Medical Cannabis Treatment Basics

The endocannabinoid system and evidence-based guidance

Utah Department of Health & Human Services

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No financial disclosures

- Family Medicine Physician in St. George, UT
- Intermountain Health Sunset Clinic
- Utah Cannabis Research Review Board
    - Utah Department of Health and Human Services
- Qualified Medical Provider (QMP) in the Utah cannabis program
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Presentation goals

Increase	Increase awareness and perception of Medical Cannabis Therapy
Achieve	Achieve a basic understanding of the Endocannabinoid System
Learn	Learn treatment basics and evidence-based guidelines

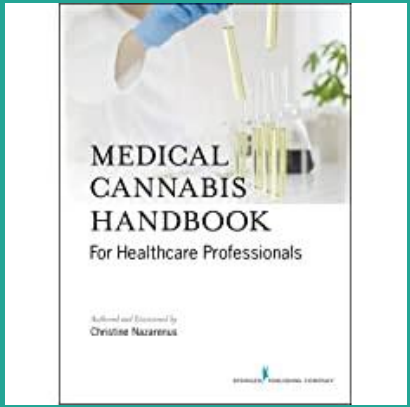
The need for cannabis education

- Like it or not, it is here!
- Patients are using it with or without you
- It is not as bad as you may think. In fact, it has been very good
- It is a useful treatment and appropriate for primary care
- Stewardship- if we don’t do it, then somebody else will

Changing environment

- Cannabis use and exposure is increasing
- The laws and regulations are in constant flux
- Research and clinical knowledge is increasing
- Public perception is variable and evolving
- Medical providers need to become educated and keep up to date

Initial references



- Medical Cannabis Handbook for Healthcare Professionals
  - Christine Nazarenus – Medical Marijuana 411
- Utah Department of Health Medical Cannabis Program
  - https://medicalcannabis.utah.gov/wp-content/uploads/2022/06/Guidance-on-the-Suggested-Use-of-Medical-Cannabis_v1_Final.pdf

Cannabis timeline

- Long history dating back to the ancient Chinese, Egyptians, Greeks, Romans and other civilizations.
- 1840 - In modern times it was brought to the UK by Dr William O'Shaughnessy.
- 1850 - Cannabis was added to the U.S. Pharmacopeia
- 1889 - *The Lancet* outlines uses of cannabis for opium withdrawal.
- 1930s - U.S. pharma companies sell cannabis oils as medicines
- 1937 - Cannabis made illegal in the U.S. (Marijuana tax act) but was actually opposed by the AMA.
- 1941 - Cannabis eliminated from the U.S. Pharmacopeia

Discovery of THC and CBD

- 1964 - the isolation of the compounds THC (and later CBD) by Raphael Mechoulam, PhD and Yehiel Gaoni, PhD at Hebrew University
- 1970 - The Controlled Substances Act places cannabis in Schedule 1
- 1972 - The Nixon-appointed Shafer Commission urges decriminalization
- 1988 - DEA Administrative Law Judge Francis Young recommends medical use of cannabis and reclassification as a prescriptive drug.

Discovery of the endocannabinoid system

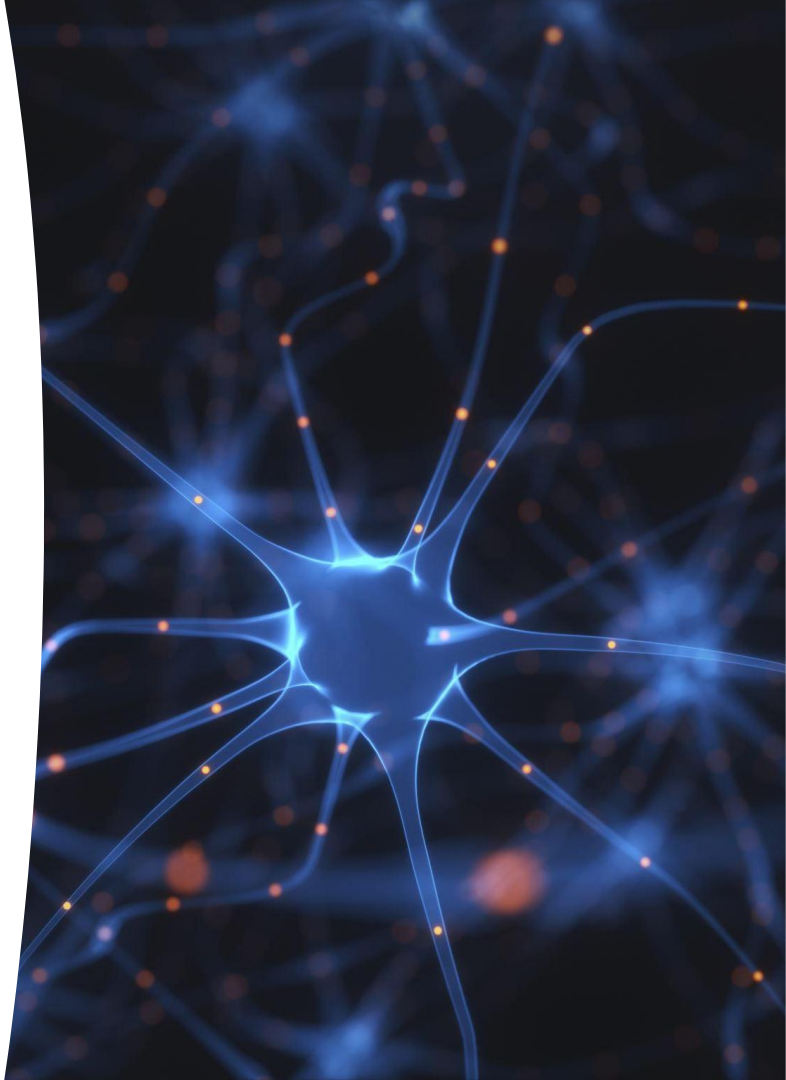
- 1988 - the American chemist, Allyn Howlett, PhD, located a large grouping of receptors in the brain that responded to THC.
- 1992 - Mechoulam's lab found a brain chemical that mirrors the effects of THC - **Anandamide**.
- Shortly after, the lab identified another brain chemical that mimics CBD, **2-Arachidonoylglycerol (2-AG)**

The timeline continues

- 1996 - California is the first state to legalize medical cannabis with Prop 215
- 2003 - U.S. Government granted a patent for the therapeutic use of “cannabinoids as antioxidants and neuroprotectants.”
- 2011 - Israeli government launches nationwide medical cannabis program.
- 2013 - Dr. Sanjay Gupta comes out in favor of medical cannabis.
- 2017 - 33 states (plus Washington D.C. and Guam) and 17 countries legalize medical cannabis.
- 2018 - Industrial Hemp included in the 2018 Farm Bill signed by Pres. Trump
- 2018 - Utah joins in legalizing Medical Cannabis
- 2020 - Utah medical cannabis program launched with Qualified Medical Providers (QMP) and 14 Dispensaries.

Endocannabinoids

- To date, there have been about 5 endocannabinoids isolated and all are derivatives of polyunsaturated fatty acids, closely related to Omega-3 fatty acids.
- The two most common and most studied are:
    - **Anandamide** and **2-AG.**
- They are present in cell membranes throughout the body.
- Unlike other neurotransmitters, they become synthesized “on demand” rather than being stored in vesicles.



The Endocannabinoid System (ECS)

- Master Regulator of the Body. Function is broad and complex.
- Deeply involved in maintaining **Homeostasis**, **Neuroprotection**.
- There are probably more physiological processes that have yet to be discovered.
- Endocannabinoids serve as primary messengers across nerve synapses.
- They modulate the flow of neurotransmitters
    - keeping the nervous system running smoothly.
- It is a large and sprawling system involving many organs
    - which may make it difficult to design drugs that target one function.

ECS Receptor Functions

- They are the densest receptors in the brain.
- Relays information about the various states of cells, tissues and organs.
- Nerve transmission, memory, mood, emotion, pain perception, feeding, reproduction, metabolism, nerve protection, adaptability, and brain development.

Endocannabinoid receptor locations

- CB1 -- Brain/CNS/Spinal cord and Glands
  - Cortical regions, Cerebellum, Brainstem, Basal Ganglia, Olfactory Bulb, Thalamus, Hypothalamus
    - Interestingly none in the cardiac & respiratory centers of the brainstem
  - Pituitary, Thyroid, Upper Airways, Adrenals, Ovaries, Uterus, Prostate, Testes
- CB2 -- Peripheral
  - Lymphatic and Immune System, Spleen, Thymus, Tonsils, Blood, Skin
- CB1 & CB2
  - Eye, Stomach, Heart, Pancreas, Digestive Tract, Bone

CB1 Receptors

- Primarily CNS
- CB1 is the main target of **anandamide** as well as THC (its mimetic phytocannabinoid).
- **2-AG**, and therefore **CBD**, is active at both receptors CB1 & CB2.
- Affects functions of movement, anxiety, stress, fear, pain, appetite, reward, and motor control.
- Activation causes psychoactivity.
- Cannabis use can cause effects on: short term memory, cognition, mood and emotion, muscle motor function, pain perception, and nerve protection.

CB2 Receptors

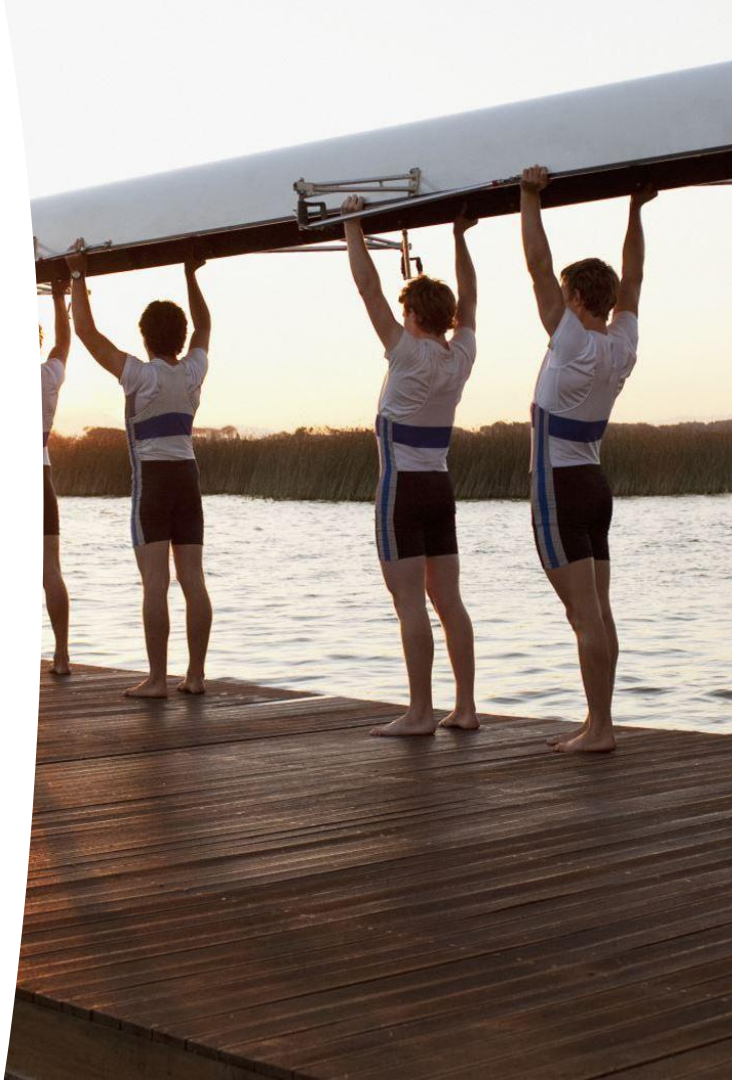
- Found in blood cells, spleen and connective tissue
- **2-AG**, and therefore **CBD**, activates CB2.
- Control the release of cytokines - immune regulatory proteins - that are linked to inflammation during illness or after injury.
- No psychoactivity

How Cannabinoids Attach to Receptors

- Lock and key paradigm but is more intricate that other receptor systems.
- CB1 has at least two landing spots, one for THC and another for CBD.
- With low CBD, then THC can bind to the other site →more psychoactivity.
- Therefore, CBD modulates the effects of THC.

The entourage effect

- When CBD is combined with THC, the entourage effect of the two molecules magnifies the positive medical aspects - such as pain relief - while reducing the adverse effects, such as short-term memory loss and anxiety.
- Other minor cannabinoids and Terpenes may also contribute to the Entourage Effect.



Retrograde inhibition

- Unlike other receptor systems, information in the ECS can flow backwards or “upstream”
- This can down regulate signal transmission to protect from hyperactivity - Neuroprotection
- Useful in certain illness such as epilepsy - shut down the “electrical storm” of a seizure
- This also explains why even though users can develop tolerance, there is low toxicity or risk of death with excessive use. It will downregulate the number of receptors and create a limit on how much THC it can withstand.

Cannabinoids

- There are over 600 Chemical compounds in the cannabis plant.
- Over 113 cannabinoids have been discovered.
- Major cannabinoids = CBD & THC
- Minor cannabinoids:
    - CBG, CBN, CBC, THCv

THC - Tetrahydrocannabinol

- Binds to CB1.
- Mimetic to anandamide.
- Neuroprotective with analgesic effects.
- Most illicit drugs are considered to be neurotoxic; THC seems to be neuroprotective.
- Psychoactive and euphoric effects.
- Treats anxiety, glaucoma, insomnia, muscle spasticity, nausea, appetite, and pain.

CBD - Cannabidiol

- Binds primarily to CB2 but can be second binder to CB1.
- Mimetic to 2-AG.
- 40% of the plant's extract. Can be extracted also from Hemp.
- Not psychoactive. Mitigates the psychoactivity of THC.
- Treats anxiety, seizures, inflammation, depression, migraines, inflammatory bowel disease, and pain.

CBG - Cannabigerol

- 3rd most prevalent
- Analgesic
- Not psychoactive
- Antiseptic & antibiotic properties
- Anti-inflammatory, antifungal properties
- Lowers blood pressure and inhibits tumor growth
- Treats IBD and IBS
- Great addition to the Entourage effect. (Tincture 1:1:1)

CBN - Cannabinol

- Not produced by the plant but is a breakdown product that occurs after oils have dried out.
- Partial agonist at the CB1 receptors, but has a higher affinity to CB2 receptors.
- Not psychoactive but does cause sedation when combined with THC.
- Anti-seizure, antibacterial and analgesic effects.

Terpenes

- Powerful odor molecules that are found primarily in the plant's trichomes.
- Thanks to terpenes for the enduring pungency of cannabis.
- Cannabis has about 200 different terpenes.
- Many of these are key components in lemon, pepper, lavender, hops, and pine.
- Several are being studied for their anti-inflammatory, analgesic, and sedative effects.
- Likely adds to the Entourage effect.

FDA approved Cannabinoid Pharmaceuticals

- Dronabinol (Marinol) - synthetic THC approved in 1985.
  - Poorly tolerated, dysphoria, sedating
  - No Entourage effect
- Others: Nabilone (Cesamet), Dronabinol (Syndros), Cannabidiol (Epidiolex)

Whole flower preparation

Advantages	• lower cost • widely available • Contains all cannabinoids and terpenes
Disadvantages	• cannabinoid content may not be high enough • carcinogens and plant materials may be inhaled • improper storage → mold and plant degradation

Plant Derivations (a quick word) Indica, Sativa & Hybrids

- Cannabis Origin - believed to be the Caucasus Mountains (Kazakhstan)
- **Indica** strains developed in Central Asia in harsh climates → shorter, bushy, rounder leaves, mature faster. Less cerebral psychoactivity and more physically "sleepy"
- **Sativa** strains developed in the Middle East & Africa → taller, gangly, narrow leaves, mature slowly. Psychoactivity is more energetic. Talkative, nervousness, bursts of creativity.
- Most plants in North America have been hybridized over 50-60 years so these terms are mostly meaningless but still survive in the common lexicon. Unreliable in predicting effects.


Indica
Sativa
Ruderalis
Hybrid
shutterstock.com · 1696022350

Inhalation/vaporization

Advantages	• Immediate onset • Easy titration and adjustment • No harmful byproducts • Clean
Disadvantages	• Oils can clog machines • Machines may be expensive and require maintenance • Proper use required

Edibles

Advantages	• Long duration & stronger effects • dosing easier and more precise • no harmful byproducts
Disadvantages	• Onset is delayed, • risk of over-consumption • risk of accidental consumption • potential allergies

Tinctures/oral mucosa

Advantages	• Easy to use and titrate • More ratios of CBD:THC available • Minor cannabinoids and terpenes can be added • Can add to food or beverages • Long shelf-life & flexibility • Discrete and portable
Disadvantages	• Inconsistencies in formulations and labeling

Topicals

Advantages	• Avoids first-pass metabolism • Localized pain management • Reduces inflammation and arthritis • Non-psychoactive even with THC
Disadvantages	• Possible irritation • Low skin penetration • Potential allergy

Patient centered dosing

- Extremely individualized
- Method of delivery
- Ratio of cannabinoids
- “Start low and go slow”

Edibles dosing

- Wait, Wait Wait! It can take 40 min to 2 hours
- Start 1-5 mg (usually 2.5mg)
- Experienced users 5-10 mg
- “Professional” users 10-15mg or 20mg
- Absorption enhanced : when delivered in lipids (butter, coconut oil, sesame oil) and on an empty stomach

Cannabinoid ratios or chemotypes

THC predominant = Chemotype I

- THC:CBD ratio >10:1

Balanced Ratio = Chemotype II

- THC:CBD <10:1 and >2:10

CBD predominant = Chemotype III

- THC:CBD < 2:10
- non-psychoactive

Separated Dosing Protocol

CBD 15-20 mg.

- Increase by 5-10 mg increments

THC 1-2.5 mg.

- Increase dose by 2.5 mg increments.
- Beginner 1-2.5 mg, Experienced 5-10 mg, “Professional” 10-20mg

Side Effects

- Side effects - usually from too much THC
- Fatigue
- Anxiety
- Euphoria
- Impairment of mental status
- Tachycardia
- Drop in blood pressure
- Dizziness
- Side effects are usually mild or moderate and usually resolve quickly

The Biphasic Effect

- Low doses and high doses can have opposite effects.
- Low doses of THC tend to stimulate, while high doses sedate.
- Too much THC can amplify mood disorders and anxiety
- Too much THC can impact short-term memory.
- In some conditions (MS & Pain), high doses can actually be less effective than low doses.
- CBD, in contrast, has little to no adverse effects.

Drug-Drug Interactions

- Cannabinoids can be administered safely with most drugs
- May affect the cytochrome P450 enzyme system.
    - but no significant interactions have been reported with Marinol or Sativex.
- May lower blood pressure
- THC can escalate heart rate for several minutes after inhalation
- Can increase sedation when mixed with alcohol, benzos, antihistamines, sleep aids and opiates.
- Can increase the cardiac effects of amphetamines, antidepressants, beta blockers and diuretics.
- Can increase the INR values with warfarin and maybe other anticoagulants.

Contraindications

- Pregnant
- Lactation
- Cardiac Conditions (unstable)
  - Ischemic heart disease, Arrhythmia, CHF, uncontrolled HTN
- History of Allergic Reaction to Cannabinoids
- Psychiatric diagnoses – Schizophrenia Spectrum
- Immunocompromised or on immunosuppressives

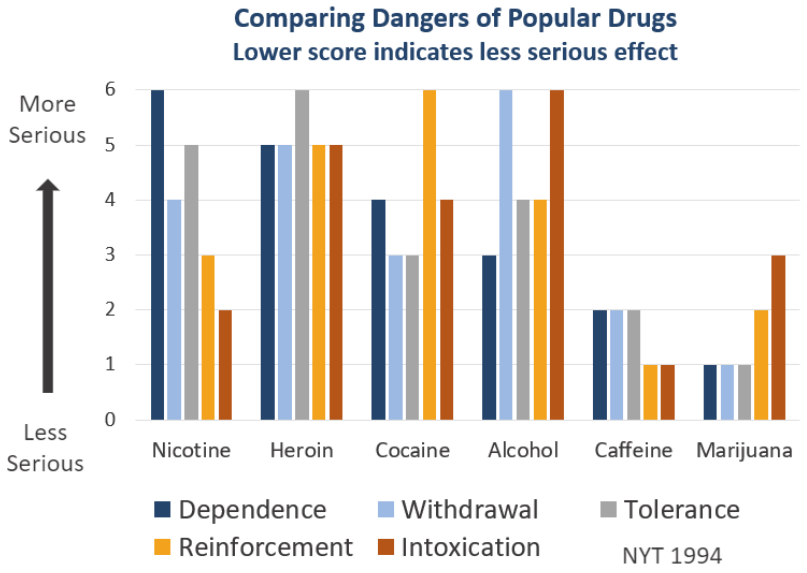
Warnings, Precautions and Adverse Reactions

- **Children & Youth under 25**
- Impaired **Cognition**
- **Altered Mental Status**
- Psychomotor Performance and Driving
- Alcohol Use
- CNS-Sedating Medications
- Use in the Elderly
- Cannabis Use Disorder (CUD)
- **Cannabis Hyperemesis Syn.**

- Seizures & Epilepsy
- Bipolar & other mood disorders
- Depression & Suicidality
- Anxiety
- Pre-existing Substance use
- Pre-existing Pulmonary disease
- DKA risk
- Osteoporosis
- Transaminase elevation
- Cancer

Drug use and abuse

- **Neil Benowitz**
  State of the Art Review, NEJM 2010
  Science Advances, 2019

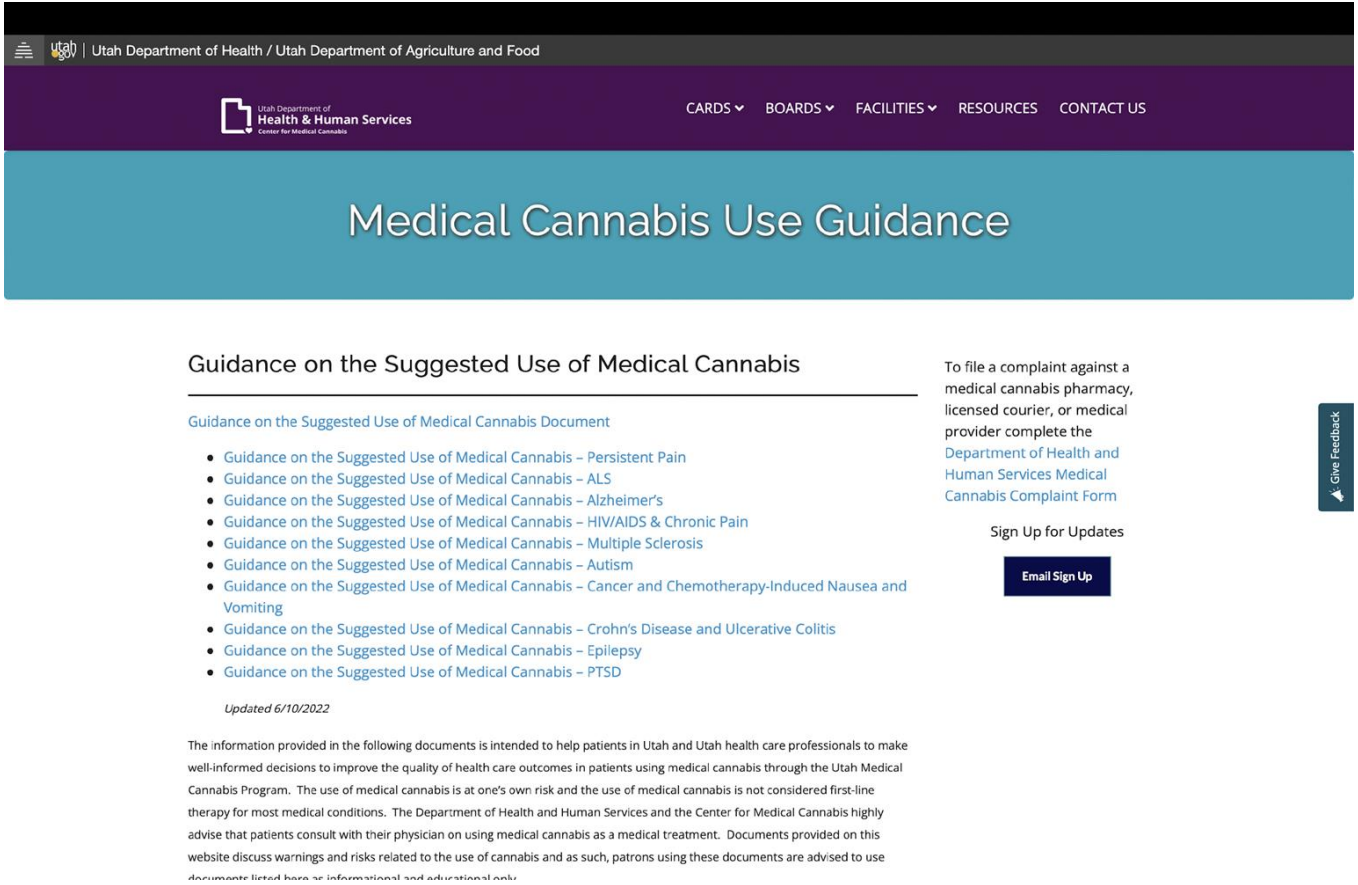


Patient Selection

- Probably the most important part of Medical Cannabis Therapy
- Qualifying condition (and absence of contraindications)
- Age & Experience
- Experience with other controlled substances, treatments & medicine
- Mindset about Cannabis & willingness to be objective
- Ability to self-evaluate, calculate dose, journal effects
- Realistic expectations
- Set goals of therapy
- Well known to the provider & good communication
- Able and willing to follow up

Current Qualifying Conditions in Utah

- ALS
- Alzheimer’s
- Autism
- Cachexia
- Crohn’s disease or Ulcerative colitis
- Epilepsy or debilitating seizures
- HIV or AIDS
- MS or debilitating muscle spasms
- Persistent & unresponsive nausea
- PTSD (with stipulations)
- Terminal Illness, Hospice care, rare disease
- Chronic or Persistent Pain (>2 weeks)
- Acute Pain (<2 weeks)


utah.gov | Utah Department of Health / Utah Department of Agriculture and Food
Utah Department of Health & Human Services
Center for Medical Cannabis
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Medical Cannabis Use Guidance
Guidance on the Suggested Use of Medical Cannabis
Guidance on the Suggested Use of Medical Cannabis Document
Guidance on the Suggested Use of Medical Cannabis – Persistent Pain
Guidance on the Suggested Use of Medical Cannabis – ALS
Guidance on the Suggested Use of Medical Cannabis – Alzheimer's
Guidance on the Suggested Use of Medical Cannabis – HIV/AIDS & Chronic Pain
Guidance on the Suggested Use of Medical Cannabis – Multiple Sclerosis
Guidance on the Suggested Use of Medical Cannabis – Autism
Guidance on the Suggested Use of Medical Cannabis – Cancer and Chemotherapy-Induced Nausea and Vomiting
Guidance on the Suggested Use of Medical Cannabis – Crohn's Disease and Ulcerative Colitis
Guidance on the Suggested Use of Medical Cannabis – Epilepsy
Guidance on the Suggested Use of Medical Cannabis – PTSD
Updated 6/10/2022
The information provided in the following documents is intended to help patients in Utah and Utah health care professionals to make well-informed decisions to improve the quality of health care outcomes in patients using medical cannabis through the Utah Medical Cannabis Program. The use of medical cannabis is at one's own risk and the use of medical cannabis is not considered first-line therapy for most medical conditions. The Department of Health and Human Services and the Center for Medical Cannabis highly advise that patients consult with their physician on using medical cannabis as a medical treatment. Documents provided on this website discuss warnings and risks related to the use of cannabis and as such, patrons using these documents are advised to use
To file a complaint against a medical cannabis pharmacy, licensed courier, or medical provider complete the Department of Health and Human Services Medical Cannabis Complaint Form
Sign Up for Updates
Email Sign Up
Give Feedback

Chronic or Persistent Pain

- **Moderate** Evidence
  - https://medicalcannabis.utah.gov/wp-content/uploads/2022/06/Persistent-Pain_v1_Final.pdf

Multiple Sclerosis

- **Substantial evidence** for muscle spasticity in MS
  - https://medicalcannabis.utah.gov/wp-content/uploads/2022/06/Multiple-Sclerosis_v1Final.pdf

Autism or Dementia

- Comorbid agitation or difficult behaviors - very limited short-term studies. Anecdotal positive reports, but some have no effect or may increase agitation.
- Insufficient evidence to support or refute
  - https://medicalcannabis.utah.gov/wp-content/uploads/2022/06/Autism_v1_Final.pdf
  - https://medicalcannabis.utah.gov/wp-content/uploads/2022/06/Alzheimers_v2_Final-Approved-10.12.21.pdf

Inflammatory Bowel Disease – Crohn's & Ulcerative Colitis

- While the ECS remains a good potential target for treatment, no conclusive evidence. More studies needed.
    - https://medicalcannabis.utah.gov/wp-content/uploads/2022/06/Crohns-UC_v1_FINAL.pdf

Epilepsy

- Many historical reports of benefits. Current studies are complicated.
- Measurement of decreased seizure frequency or quality of life?
- 80% reported decreased seizures, 13% reported increased frequency - study was stopped. What do we do with that?
    - What type of cannabis was used – extreme variability
    - https://medicalcannabis.utah.gov/wp-content/uploads/2022/06/Epilepsy_v1_Final.pdf

PTSD

- There is currently no placebo-controlled trial data to guide or recommend the use of medical cannabis as first-line treatment for PTSD or comorbid symptoms.
- Some anecdotal reports and observational studies suggest possible short-term benefits in some individuals.
    - https://medicalcannabis.utah.gov/wp-content/uploads/2022/06/PTSD_v1_Final.pdf

Oral Cannabis Protocol

Initial	Initial Dose: CBD 5 to 10 mg + THC 1 to 2.5 mg, once to twice daily**
Increase	Increase CBD by 10 mg (5 mg twice daily) per every 2 to 3 days if tolerated until the patient reaches their goals or to a maximum of 40 mg/day.
Titrate	If goals are not met with this ratio of CBD to THC, titrate THC by increasing it by 2.5 mg/day every 2 to 7 days as tolerated to a maximum daily dose of 40 mg/day THC and 40 mg/day CBD.

Dosing guideline references

**Consult with the registered Utah cannabis pharmacy pharmacist to help obtain a product that best conforms with these recommendations and allows for step-wise initiation and titration.*
***Adapted from Bhasker et al. expert opinion dosing guidance for chronic pain (1)*
1. *Bhaskar A, et al. Consensus recommendations on dosing and administration of medical cannabis to treat chronic pain: results of a modified Delphi process. Journal of Cannabis Research, 2021; 3 (1):22*

Review and Summary

- Medical Cannabis Therapy is here to stay
- It can be safe and effective for several conditions
- Research is ongoing – especially as laws are changing
- Overcome stigma and barriers
- We can either lead or be led
- **Stewardship**

Review and Summary: The Endocannabinoid System

- Neuroprotective and promotes **Homeostasis**
- Large and sprawling, affecting many systems
- Master regulator that modulates neurotransmission
- The two known endocannabinoids are anandamide & 2-AG

Review and Summary: THC & CBD and minor cannabinoids

- The Entourage Effect & the Biphasic effect
- The Ratio of CBD:THC is essential
- Dosing: Start Low and Go Slow!
- **Patient Selection** and tailoring therapy

Qualified Medical Provider

- How to become a Qualified Medical Provider (QMP) https://medicalcannabis.utah.gov/providers/become-a-qualified-medical-provider/
  - Get trained (4 hours)
  - Apply online with the Utah DHHS
  - Registration fee
- DHHS Approved Medical Cannabis Continuing Education https://medicalcannabis.utah.gov/providers/continuing-education/
  - Intermountain Interprofessional Continuing Education Initial Training
  - Medical Marijuana 411
  - University of Utah Health Continuing Medical Education
  - TheAnswerPage

Limited Medical Provider (LMP) program

- Providers licensed to prescribe controlled substances can prescribe up to 15 patients with qualifying conditions and age>21 without official training.

- LMP guide
  - https://medicalcannabis.utah.gov/wp-content/uploads/Copy-of-Medical-Cannabis-Limited-Medical-Provider-Guide.pdf

- LMP form
  - https://medicalcannabis.utah.gov/wp-content/uploads/LMP-06122023.pdf

More References

- https://medicalmarijuana411.com/product/medical-cannabis-handbook/
- https://medicalcannabis.utah.gov/resources/provider-resources/medical-cannabis-guidance/
- https://medicalcannabis.utah.gov/wp-content/uploads/2022/06/Guidance-on-the-Suggested-Use-of-Medical-Cannabis_v1_Final.pdf
- https://intermountainhealthcare.org/health-information/medical-cannabis/
- https://intermountain.cloud-cme.com/course/courseoverview?P=0&EID=20813
- https://health.utah.gov/wp-content/uploads/MedCanFactSheet4-8-19.pdf

Questions