

## Medical Cannabis

Drug Interactions and Adverse Effects

## Learning Objectives

- ▶ Review the New Mexico Cannabis Program.
- ▶ Describe how cannabis works in the body.
- ▶ Identify available dosage forms and their benefits and cautions.
- ▶ Identify common adverse effects of medical cannabis use.
- ▶ Describe medical cannabis drug interactions.
- ▶ Identify contraindications to medical cannabis use.
- ▶ Describe common effects of cannabis and review uses in specific disease states.

## Medical Cannabis in New Mexico

- ▶ Lynn and Erin Compassionate Use Act, N.M. Stat. Ann. § 30-31C-1 (2007)
  - ▶ N.M. Stat. Ann. §26-2B-3(F) (2007)
- Under the Medical Cannabis program, patients are allowed to possess up to 6 ounces of medical cannabis over a 90 day period. Limit can be raised if necessary on case by case basis.
- With a Personal Production License, a patient is allowed to grow up to 16 plants at home, with only 4 being mature and 12 being immature and any given time.
- As of April 2018, over 50,000 patients were enrolled in the Medical Cannabis Program.
- ▶ 46% increase from last year.

## New Mexico Medical Cannabis Program

- ▶ Patient Qualifying Criteria
  - ▶ The patient has a medical condition that is listed under the qualifying medical conditions for the Medical Cannabis Program.
  - ▶ The patient's medical condition is chronic and debilitating.
  - ▶ Standard medical treatments have failed to provide adequate relief for the patient.
  - ▶ The benefits of using medical cannabis outweigh the side effects.

## New Mexico Medical Cannabis Program: Application Process

The application is sent to the New Mexico Department of Health. It must include:

- ▶ Certification form signed by a medical practitioner.
- ▶ Must have a valid New Mexico Driver's License or state ID.
- ▶ Signed release of information form.
- ▶ Medical records proving that you have the medical condition stated on the application.

The NM Department of Health has 30 days to review the application. If the patient is approved, they will receive an ID card in the mail. If denied for reasons other than application issues, the patient must wait 6 months to apply again.

## Qualifying Conditions

- ▶ Amyotrophic Lateral Sclerosis (ALS)
- ▶ Cancer
- ▶ Crohn's Disease
- ▶ Epilepsy
- ▶ Glaucoma
- ▶ Hepatitis C infection currently receiving antiviral treatment (proof of current antiviral treatment required)
- ▶ HIV/AIDS
- ▶ Huntington's Disease
- ▶ Hospice Care
- ▶ Inclusion Body Myositis
- ▶ Inflammatory autoimmune-mediated arthritis
- ▶ Intractable Nausea/Vomiting
- ▶ Multiple Sclerosis
- ▶ Damage to the nervous tissue of the spinal cord, with (proof of objective neurological indication of intractable spasticity required)
- ▶ Painful Peripheral Neuropathy
- ▶ Parkinson's disease
- ▶ Post-Traumatic Stress Disorder
- ▶ Severe Chronic Pain
- ▶ Severe Anorexia/Cachexia
- ▶ Spasmodic Torticollis (Cervical Dystonia)
- ▶ Ulcerative Colitis

## Introduction to Cannabis

- ▶ DEA Schedule I
- ▶ Also known as marijuana, pot, weed, dope, gānga, etc.
- ▶ Over 99% of medical cannabis is derived from *Cannabis sativa* and *Cannabis indica* plants despite wide variety of availability.
- ▶ Active chemicals responsible for the medicinal effects of cannabis are called cannabinoids.



[Golden State Collective Cannabis Laboratories]

## Compounds in Cannabis

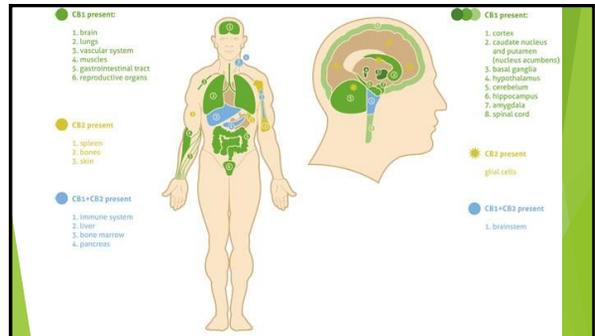
Over one hundred cannabinoids have been isolated.

- ▶ The most important cannabinoids are tetrahydrocannabinol (THC) and cannabidiol (CBD). THC known to produce psychoactive effects and CBD producing relaxing effects.
  - ▶ *Sativa*'s cannabinoid profile is characterized by high THC levels and low to no CBD levels.
  - ▶ *Indica*'s cannabinoid profile is characterized by a balanced mix of THC with slightly higher levels of CBD.
  - ▶ Little is known about the effects of other cannabis constituents.
- ▶ Terpenoids and flavonoids are other cannabis constituents. They are responsible for the strong odor. (Corral, 2007)
- ▶ As many as 560 other constituents occur in the plant (EISOHLY et al. 2017)

## Site of Action: The Endocannabinoid System (ECS)

The ECS consists of:

- ▶ Cannabinoid receptors
  - ▶ CB1 receptors are primarily found in the brain and CNS.
  - ▶ CB2 receptors are mostly in the peripheral organs.
- ▶ Endocannabinoids that bind to the receptors: anandamide and 2-AG
  - ▶ THC and CBD are plant cannabinoids that mimics the binding of endocannabinoids.
- ▶ Metabolic enzymes that break down endocannabinoids after they are used
  - ▶ FAAH
  - ▶ MAGL
  - ▶ These enzymes do not break down cannabinoids which is why they tend to stick around longer.



## Common Modes of Administration & Formulations

Inhalation by smoking or vaporization	Oral	Ora-Mucosal or Sublingual	Topical or Rectal
Herbal Cannabis, resin, concentrates	Prescription cannabinoids, edibles, tinctures	Lollipops, lozenges, nabiximols	Herbal cannabis, resin, concentrates

## Pros and Cons of Administration and Formulations

Method	Smoking	Vaporizing	Edibles, oil, capsules, etc.	Tinctures, gum, & mints	Topical	Transdermal	Suppositories	Raw Cannabis (Juicing)
PROS	-Quick Dosing	-Quick dosing -Less lung/throat irritation -Can target specific cannabinoids	-Longer effect -Easier to maintain steady blood levels	-Quick onset and easy to dose -Cost effective -Absorption can be slowed	-Great for local pain relief and many skin ailments -No psychoactive effects	-Continuous dosing over time -Can be found in the form of THC or CBD	-Pain relief with no psychoactive effects -Good for nausea and for cancer patients who cannot tolerate THC	Positive health effects of cannabinoids without psychoactive effects
CONS	-Throat/lung irritation -40% is lost	-Costly -Intense flavor	-Difficult to dose -Start low, go slow	-Alcohol base can burn -Easily causes stains		-Costly -Dosing dependent on body fat	-May cause drowsiness -Uncomfortable application	Leaves and buds must be fresh

## Common Adverse Effects

- ▶ Altered sense of time
- ▶ Anxiety
- ▶ Ataxia
- ▶ Bronchitis
- ▶ Changes in visual perceptions
- ▶ Cough
- ▶ Decreased eye blink rate
- ▶ Dizziness
- ▶ Dry Mouth
- ▶ Dysphoria
- ▶ Reddened eyes
- ▶ Reduced coordination
- ▶ Reduced tear flow
- ▶ Sedation
- ▶ Slowed pupillary response to light

## Drug-Cannabis Interactions

Nature of Interaction	Interacting Agents
Enhanced CNS depression	All CNS depressants
Enhanced cardiotoxicity	Sympathomimetics: stimulants (caffeine, amphetamine, methylphenidate, cocaine, etc.), beta adrenergic agonists, decongestants, etc. Anticholinergics: tricyclic antidepressants, anticonvulsants, cyclobenzaprine, antihistamines, overactive bladder products, etc.
Decreased platelet aggregation, prolonged bleeding	All Anticoagulants Note: also interferes with warfarin due to decreased protein binding
Antiestrogenic effects	Estrogen-based contraceptives or replacement therapy

## Drug-Cannabis Interactions (cont.)

Metabolic Drug-Cannabis Interactions	Interacting Agents
Decreased CYP2E1 substrate effect	Acetaminophen, Anesthetics, Theophylline, etc.
cannabis may increase CYP3A4 substrate effect	Lovastatin, Clarithromycin, Cyclosporine, Diltiazem, Estrogens, Indinavir, Triazolam, etc.
CYP3A4 inducers decrease cannabis effect	Carbamazepine, Phenobarbital, Phenytoin, Rifampin, etc.
CYP3A4 inhibitors increase cannabis effect	<b>Strong:</b> Boceprevir, Clarithromycin, Darunavir, Indinavir, Itraconazole, Ketoconazole, Lopinavir, Nefazodone, Ritonavir, etc. <b>Moderate:</b> Aprepitant, Diltiazem, Erythromycin, Fluconazole, Grapefruit juice, Imatinib, Verapamil

## Drug-Cannabis Interactions (cont.)

Metabolic Drug-Cannabis Interactions	Interacting Agents
Cannabis increases CYP2C9 inhibitor effect	Capecitabine, Fluorouracil, Gemfibrozil, Sulfisoxazole, etc.
Cannabis (smoked) decreases CYP1A2 substrate effect	Duloxetine, Estrogens, Mirtazapine, Melatonin, Olanzapine, Ropinirole, Theophylline, etc.
Cannabis inhibits p-glycoprotein substrate efflux/increases effect	Chemotherapeutic agents, Antifungals, Protease inhibitors, H2 antagonists, Digoxin, Corticosteroids, Erythromycin, Cyclosporine, etc.

## Drug Interactions Cytochrome P450 Enzymes

- ▶ THC
  - ▶ Metabolized by CYP3A4 and CYP2C9
  - ▶ CYP3A4 metabolizes about a quarter of all drugs. (Stout SM, Cimino NM. 2014)
  - ▶ Ketoconazole, CYP3A4 inhibitor, was reported to increase peak concentration and area under the curve of THC by 1.2 and 1.8 fold.
  - ▶ Other CYP3A4 inhibitors are expected to have the same effect. Examples include: clarithromycin, erythromycin, cyclosporine, verapamil, itraconazole, voriconazole, and boceprevir
  - ▶ Rifampin, a CYP3A4 inducer, has been reported to reduce THC levels by 20-40%.
- ▶ CYP2C9-Poor Metabolizers have been shown to have 3-fold higher concentrations of THC compared to CYP2C9-Extensive Metabolizers (Sachse-Seeboth C et al. 2009)
- ▶ CYP2C9 inhibitors expected to inhibit THC elimination: amiodarone, cimetidine, cotrimoxazole, metronidazole, fluoxetine, fluvoxamine, fluconazole, and voriconazole

## Drug Interactions Cytochrome P450 Enzymes

- ▶ CBD
  - ▶ Substrate of CYP3A4 and CYP2C19
  - ▶ Like THC, ketoconazole was found to increase plasma concentration of CBD by 2-fold, while rifampin reduced CBD levels by 50-60%. CYP3A4 inhibitors and inducers are expected to have a similar effect.
  - ▶ A study done with CBD and omeprazole, a CYP2C19 inhibitor, showed no alterations in plasma concentrations. (Sachse-Seeboth C et al. 2009)

## Drug Interactions Cytochrome P450 Enzymes

- ▶ CYP1A2 induction
  - ▶ Smoking more than 2 joints of marijuana a week (but not oral administration) was found to increase the metabolism of theophylline and chlorpromazine, resulting in 50% decreased plasma concentration. (Jusko WJ, 1979)
  - ▶ A case report noted increased warfarin response in a patient who reported smoking 4 to 5 joints/week. (Yamreudeewong W, 2009)
- ▶ Theoretically, cannabis can decrease serum concentrations of clozapine, duloxetine, naproxen, cyclobenzaprine, olanzapine, haloperidol, and chlorpromazine. (Flockhart 2007, Watanabe et al 2007)

## Drug-Cannabis Interactions: "Pain" Medications

Medication	Nature of Interaction	Potential Outcome
Acetaminophen	CNS depression CYP2E1	Sedation, impaired, etc. Decreased ABAP efficacy
NSAIDs	CNS depression Combined renal assault	Impaired, falls, renal impairment, etc.
Anticonvulsants	CNS depression Carbamazepine/CYP3A4	Impaired, falls, etc. Increased cannabis metabolism
TCAs	CNS depression Anticholinergic	Impaired, falls, etc. Increased HR, arrhythmia, slow GI, delirium
Other antidepressants	CNS depression	Impaired, falls, etc.
Opioids	CNS depression	Impaired, falls, respiratory depression, death (!)

## Clinical Aspects: Contraindications

- ▶ Contraindications
  - ▶ Psychosis - should only be used under well-monitored conditions using strains with minimal or no THC content. (Ko, G, 2016)
  - ▶ Bipolar Disorder - Kim et al. found that cannabis use was associated with lower rates of remission over a 2-year follow-up period. Minimal to no THC content recommended for these patients.
  - ▶ Cannabis allergies - minor rhinoconjunctivitis symptoms can be treated with antihistamines, decongestants, or steroids. Allergies are found in 8% of the general population. (Ko, G, 2016)

## Common Effects

## Appetite

- ▶ In mice, THC has been found to bind at the cannabinoid type-1 receptor located in the olfactory bulb. (Marsicano, G, 2014)
  - ▶ Binding at this receptor was found to promote food intake in fasted mice by increasing odor detection. Increasing the ability to smell the food lead them to eating more ft.
- ▶ The study suggests that THC manipulates the natural system and mimics the same sensation as when we are deprived of food.
  - ▶ Forcing the mice to fast for 24 hours dramatically increased natural levels of cannabinoids in the olfactory bulb.
- ▶ This process is thought to be the same in humans, but the full mechanism of appetite stimulation is still unknown.
- ▶ Cannabis is used to stimulate appetite in conditions such as cancer, anorexia, cachexia, and much more.

## Cannabis in Cardiovascular Disorders

Pros	Cons
Reduction in tobacco prevalence	Increase in HR/BP
Lower prevalence of obesity and diabetes among cannabis users	Postural hypotension
Modulation of common cardiovascular risk factors	Development of A. fib/ischemia
Associated with lower levels of fasting insulin	Increased acute coronary events
	Increased risk of stroke/TIA
	Development of ventricular tachycardia/fibrillation

[Coyal, H, et al. 2017]

## Cognition

- ▶ A 2016 study asserted that marijuana use improves executive function by improving symptoms of debilitating conditions such as chronic pain or anxiety that are believed to impair cognitive function. (Gruber, S et al. 2016)
- ▶ Executive function include the ability to plan, organize, solve problems, make decisions, remember, and control emotions and behavior.
- ▶ After 3 months of medical marijuana use, patients performed better on cognitive tasks.
  - ▶ All patients were adults aged 32 to 74, examined for an IQ of at least 75 and all had at least a high school diploma.

## Cognition (cont.)

- ▶ These are results from a 2011 literature review analyzing executive function in cannabis users 0-6 hours after use, 7 to 20 hours after use, and 3 weeks after use. (Crean, R et al. 2011)
- ▶ This information is great for helping patients understand cognitive liabilities with continued cannabis use.

A Summary of Research Findings on the Effects of Cannabis on Executive Functions

Executive Function Measured	Acute Effects	Residual Effects	Long-Term Effects
Attention/Concentration	Impaired (light users) Normal (heavy users)	Mixed findings	Largely normal
Decision Making & Risk Taking	Mixed findings	Impaired	Impaired
Inhibition/Impulsivity	Impaired	Mixed findings	Mixed findings
Working Memory	Impaired	Normal	Normal
Verbal Fluency	Normal	Mixed findings	Mixed findings

Note: Acute Effects denotes 0-6 hours after last cannabis use, Residual Effects denotes 7 hours to 20 days after last cannabis use, Long-Term Effects denotes 3 weeks or longer after last cannabis use.

## Lung Function

- ▶ Most patients who smoke marijuana also smoke tobacco products, making the effects of cannabis smoking difficult to understand.
- ▶ The effects of tobacco smoking are well known, including cough, sputum production, wheezing, shortness of breath, narrowing of airways.
  - ▶ Combining tobacco and cannabis appears to have synergistic adverse effects, increasing respiratory symptoms over tobacco use alone.
- ▶ The risk of COPD is not increased with smoking cannabis.
- ▶ The risk of lung cancer is not increased with smoking cannabis.
- ▶ Some studies have shown an increase in forced vital capacity (FVC) in cannabis smokers, suggesting bronchodilation.
  - ▶ Mechanism is not understood.

[Ribeiro, L et al. 2016]

## Nausea and Vomiting

- ▶ Dronabinol (Marinol) and Nabilone (Cesamet) are synthetic cannabinoids approved for the treatment of refractory nausea and vomiting associated with chemotherapy.
  - ▶ Despite being available for over 20 years, they are still not widely used.
- ▶ The dorsal vagal complex(DVC) in the brainstem is the regulator of nausea/vomiting.
- ▶ The DVC along with the GI tract have endocannabinoid receptors that have shown to have anti-emetic responses when activated by THC.
- ▶ Cannabis is used to treat nausea and vomiting in patients with cancer, patients currently undergoing hepatitis C treatment, etc.

## Pain: Nociceptive

- ▶ Pain can be weakened by reducing pain signals at the site of injury or by blocking the inflammatory process. Pain can also be weakened by dampening their effects as the signals travel from the spinal cord to the brain.
- ▶ THC and CBD work in all of these methods
- ▶ Long term use of THC can weaken effects due to overactivation of CB1 receptors.
  - ▶ It is recommended to use balanced THC and CBD products.

## Pain: Neuropathic

- ▶ Neuropathic pain relief is seen with the activation of CB1 receptors.
  - ▶ This suggests that the mechanism of pain relief is weakening the strength of pain signals in the spinal cord.
- ▶ Like in nociceptive pain, long term use of THC can weaken effects due to overactivation of CB1 receptors.
  - ▶ It is recommended to use balanced THC and CBD products.

## Reproductive Effects: Pregnancy and Lactation

- ▶ Cannabis use during pregnancy is **NOT** recommended.
- ▶ Use of cannabis during pregnancy may cause adverse effects on early neurodevelopment.
  - ▶ Fetuses exhibit CNS cannabinoid receptor type 1 as early as 14 weeks gestation.
  - ▶ Studies noted children exposed to marijuana in utero had lower test scores on visual problem solving, visual-motor coordination, and visual analysis.
- ▶ There is a possible increased risk of preterm birth.
- ▶ Lactation
  - ▶ THC and its metabolites are excreted in breast milk
  - ▶ Insufficient data to evaluate the effects of marijuana and metabolites on infants during lactation and breastfeeding, therefore, breastfeeding is discouraged while using.

[American College of Obstetricians and Gynecologists 2017]

## Reproductive Effects: Fertility

- ▶ Fertility effects in men
  - ▶ Some studies indicate that chronic use of marijuana may decrease plasma testosterone and decreases sperm count, concentration, and motility. (Reprotox.org, Metz and Stokrath 2015)
  - ▶ However, many of these studies did not take into account other lifestyle factors such as cigarette smoking, alcohol/caffeine intake, sexual behaviors, and use of other recreational drugs, which were all possible confounders. (Gundersen T, et al. 2015)

## Specific Disease States

### Amyotrophic Lateral Sclerosis (ALS)

- ▶ ALS is characterized by the breakdown of nerve cells that result in reduced functionality of the muscles.
- ▶ Medication and therapy can slow ALS progression and reduce symptoms, but there is no cure.
- ▶ In mice, cannabis was found to have antioxidative, anti-inflammatory, and neuroprotective effects.
  - ▶ This resulted in prolonged neuronal cell survival, delayed onset, and slower disease progression.
- ▶ Cannabis has since been used for symptom management of ALS including analgesia, muscle relaxation, bronchodilation, saliva reduction, appetite stimulation, and sleep induction.

[Carter, GT et al. 2010]

### Epilepsy

- ▶ Many patients with epilepsy can be controlled with conventional treatment approaches. Cannabis is **NOT** recommended for these patients.
- ▶ Open-label studies are currently being performed in the U.S. with Epidiolex (Devinsky, O. 2015)
  - ▶ Epidiolex is a purified, 99% oil-based CBD extract produced by GW Pharmaceuticals
  - ▶ 214 patients, all with epilepsy that did not respond to current available treatments.
  - ▶ Seizures decreased by ~54%
- ▶ Patients on clobazam seemed to have better response than those who were not on the medication.
- ▶ CBD has been reported to interact with the metabolites of valproic acid and clobazam resulting in adverse effects such as increased liver enzymes and excessive tiredness.

[epilepsy.com]

### Glaucoma

- ▶ The benefits do not outweigh the negative side effects.
- ▶ Smoking marijuana does lower eye pressure, however, only lasts 3 to 4 hours.
  - ▶ Other dosage forms have proven to be less effective.
- ▶ Keeping eye pressure low around the clock would result in 6-8 times/daily dosing, making it impossible to perform daily living activities.

[glaucoma.org, Updated Oct 2017]

## HIV/AIDS

- ▶ Cannabis has been used to combat the side effects of HIV, including weight loss, depression, anxiety, nausea, and loss of appetite.
- ▶ In 2017, a study was published that suggests THC aids in slowing disease progression from HIV to AIDS. (Henriquez, JE. 2017)
- ▶ THC suppresses secretion of interferon alpha by plasmacytoid dendritic cells (pDCs).
  - ▶ Prolonged pDC function is strongly correlated with HIV developing into AIDS.

## Hospice Care

- ▶ The focus of hospice care include pain and symptom control.
- ▶ Cannabis is used to help manage pain, anxiety, spasms, nausea, appetite, and sleep problems.
- ▶ Cannabis has not been approved in all states for hospice care, however it IS approved in New Mexico.

## Inflammatory Bowel Disease Ulcerative Colitis/Crohn's Disease

- ▶ Cannabis is reserved for symptomatic control in patients with severe IBD refractory to conventional treatments.
- ▶ CB1 and CB2 activation has resulted in inhibitory pathways in the GI tract through reduction of vagal cholinergic tone in mice. (Ahmed, W. 2016)
- ▶ It is unclear how effective cannabis use is in humans due to lack of research.
- ▶ The distribution of receptors in the GI tract offer possible targets for IBD management in humans.

## Summary

- ▶ Cannabis is generally well-tolerated.
- ▶ Adverse changes in cognitive function, especially executive function, may occur.
- ▶ Cannabis should be avoided by pregnant women and nursing mothers.
- ▶ Cannabis should be avoided in those at risk of psychosis or other unstable mental conditions.
- ▶ Drug interactions are a concern.
  - ▶ Concomitant use of CYP3A4 or CYP2C9 inhibitors with THC and CBD will increase plasma concentrations of THC and CBD. Concomitant use with CYP3A4 or CYP2C9 inducers will metabolize THC and CBD more rapidly.
  - ▶ Cannabis induces CYP1A2, and can reduce levels of drugs metabolized by CYP1A2.

## Resources



▶ <https://nmhealth.org/about/mcp/svcs/info/>

▶ <https://ascph.org>

▶ <https://www.facebook.com/ASCPh1/>

▶ <https://www.cdc.gov/marijuana/index.htm>



American Society of Cannabis Pharmacists

