





## Cannabis, what basics do clinicians **NEED** to know

Theresa Mallick-Searle, MS, PMGT-BC, ANP-BC  
Stanford Health Care, Division Pain Medicine

[Tmallick@stanfordhealthcare.org](mailto:Tmallick@stanfordhealthcare.org)

 @tmallic

 <https://www.linkedin.com/in/theresa-mallick-searle>

## Disclosures

---

- Speakers' bureau: Allergan & Lilly Pharmaceuticals.
- Any unlabeled/unapproved uses of drugs or products referenced will be disclosed.
- Covering a very **LARGE** topic in a short amount of time.

## Speaker's Expectations

---

- You have heard about cannabis.
- You know a little about the differences between THC & CBD.
- You have a vague grasp of the endocannabinoid system.
- Your patient **wants to try/has questions about/likes to joke about/is using** cannabis.
- You are “a busy clinician and have 15 (**maybe 20**) minutes to learn all that I need to know about cannabis.”

## Objectives

---

Explore	dosing, metabolism, and drug interactions.
Review	safety considerations for both patients and clinicians.
Recommend	ways to negotiate the dispensary.

This updated lecture will provide the busy clinician with the basics that they need, to safely discuss medical cannabis and provide patients with the essentials to move forward safely.



## Agriculture Improvement Act/Hemp Farming Act 2018

---

- Removed hemp for the US list of scheduled substances.
- Did not remove hemp derived cannabinoids from the list of scheduled I substances.
- Amended the definition of marijuana → included an exemption for hemp → defined as “any part” of the Cannabis sativa L. plant → containing no more than 0.3% THC.
- Ongoing legislation → federal & regulatory agency guidance.
- States setting their own rules for the hemp industry.
- USDA has broad regulatory “authority” over hemp industry.

# Endocannabinoid System: Endogenous-Homeostatic regulatory system-Inherited by all mammals

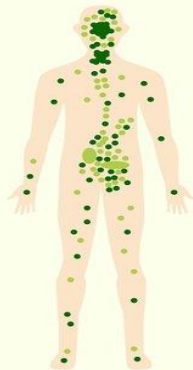
## HUMAN ENDOCANNABINOID SYSTEM

THE MOST WELL KNOWN CANNABINOID RECEPTORS, CB1 AND CB2, ARE PROTEINS THAT ARE IMBEDDED IN THE MEMBRANE OF CELLS. THESE SURFACE PROTEINS ARE THEN ATTACHED TO ANOTHER PROTEIN THAT DETERMINES THE SIGNALING DIRECTION ACTIVATION OR INHIBITION

### CB1

CB1 Receptors target :

- Appetite
- Immune cells
- Motor activity
- Motor coordination
- Pain perception
- Short term memory
- Thinking



### CB2

CB2 Receptors target :

- Adipose tissue
- Bone
- Cardiovascular system
- Central nervous system
- Eyes
- Gut
- Immune system
- Kidneys
- Liver
- Pancreas
- Reproductive system
- Respiratory tract
- Skeletal muscle
- Skin
- Tumors

### CB1

CB1 Receptors are primarily found in the brain and central nervous system, and to a lesser extent in the other tissues.

### CB2

CB2 Receptors are mostly in the peripheral organs especially cells associated with the immune system.

# Clinical Endocannabinoid Deficiency

---

Ethan Russo, MD (2004/2016)

- The ECS theory of disease.
- Lack of sufficient endocannabinoids/  
dysregulation of the ECS.
- Result in higher susceptibility  
(fibromyalgia, irritable bowel syndrome,  
depression, anxiety, migraine).
  
- Phytocannabinoids (THC, CBD) can  
bind to the cannabinoid receptor sites  
(CB1, CB2), and mimic the physiological  
processes seen with binding of the  
endocannabinoids.

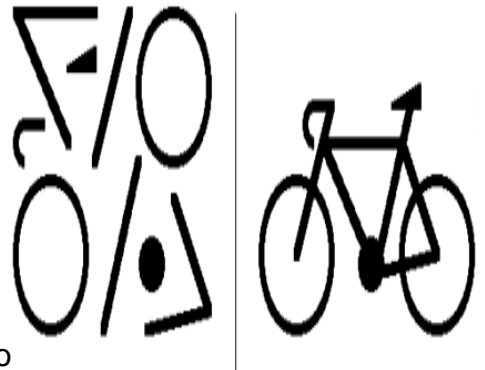




## Entourage effect: sum of the parts

---

- The entourage effect is a proposed mechanism by which cannabis compounds act synergistically to modulate the overall physiological effects of the plant.
- Example: CBD + THC = possibly mitigating some of the psychosis-like effects of THC.
- Cannabis is a multimodal treatment. It can be used to treat multiple symptoms & conditions concurrently, which can therefore help to reduce polypharmacy burden.

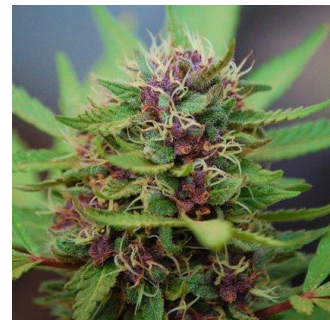


## What is cannabis sativa (aka marijuana)?

---

It is a Plant w/over 400 different chemicals:

- >60 types of cannabinoids
  - delta-9-tetrahydrocannabinol (THC)
  - Cannabidiol (CBD)
  - Cannabinol (CBN)
  - Cannabichromene (CBC)
  - Cannabigerol (CBG)
  - Tetrahydrocannabivarin (THCV)
- Flavonoids, Terpenes, Terpenoids
- Fungus? Bacteria? Pesticides?
- Byproducts of manufacturing (solvents, heavy metals)



## Current Reviews/Meta-analysis



Cochrane Database of Systematic Reviews

Cannabis-based medicines for chronic neuropathic pain in adults (Review)

2018

Mücke M, Phillips T, Radbruch L, Petzke F, Häuser W

■ META-ANALYSIS

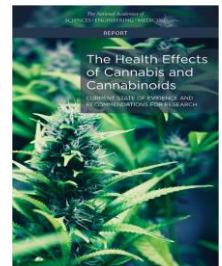
Anesth Analg 2017;125:1638-52

### Selective Cannabinoids for Chronic Neuropathic Pain: A Systematic Review and Meta-analysis

Howard Meng, MD,\* Bradley Johnston, PhD,†‡§|| Marina Englesakis, MLIS,¶|| Dwight E. Moulin, MD,# and Anuj Bhatia, MBBS, MD, FRCPC, FRCA, FFPMRCA, FIPP, EDRA, CIPS\*

JAMA. 2015;313(24):2456-2473. doi:10.1001/jama.2015.6358

The National Academies of  
SCIENCES • ENGINEERING • MEDICINE



Original Investigation

### Cannabinoids for Medical Use A Systematic Review and Meta-analysis

Penny F. Whiting, PhD; Robert F. Wolff, MD; Sohan Deshpande, MSc; Marcello Di Nisio, PhD; Steven Duffy, PgD; Adrian V. Hernandez, MD, PhD; J. Christiaan Keurentjes, MD, PhD; Shona Lang, PhD; Kate Misso, MSc; Steve Ryder, MSc; Simone Schmidtkofer, MSc; Marie Westwood, PhD; Jos Kleijnen, MD, PhD

# Can I get my patient into a clinical trial?

<https://clinicaltrials.gov/>

 U.S. National Library of Medicine

**ClinicalTrials.gov**

[Find Studies](#) ▾

[About Studies](#) ▾

[Submit Studies](#) ▾

[Resources](#) ▾

[About Site](#) ▾

[PRS Login](#)

ClinicalTrials.gov is a database of privately and publicly funded clinical studies conducted around the world.

Explore 367,204 research studies in all 50 states and in 219 countries.

See [listed clinical studies related to the coronavirus disease \(COVID-19\)](#)

ClinicalTrials.gov is a resource provided by the U.S. National Library of Medicine.

Find a study (all fields optional)

Status ⓘ

Recruiting and not yet recruiting studies  All studies ⓘ

Condition or disease ⓘ (For example: breast cancer)

X



TELL ME EVERYTHING I NEED TO KNOW IN  
≈20 MINUTES!

## Important Talking Points

---

- Encourage open/non-judgmental dialogue.
- Driving “under the influence”.
- Recommend obtaining medical marijuana card issued by state.
- Traveling considerations.
- Provide website resources.
- Share the extend of the research that is known .
- Discuss drug to plant interactions, side effects, risk of addiction.
- Know what to look for in products.
- How to recognize who is behind the counter in the dispensary.



## Traveling

Interstate transportation of these products is federally illegal.

---

- TSA security does not search for marijuana or other illegal drugs, but if any illegal substance is discovered during security screening, TSA will refer the matter to a law enforcement officer.
- Marijuana is illegal under federal law, & federal law governs airplane travel in this country.
- Recently, the TSA updated its rules for flying with medical marijuana, allowing travelers to now carry products like Cannabidiol (CBD) oil that contain < 0.3% THC. Passengers can bring products that are approved by the FDA in their checked or carry-on luggage.



**Amtrak** “The use or transportation of marijuana in any form for any purpose is prohibited, even in states or countries where recreational use is legal or permitted medically.”

**Greyhound** bans alcohol/drugs “anywhere on the bus (including in your checked baggage).”

## Driving under the influence/Driving impaired

---

- Decreases reaction time.
- Feelings of drowsiness or inattention.
- Poor coordination affecting the mechanics of driving (steering, working, braking, etc.).
- Alters rational decision making.
- Alters the ability to judge car's position on the road, road signs, location of other vehicles/object/pedestrians.
- ANYTHING THAT A POLICE OFFICER DEEMS APPROPRIATE!

**Tip:** If documenting the discussion of cannabis use either recreationally or medicinally with a patient -

DOCUMENT the advisement of risks with automobile usage.





## Drug Testing for Cannabis

---

### Many factors:

- Route of administration (inhaled, oral, topical)
  - Duration of use (acute v/s chronic usage)
  - Blood, sweat, tears (hair, saliva)
  - Sensitivity of the test (immunoassay – screening;  
v/s GC-MS – confirmatory)
  - Genetics – CYP450 variations, adipose tissue
- In general, the detection time is longest in hair→ urine, sweat, oral fluid & blood.
- The average limit or cut-off level for testing positive on a drug test for marijuana (THC) is 50 ng/ml (15 ng/ml for GC-MS).



## Drug Testing for Cannabis

### Cannabinoid Test Results

**12/01/2018**

Cannabinoid analysis utilizing High Performance Liquid Chromatography (HPLC, QSP 5-4-4-4)

	mg/g	%	LOD mg/g	LOQ mg/g
THC	ND	ND	0.000034	0.001
THCa	ND	ND	0.000066	0.001
CBD	10.797	1.0797	0.000057	0.001
CBDa	ND	ND	0.000038	0.001
CBN	ND	ND	0.000029	0.001
CBDV	0.049	0.0049	0.000065	0.001
CBDVa	ND	ND	0.00003	0.001
CBG	ND	ND	0.000086	0.001
CBGa	ND	ND	0.000072	0.001
THCV	ND	ND	0.000035	0.001
$\Delta 8$ - THC	ND	ND	0.000083	0.001
CBC	ND	ND	0.000095	0.001
<b>Sum of Cannabinoids:</b>	<b>10.846</b>	<b>1.0846</b>	<b>845.988 mg/Unit</b>	
Total THC ( $\Delta 9$ THC+0.877*THCa)	ND	ND		ND
Total CBD (CBD+0.877*CBDa)	10.797	1.0797	842.166 mg/Unit	

## Pharmacokinetics: delta-9-tetrahydrocannabinol

---

- THC psychoactive cannabinoid
- Highly lipophilic
- Rapidly absorbed through lungs after inhalation, quickly reaching high serum concentration
- Systemic bioavailability is ~23-27% for daily users, ~10-14% occasional users
- Extensive liver (first pass) metabolism; cytochrome P450
- >65% excreted in the feces, ~20% urine
- t<sub>1/2</sub> occasional users is 1-2 days, daily users up to 2 weeks

## Stirring the Pot: Potential Drug Interactions

---

- CYP450 → Main metabolic pathway for cannabinoids
- Studies of THC, CBD, and CBN inhibition and induction of major human CYP450 isoforms generally reflect a low risk of clinically significant drug interactions with most use, but specific human data are lacking. (Stout & Cimino, 2014; Alsherbiny & Li, 2019)
- CNS depressants, antidepressants, central nervous system drugs – potentiate effects of THC.
- Any medications that are metabolized through the same pathways could result in less or more of the drug's effects.
- For scientific reviews: *Drug Metabolism Reviews*.
- Epocrates is a good quick reference for cannabidiol and synthetic THC (dronabinol).

# Mental Health

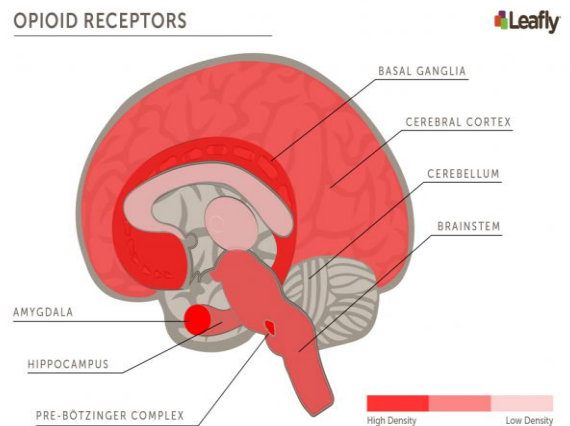
Cannabis (THC) appear to affect the same reward system as alcohol, cocaine, opioids.

Evidence for cannabis physiological & psychological dependence:

- irritability, anxiety, disturbed sleep, craving

Mental wellness

- Worsen sub-clinical, stable mental illness
- Effects on motivation
- Psychosis in genetically susceptible individuals



## Cannabis use and risk of opioid use disorder

---

- Logistic regression models to assess association between cannabis use (2001-2002) and non-medical prescription opioid use & prescription opioid use disorder (OUD) (2004-2005) using DSM-IV criteria.
- Cannabis use led to ↑non-medical prescription opioid use and OUD.
- Adults with pain and cannabis use saw ↑non-medical opioid use.

(Olfson, et al., 2018)

## Tolerance & Adverse Effects (AEs)

---

### Tolerance

- Mood, sleep
- Psychomotor performance
- Arterial pressure
- Antiemetic properties

### Common AEs

- **Anticholinergic effects** (dry mouth, blurry vision, urinary retention, tachycardia, constipation, hypertension).
- **CNS effects** (ataxia, cognitive dysfunction, hallucination).

### Cannabis Hyperemesis Syndrome

## At The Dispensary: virtual/in-person/www

---



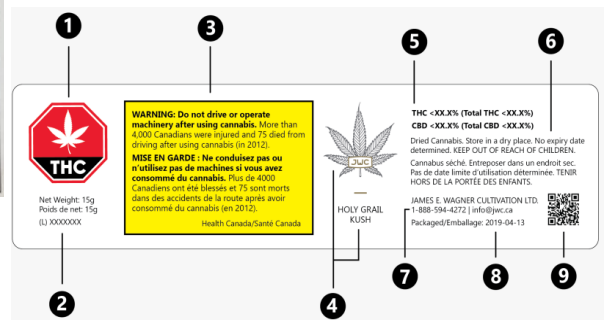


# Recommend only products that are properly labeled

- Label information should include the ingredients and the milligrams of each cannabinoid per dose.
- Recommend only products from companies that test for potency, pesticides, mold, and bacteria.
- Mindful of byproducts of production (e.g., solvents).

PROFILE			
<b>SOUR DREAM</b>			
CREATED BY MORNING SUN FARMS			
DOSE: 4 second draw on a fully charged CCELL™			
Cannabinoids Per Dose	Doses Per 500mg Cartridge		
<b>3.01mg</b>	<b>110 doses</b>		
BATCH ID	TEST BY		
S1030175029	10/04/2018		
CULTIVATION DATE	PRODUCTION DATE		
SUMMER 2017	10/04/2017		
CANNABINOIDS			
	%	Total	per Dose
THC	56.2%	281	2.55
THCa	5%	25	2.2
CBD	2.6%	13	1.2
CBG	7%	3.5	0.03
CBN	7%	3.5	0.03
CBGa	6%	3	0.03
CBGa	4%	2	0.02
TERPENES			
	%	Total	per Dose
CARYOPHYLLENE	1.72%	8.6	—
HUMULENE	87%	4.35	—
LIMONENE	38%	1.9	—
TERPINOLENE	23%	1.15	—
MYRCENE	19%	0.95	—
β-PINENE	13%	0.65	—
α-PINENE	11%	0.55	—
OSGARDIOL	10%	0.5	—
UNKNOWN	2.77%	13.85	—

Cannabaceutical™ Facts	
Tested On: <b>January 1, 2011</b>	
	YOUR LOGO HERE
<b>Blue Dream</b>	
<i>Sativa Hyb.</i>	
14.20% Wt. Loss on Drying	
Δ <sup>9</sup> -THC Max:	<b>13.6 %</b>
Δ <sup>9</sup> -THCA	14.9 %
Δ <sup>8</sup> -THC	0.53 %
<b>CBD Max:</b>	<b>7.60 %</b>
CBDA	8.12 %
CBD	0.48 %
<b>CBN:</b>	<b>0.25 %</b>
<b>Safety Screen</b>	
Total Aerobic	<b>GOLD</b>
Enterobacteria	<b>SILVER</b>
Yeast & Mold	<b>BRONZE</b>
Pesticides	<b>PASS</b>
Patients can visit <a href="http://www.TheWercShop.com">www.TheWercShop.com</a> to learn more about this label and the test types reported.	
<small>Do not use while operating a car or heavy machinery. Keep out of reach of children. For medical use only. % = 90%</small>	



## Chemical Varieties/”chemovars”

---

Though cannabis is biologically classified as a single species: *Cannabis Sativa*, there are at least three distinct plant varieties:

- Cannabis Sativa
  - Cannabis Indica
  - Cannabis Ruderalis
- (Pennisi, 2017)

[www.leafly.com](http://www.leafly.com)

[www.safeaccessnow.org/using\\_medical\\_cannabis](http://www.safeaccessnow.org/using_medical_cannabis)

### Indica



**Morphology:** Short and bushy; suitable for indoor gardens

**Geographical Origins:** Areas between 30 to 50 degrees latitude.

**Effects:** Tend to be sedating and relaxing with full-body effects

**Symptom Relief:** Anxiety, insomnia, pain, muscle spasms

↓THC ↑CBD

### Sativa



**Morphology:** Tall and thin; suitable for outdoor gardens

**Geographical Origins:** Areas between 0 and 30 degrees latitude

**Effects:** Tend to be uplifting and creative with cerebrally-focused effects

**Symptom Relief:** Depression, ADD, fatigue, mood disorders

↑THC ↓CBD

## Practical Dosing

---

**Regardless of the specific physiological system, the effects of cannabis are dependent on many factors:**

- Dose, variety
- Route (Inhalation, oral, transmucosal, transdermal, topical)
- Timing
- General health (medical co-morbidities), Age
- Use of other substances/medications
- Chronic user of cannabis versus naive

[https://www.colorado.gov/pacific/sites/default/files/MED%20Equivalency\\_Final%2008102015.pdf](https://www.colorado.gov/pacific/sites/default/files/MED%20Equivalency_Final%2008102015.pdf)

## LACK OF STANDARDIZATION MAKES DOSING A CHALLENGE FOR PATIENTS & PRACTITIONERS

---

### **Overconsumption:**

- Re-dosing too soon
- Delayed on-set with oral dosing (>120 minutes)
- Hostile behavior/erratic speech/mild psychosis

**The L.E.S.S. Method:** A measured approach to oral cannabis dosing

Start **L**ow

- **E**stablish potency
- **G**o **s**low
- **S**upplement as needed

(Erowid & Erowid, 2011)

## Oral versus Inhaled

	INHALED	ORALLY INGESTED
Peak Blood Levels (min)	3-10	60-120
Bioavailability (%)	10-40	<15
Time to peak psychoactive activity (min)	20	120-240

# Practical Dosing

## Average adult dosing of THC:

- Cannabis-naïve individuals 2.5-5 mg
- Daily - weekly users 10-20 mg
- Daily+ 25 mg+
- Doses exceeding 20–30 mg/day may increase adverse events or induce tolerance without improving efficacy.

<https://www.leafly.com/news/cannabis-101/cannabis-edibles-dosage-guide-chart>

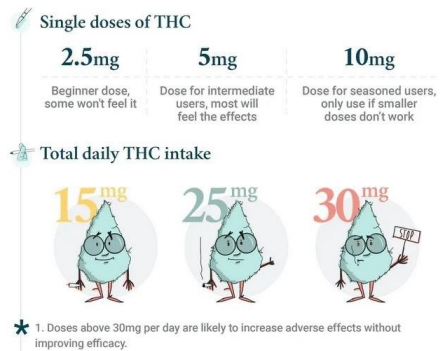
(MacCallum & Russo, 2018)

## Average adult dosing of CBD:

- 300-1500 mg/day

<https://www.webmd.com/vitamins/ai/ingredientmono-1439/cannabidiol>

(MacCallum & Russo, 2018)



## Practical Dosing

---

**Sativex® (1:1 THC/CBD): Spasticity due to multiple sclerosis.**

➤ 2.7mg/2.5mg BID

(max 32.4mg/30mg/day)

<https://www.medicines.org.uk/emc/product/602>

**Epidiolex® (CBD): Seizures (Dravet/Lennox-Gastaut)**

➤ 5 mg/kg oral BID

(max 20 mg/kg/day)

[https://www.epidiolex.com/sites/default/files/EPIDIOLEX\\_Full\\_Prescribing\\_Information.pdf](https://www.epidiolex.com/sites/default/files/EPIDIOLEX_Full_Prescribing_Information.pdf)

# Cannabidiol (CBD)

## Defining Terms:

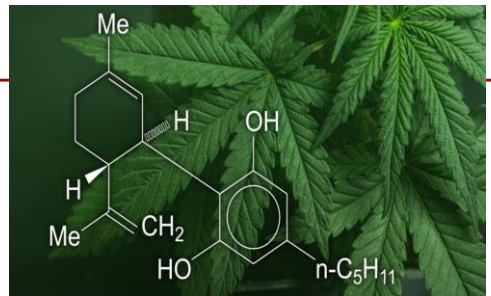
- CBD from Hemp (↑contaminants, ↓THC)
- CBD from cannabis sativa (↑THC, ↑purity)
- Hemp Oil (seeds of hemp plant, no CBD, no THC, +essential fatty acids, +omega three)

## Research:

- Epidiolex®
- Other - preliminary research included studies of anxiety, cognition, movement disorders, and pain (anti-inflammatory).
- Efficacy most antidotal (discuss current animal studies).

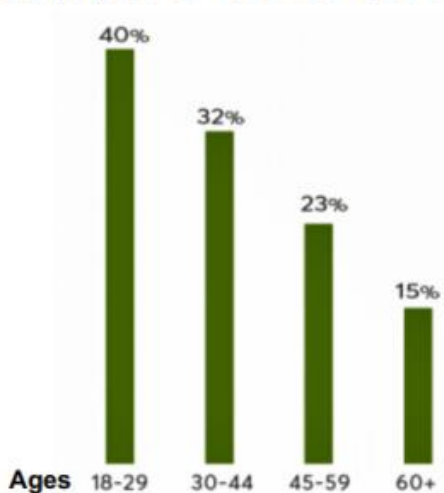
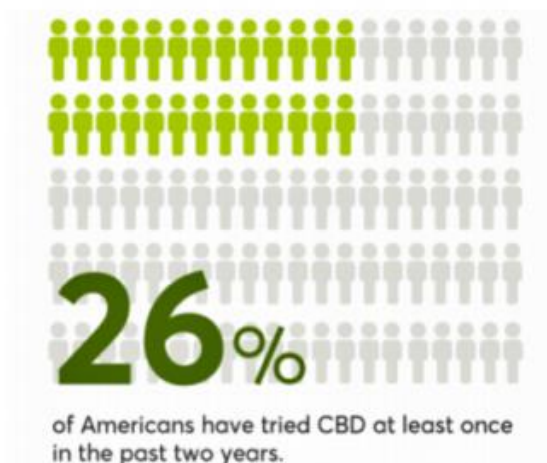
**Safety:** Dosing toxicity? Anti-inflammatory effects? CYP450 metabolism.

**Side Effects:** Fatigue, diarrhea, changes of appetite/weight, dry mouth. Transaminase elevations (reported in Epidiolex studies).





# #1: Many Adult Consumers Use CBD



Source: Jan. 2019 Consumer Reports nationally representative survey of 4,355 U.S. adults.

## How to Shop for CBD

<https://www.consumerreports.org/marijuana/how-to-shop-for-cbd/>

---

- 1. Decide Why You Want to Use CBD, and in What Form**
- 2. Consider How Much THC the Product Contains**
- 3. For Products From Hemp, Find Where It Was Grown**
- 4. Ask for Test Results**
- 5. Look for Products That List the CBD Amount**
- 6. Know What Other Terms on the Label May Mean**
- 7. Avoid Products That Make Sweeping Health Claims**
- 8. Watch Out for Vaping Products With Propylene Glycol**

## FDA Regulation of Cannabis and Cannabis-Derived Products, Including Cannabidiol (CBD)

---

On this site:

- Consumer Information
- FDA Communications
- Regulatory Resources
- Questions and Answers

<https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-including-cannabidiol-cbd>

## Practical Discussion in the Office

---

- Patient provider treatment agreement (if for medicinal use).  
<https://adai.uw.edu/mcacp/docs/treatmentagreement.pdf>
- Requirement of patient obtaining a state issued medical cannabis card.
- Documentation of counseling if recreational use discussion.
- It is not illegal to have a discussion and provide counseling.
- Having the discussion, does not mean your endorsement or condoning of behavior.
- Provide resources/handout

### The Medicinal Cannabis Treatment Agreement: Providing Information to Chronic Pain Patients via a Written Document (Wilsey, et al., 2015)

- Obligation to understand & inform patients on key issues of the evidence base on cannabinoid therapeutics.
- One way to fulfill this obligation might be to use of a written agreement to describe & minimize risks.
- Method of educating patients in a manner analogous to other treatment agreements.

## Fun Fact: When will insurance pay for my medical cannabis?

---

Headline: “**German** patient wins court case to have cannabis covered by insurance.”

2017 – Mandated that statutory health insurers cover the cost of medical cannabis: serious illness, cannabis is used where other treatments have failed, and likely to provide benefit.

2018 - Cannabis is an eligible medical expense under Revenue **Canada's** Medical Expense Tax Credit. So, you can claim expenses related to medical cannabis on your tax return, as long as you have receipts from an approved Health Canada-licensed producer and medical authorization to back up your claim.

2020 - The Ministry of Health (**Czechia** - formally the Czech Republic) announced that patients will be refunded 90% of costs of up to 30 grams per month via health insurance companies.

## Final Takeaways

---

- Familiarize yourself with
  - THC, CBD dosing
  - drug : drug (plant) interactions, side effects, withdrawal
  - local dispensaries & counsel patient to accordingly
- **Consider The Treatment Agreement**
- Continue to remember “marijuana” is Federally illegal
- Informed about state laws
- Mindful of addiction, abuse, mental health issues

## Resources

---

### **Dispensary Information: Patient Focused Certification**

<http://patientfocusedcertification.org/certification/>

- Addresses product & distribution safety.
- Based on quality standards for medical cannabis products and businesses issued by the American Herbal Products Association (AHPA) and the American Herbal Pharmacopoeia (AHP) Cannabis monograph.

<http://camcd-acdcm.ca/>

- More and more states are mandating certification and regulated licensures from dispensaries (e.g. FL).

## Resources

---

- Canadian Consortium for the Investigation of Cannabinoids (CCIC): [www.ccic.net](http://www.ccic.net)  
Accredited cannabinoid education (ACE) programs  
Informed by needs assessments, expert faculty
- International Cannabinoid Research Society (ICRS): <https://icrs.co/>
- International Association for Cannabinoid Medicine (IACM): [www.cannabis-med.org](http://www.cannabis-med.org)
- University of Washington & Alcohol and Drug Abuse Institute (ADAI)  
<http://adai.uw.edu/mcaccp/index.htm>
- Society of Cannabis Clinicians: [www.cannabisclinicians.org](http://www.cannabisclinicians.org)



## Physician/Clinician Training

---

New York:

[https://www.health.ny.gov/regulations/medical\\_marijuana/practitioner/](https://www.health.ny.gov/regulations/medical_marijuana/practitioner/)

Florida:

[http://www.flhealthsource.gov/ommu/physician\\_requirements](http://www.flhealthsource.gov/ommu/physician_requirements)

All licensed MDs/DOs – some states require specialty practice (e.g. pain management, palliative care, etc.)

MS in Medical Cannabis Science and Therapeutics at the School of Pharmacy should contact [msmedicalcannabis@rx.umaryland.edu](mailto:msmedicalcannabis@rx.umaryland.edu)

Thank You

---



## Selected References

---

1. Aggarwal SK et al. Cannabinergic pain medicine: a concise clinical primer and survey of randomized-controlled trial results. *Clin J Pain*. 2013. Feb;29(2):162-71.
2. Alsherbiny MA & Li CG. Medicinal Cannabis—Potential Drug Interactions. *Medicines (Basel)*. 2019 Mar; 6(1): 3.
3. Baron EP. Medicinal properties of cannabinoids, terpenes, and flavonoids in cannabis, and benefits in migraine, headache, and pain: An update on current evidence and cannabis science. *Headache Currents*. July/August 2018: 1139-1158.
4. Bergamaschi MM, Queiroz RHC, Zuardi AW, et al. Safety and side effects of cannabidiol, a Cannabis sativa constituent. *Current drug safety*. 2011;6:237-249.
5. Blake DR et al. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. *Rheumatology (Oxford)* 2006;45:50–2.
6. Bonnet U & Preuss UW. The cannabis withdrawal syndrome: current insights. *Subst Abuse Rehabil*. 2017 Apr 27;8:9-37.
7. Burstein S. Cannabidiol (CBD) and its analogs: a review of their effects on inflammation. *Bioorg Med Chem*. 2015;23(7):1377-85.
8. Devinsky O, Cilio MR, Cross H, et al. Cannabidiol: Pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. *Epilepsia*. 2014;55(6): 791–802.
9. Erowid E, Erowid F. "The L.E.S.S. Method: A Measured Approach to Oral Cannabis." *Erowid Extracts* Nov 2011;21:6-9.

## Selected References

---

10. Fine PG et al. The endocannabinoid system, cannabinoids, and pain. *Rambam Maimonides Med J*. 2013 Oct 29;4(4):e0022.
11. Guindon J & Hohmann A. The endocannabinoid system and pain. *CNS Neurol Disord Drug Targets* 2009;8:403-421.
12. Hill KP. Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems: A Clinical Review. *JAMA*. 2015 Jun 23-30;313(24):2474-83.
13. Laprairie RB, Bagher AM, Kelly ME, Denovan-Wright EM. Cannabidiol is a negative allosteric modulator of the cannabinoid CB1 receptor. *British Journal of Pharmacology*. 2015;172(20):4790-4805.
14. MacCallum CA & Russo EB. Practical considerations in medical cannabis administration and dosing. *European Journal of Internal Medicine* 2018;49:12–19.
15. Martin-Sanchez E et al. Systematic review and meta-analysis of cannabis treatment for chronic pain. *Pain Med*. 2009Nov;10(8):1353-68.
16. Moulin D et al. Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society. *Pain Res Manag*. 2014 Nov-Dec; 19(6):328-35.
17. Nugent S, Morasco B, O'Neil M, et al. The effects of cannabis among adults with chronic pain and an overview of general harms. *Annals of Internal Medicine* 2017;167(5):319-332.
18. Olfson M, Wall MM, Liu SM, Blanco C. Cannabis Use and Risk of Prescription Opioid Use Disorder in the United States. *Am J Psychiatry*. 2018 Jan 1;175(1):47-53. doi: 10.1176/appi.ajp.2017.17040413.

## Selected References

---

19. Pennisi E. A new neglected crop: cannabis. *Science*. 2017;356(6335):232-233.
20. Rani Sagar D, Burston JJ, Woodhams SG, Chapman V. Dynamic changes to the endocannabinoid system in models of chronic pain. *Philos Trans R Soc Lond B Biol Sci*. 2012 Dec 5;367(1607):3300-11.
21. Rhyne DN, Anderson SL, Gedde M, Borgelt LM. Effects of Medical Marijuana on Migraine Headache Frequency in an Adult Population. *Pharmacotherapy*. 2016 May;36(5):505-10.
22. Russo E. Cannabinoids in the management of difficult to treat pain. *Ther Clin Risk Manag* 2008;4(1):245-259.
23. Russo EB. Clinical Endocannabinoid Deficiency Reconsidered: Current Research Supports the Theory in Migraine, Fibromyalgia, Irritable Bowel, and Other Treatment-Resistant Syndromes. *Cannabis and Cannabinoid Research* 2016 1(1):154-165.
24. Russo EB. Cannabidiol Claims and Misconceptions. *Trends Pharmacol Sci*. 2017 May;38(5):499.
25. Stout SM & Cimino NM. Exogenous cannabinoids as substrates, inhibitors, and inducers of human drug metabolizing enzymes: a systematic review. *Drug Metab Rev*. 2014 Feb;46(1):86-95.
26. Verstraete AG. Detection times of drugs of abuse in blood, urine, and oral fluid. *Ther Drug Monit*. 2004 Apr;26(2):200-5.
27. Walsh Z, Gonzalez R, Crosby K, et al. Medical cannabis and mental health: a guided systematic review. *Clin Psychol Rev* 2017;51:15-29.
28. Wilsey B, Atkinson JH, Marcott TD, Grant I. The Medicinal Cannabis Treatment Agreement: Providing Information to Chronic Pain Patients via a Written Document. *Clin J Pain*. 2015; 31(12): 1087–1096. doi:10.1097/AJP.000000000000145.