- Pain
  - Acute pain
    - Smoked, oral THC, cannabis extract, nabilone, mixed results in clinical studies with low oral THC having analgesic effect and high dose causing hyperalgesia
  - Chronic pain: neuropathic pain, chronic non-cancer pain
    - Consistent evidence of efficacy of smoked and vaporized cannabis, nabiximols, dronabinol in chronic pain, and in treatment resistant cases
    - Cancer pain: cannabinoids dronabinol and nabiximols modest analgesic effect of dronabinol and modest and mixed analgesic effect of nabiximols on cancer pain
  - Opioid sparing effects with the use of cannabinoids suggested through case studies
  - Headache and migraine limited and mixed results


Health Canada Report on Cannabis Therapeutic Uses

- Arthritis and Musculoskeletal Disorders
  - CB1 and CB2 activation alleviates OA, THC and CBD relieve symptoms of rheumatoid arthritis (RA), modest effect of nabiximols on RA
  - Limited clinical evidence about dronabinol and nabilone showing modest effect on decreasing pain, anxiety, improving sleep

- Movement Disorders
  - Dystonia
    - CB1-2 agonists alleviate dystonia-like symptoms, CBD delays dystonia progression
  - Parkinson’s disease
    - Mixed evidence from clinical studies of cannabinoid effects on symptoms
  - Tourette’s syndrome
    - Oral THC may improve symptoms of Tourette’s

### Health Canada Report on Cannabis Therapeutic Uses

<table>
<thead>
<tr>
<th>Glaucoma</th>
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<tbody>
<tr>
<td>Oral administration of THC reduces intraocular pressure (IOP) while oral administration of CBD may increase IOP</td>
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<tr>
<th>Asthma</th>
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<tr>
<td>Smoked or vaporized cannabis may act as a lung irritant and worsen asthma symptoms</td>
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<th>Stress and psychiatric disorders</th>
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<tr>
<td>Anxiety and Depression</td>
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<tr>
<td>Low doses of THC have anxiolytic, mood-elevating effects; high doses of THC anxiogenic and mood lowering effects</td>
</tr>
<tr>
<td>Prescription cannabinoids and THC-containing cannabis improve symptoms of anxiety in patients with other chronic diseases (AIDS/HIV, MS, chronic neuropathic pain)</td>
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<tr>
<td>CBD may have anxiolytic effects, cannabis with 1:1 THC:CBD attenuates mood perturbations</td>
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<td>Cannabis and THC-rich cannabis, THC increases the risk of schizophrenia and psychosis</td>
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<tr>
<td>CBD may attenuate THC-induced psychosis</td>
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<th>Alzheimer’s disease and dementia</th>
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<tr>
<td>THC and CBD protect from oxidative stress and inflammation in animal models of AD</td>
</tr>
<tr>
<td>Oral THC and nabilone, improves symptoms associated with AD (behavior, sleep, agitation, nocturnal motor activity, resistiveness)</td>
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<th>Inflammation</th>
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<tr>
<td>Mixed evidence on role of cannabinoids (THC, CBD) may be protective or harmful in modulate of inflammation in skin diseases such as dermatitis, psoriasis and pruritus</td>
</tr>
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### Health Canada Report on Cannabis Therapeutic Uses

- **Gastrointestinal Disorders** (irritable bowel syndrome, inflammatory bowel disease, hepatitis, pancreatitis, metabolic syndrome/obesity)
  - Irritable bowel syndrome
  - Cannabinoids slow GI transit
  - Cannabinoids (CB1-2 receptor agonists, THC, CBD, others) may limit intestinal inflammation and disease severity
  - Cannabis use associated with acute pancreatitis, limited evidence in the treatment of acute or chronic pancreatitis

- **Antineoplastic**
  - THC, CBD, CBG, CBDA block growth of cancer cells in vitro and anti neoplastic properties in vivo
  - Limited evidence from observational studies that cannabis use was used to alleviate symptoms of cancer such as weight loss, pain, depression, chemosensory alterations

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### Acute Intoxications

- **Psychological effects**: visual hallucinations, anxiety, depression, paranoid, psychosis for 4 to 6 hours

- **Physical effects**: rapid heartbeat, dryness of mouth and throat, drowsiness, muscular incoordination

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Smoked and Vaporized Cannabis

- Fastest onset of action
- Lipophilic delta 9 THC
- Psychotropic effect start within seconds to minutes, lasting 2-3 hours
- Vaporized cannabis is believed to remove toxic components
  - Heating cannabis suppresses irritating respiratory toxins and still allow active cannabinoid to be formed
  - More efficient extraction of delta-9 THC
  - Advantageous to smoking and avoids or reduced amount of toxic byproducts such as tar, carbon monoxide, polycyclic aromatic hydrocarbons

Dangers of Vaporized Cannabis

- The perceived safety of vaporized cannabis led to a rise in the consumption of vaped cannabis, vaped THC, and proliferation of devices and pens
- Rise in lung illnesses was reported and fears from the scientific community claiming that composition of cannabis within devices was unknown and could not be tested
  - 2,500 vaping-related illnesses and 54 deaths in the US have been reported as of December 2019
- Safety and toxicity of vaped cannabis is unknown and may lead to lung diseases or cancer
- Vaping oils contain additives, solvents, flavor enhancers, vitamin E acetate that are lung toxic
- Vaping THC is not recommended per health authorities

Dosage of Smoked Cannabis

- A typical joint contains 500mg to 1g of cannabis plant matter
  - THC content vary between 7.5 and 225mg (1-30%)
  - CBD content between 0 and 180mg (0-24%)
- Clinical trials typically evaluate 800mg and 900mg (mean weight of cannabis in a joint is 320mg)
- Plasma levels of THC >10ng/ml are required for suppression of CINV or 5-10ng/ml
- 25-50mg/puff of cannabis plant material is obtained through the smoke. The actual THC that reaches blood concentration is 25% of the total THC obtained through smoking cannabis
- Most patients smoke 1-3g (compared to a recommended 400mg)
- Recommendation of medical marijuana is 1 inhalation of 9% THC that can be increased to 1 inhalation 4 times a day
  - No driving 3 to 4 hours after inhaled marijuana, 6 hours after oral, and 8 hours if a high is noted

Pharmaceutical Cannabinoids - Oral Cannabis

- Slower onset of action, psychotropic effects start at 30-90 minutes
- Leads to 5 to 6 times lower blood concentration of THC than smoked cannabis
- Longer duration of action and longer lasting effects of 4-12 hours
- Delta-9 THC is added to and ingested through foods such as brownies, cakes, oils, butters, cookies, and tea
### Pharmaceutical Cannabinoids – Oral Forms of Delta-9 THC from *Cannabis Sativa*

- **Dronabinol (Marinol®, Syndros®)**
  - FDA-approved for chemotherapy-induced nausea/vomiting, AIDS-associated anorexia and weight loss (Schedule III)
  - Off-label use for moderate to severe obstructive sleep apnea
  - Marinol® is available in 2.5, 5, and 10mg tablets taken 1-2 times per day
  - Syndros® is available in 5mg/ml solution, calibrated syringe of 5mg
- **Anorexia**
  - Marinol® 2.5mg 2 times per day, dosage range is 2.5-40mg per day
  - Syndros® 2.1mg twice a day
- **CINV**
  - Marinol® 5mg/m² for 4 to 6 doses per day
  - Syndros® 4.2mg/m² for 4 to 6 doses per day
- **Avoid in patients with a psychiatric history, monitor patients with a history of seizure, may cause hypertension, hypotension, tachycardia or syncope**


### Pharmaceutical Cannabinoids – Oral Forms of Delta-9 THC from *Cannabis Sativa*

- **Nabilone (Cesamet®)**
  - FDA approved for chemotherapy induced nausea/vomiting (Schedule II)
  - Available in 0.25, 0.5, 1mg tablets
  - Dosage schedule: taken 3 times a day
  - Dose range 0.2-6mg/day
  - Can cause tachycardia and hypotension
  - Patients should be warned not to drive or operate heavy machinery
  - Should not be taken with alcohol and sedatives
  - Caution in patients with a history of psychiatric illness


Marijuana: Everyone Is Using It, So We Better Know About It

Pharmaceutical Cannabinoids – Cannabis Tincture of THC and CBD

- Nabiximols (Sativex®)
  - Approved in the UK and Canada
  - FDA fast track designation for the treatment of pain in patients with advanced cancer not adequately controlled on maximally tolerated opioid therapy
  - Made from a cannabis tincture containing equal amounts of THC and CBD
  - Dosage form: oro-mucosal spray delivers 2.5mg THC and 2.5 mg CBD, and other cannabis compounds
  - Dosage range 1-16 sprays per day
  - Peak concentration at 2-4 hours
  - Lower blood concentrations than smoked THC


Pharmaceutical Cannabinoids – CBD Oil

- Cannabidiol (Epidiolex®)
  - FDA approved in children 2 years and older for seizures associated with Dravet and Lennox-Gastaut syndromes
  - Oral solution 100mg/ml of 98% CBD oil
  - Dosage: 2.5mg/kg taken twice a day increased after 1 week to maintenance dosage of 5mg/kg twice a day

- Adverse events
  - Transaminase elevations
  - Monitor patients for somnolence or sedation, monitor for suicidal ideation
  - Gradually withdraw Epidiolex to minimize seizure or status epilepticus


**Adverse Events**

- **Central Nervous System**
  - THC predominant cannabis may have acute cognitive effects and induce behavioral changes, lead to structural changes in white and gray matter of the brain
  - Psychomotor functioning, driving
    - Chronic cannabis use may lead to chronic effects and impair driving functions and chronic psychomotor impairment, even when tolerance develops to its use, dose response effect with increasing THC doses leading to increased risk of motor vehicles crashes and accidents leading to injuries and death
    - Chronic heavy use of THC predominant cannabis is associated with anxiety, panic, depression and bipolar disorder
    - Acute exposure to cannabis may lead to acute, transient cognitive effects like psychosis

- **Cardiovascular, Vascular, and Cerebrovascular Health**
  - Limited evidence showing chronic cannabis use may be associated with harmful effects on vascular, cardiovascular, cerebrovascular health including myocardial infarction, stroke, arteritis

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### Adverse Events

#### Cannabis in Pregnant Women

- Results of a meta-analysis show that infants born to cannabis using mothers are more likely to be anemic, low birth weight, require neonatal intensive care.
- Prenatal marijuana exposure linked to impaired executive functioning in school, poor childhood outcomes.
- These results might be confounded with the fact that mothers use other substances concomitantly.
- Not recommended in pregnant women, women of childbearing age not on contraception, or breastfeeding.
- The American College of Obstetrics and Gynecology (ACOG) recommends pregnant women should receive recommendation to discontinue the use of cannabis.


### Clinically Significant

#### Drug Interactions

- Additive side effects when cannabis used concomitantly with CNS depressants such as sedative, hypnotics, alcohol.
- Additive effects with CYP3A4 and CYP2C9, CYP2C19 enzyme inhibitors:
  - Anti-depressants, proton pump inhibitors, antifungals, HIV protease inhibitors, grapefruit juice, isoniazid, amiodarone, calcium antagonists, macrolides, can increase THC levels and the risk of side effects.
  - Tachycardia, hypertension has been reported with concomitant use of amitriptyline, amoxapine, desipramine, amphetamines, cocaine.
  - Enzyme inducers such as carbamazepine, phenobarbital, phenytoin, St John’s Wort, rifabutin, primidone can decrease THC bioavailability and effectiveness.

Marijuana: Everyone Is Using It, So We Better Know About It

Precautions and Safety

<table>
<thead>
<tr>
<th>Suggested precautions for the use of cannabis and cannabinoids and the need to evaluate benefits vs risks</th>
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<tbody>
<tr>
<td>Use with caution in individuals with substance abuse</td>
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<tr>
<td>Use with caution in individuals taking sedatives, alcohol, or psychoactive drugs</td>
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<tr>
<td>Use with caution in patients in severe renal or liver disease including hepatitis C</td>
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<tr>
<td>Avoid use in people under the age of 18 years</td>
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<tr>
<td>Avoid use while driving or operating heavy machinery</td>
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<tr>
<td>Avoid use in people with cannabinoid or smoke hypersensitivity</td>
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<tr>
<td>Avoid use in patients with cardiopulmonary disease because of risk of hypotension, hypertension, tachycardia, syncope</td>
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<tr>
<td>Avoid use in people with pulmonary disease including asthma or chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Avoid use in people who are pregnant or breastfeeding, and women of childbearing age who are not taking contraception</td>
</tr>
<tr>
<td>Avoid in patients with psychiatric disease or with a history of psychiatric illness, particularly schizophrenia</td>
</tr>
</tbody>
</table>

Baron, EP. A comprehensive review of medicinal marijuana, cannabinoids, and therapeutic implications in medicine and headache: what a long strange trip it has been. Head Curr. 2015; 885-916.

Summary

- The uses of medical marijuana have been cited in ancient literature and are increasingly being recognized in the medical community
- Delta THC and CBD are the two essential active compounds extracted from Cannabis Sativa, THC being the psychoactive cannabinoid
- Federal restrictions on cannabis places limits on research by scientists and restricts prescribing medical cannabis by physicians and stand in contradiction with state legislation allowing medical marijuana
- Efficacy of medical marijuana have been established in chronic pain, AIDS-associated anorexia, chemotherapy induced nausea and vomiting, multiple sclerosis-related spasticity, and seizures related to Lennox-Gastaut and Davet syndromes
  - FDA approved formulations of synthetic cannabinoids dronabinol, nabiximols, nabilone are marketed for CINV and AIDS-related anorexia and cannabidiol (CBD) oil (Epidiolex) for seizures
- Cannabis must be used in caution in individuals with a history of psychiatric diseases and substance use, pulmonary diseases, cardiovascular diseases, and in pregnant women
- Physicians, healthcare providers, patients must be educated on the benefits and risks of medical marijuana and cannabis