Cannabis and Your Patient: The Good, The Bad, and The Ugly

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American College of Apothecaries Research & Education Foundation

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Disclosures

Employee of ARL Bio Pharma

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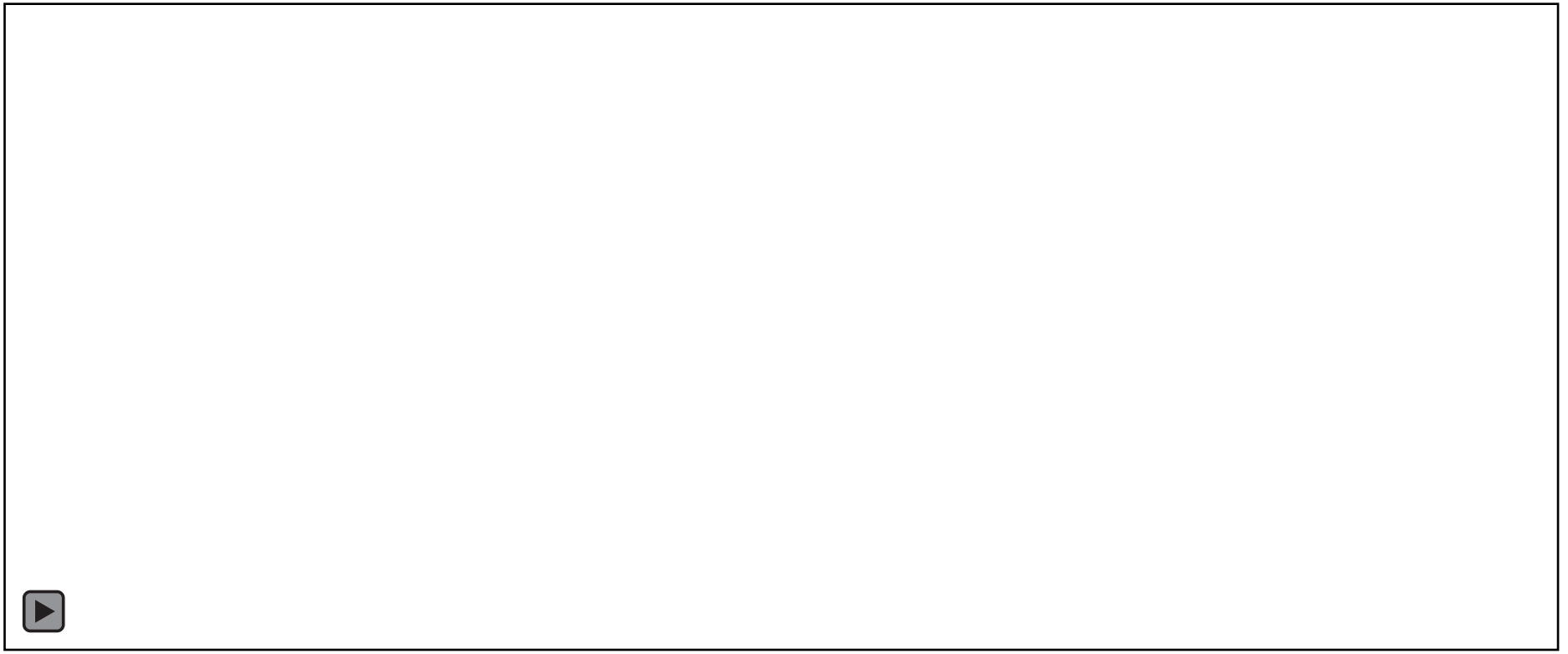

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Learning Objectives

At the conclusion of this program, the participating Healthcare provider will understand:

- Define Pharmacodynamics and Pharmacokinetics of Marijuana
- Define the Medical Implications of Marijuana Including:
  - THC and CBD
- Identify Marijuana and its Implications in Healthcare

Medical Marijuana (MM)

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History of Use

- 400 AD: First Medicinal Use (China)
- 1851: Included in *USP*
- 1937: Marihuana Tax Act Restricted Sales/Use
- 1942: Removed from USP

Bridgeman MB and Abazia, DT. Medicinal Cannabis: History, Pharmacology, and Implications for the Acute Care Setting. *Pharmacology and Therapeutics*. 2017;42(3):180-188

History of Use

- 1970: Prohibition Under Controlled Substances Act (CSA)
- 1996: California first state to legalize
- 2017: Decriminalized in 21 states and D.C.

  Recreational use legalized in 8 states

Bridgeman MB and Abazia, DT. Medicinal Cannabis: History, Pharmacology, and Implications for the Acute Care Setting. *Pharmacology and Therapeutics*. 2017;42(3):180-188

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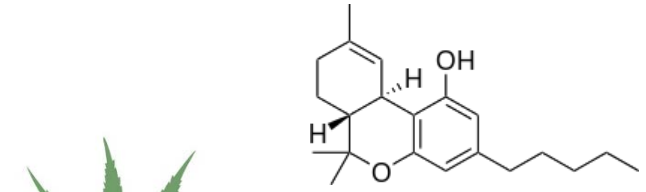
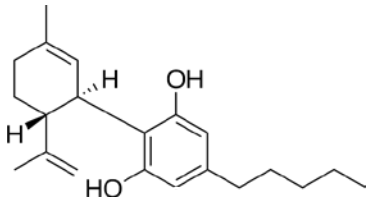
Chemical Entity vs Cultivar

- Chemical Entity
  Based on chemical profile



- Cultivar (variety)
  Domesticated Plants
  Breeding and genetic stabilization



- "Skunk #1", "Haze", "Northern Lights",
  "AK47", "Bubblegum", "White Widow

Fug-Berman A, Wood S, Kogan M, et al. *An Introduction to the Biochemistry & Pharmacology of Medical Cannabis*. Department of Health

3 Main Cultivars

- *Cannabis sativa*
- Higher THC content
- Stimulating, uplifting, energizing and creativity enhancing
- Better at treating depression, headaches, nausea and loss of appetite

Fug-Berman A, Wood S, Kogan M, et al. *An Introduction to the Biochemistry & Pharmacology of Medical Cannabis*. Department of Health

3 Main Cultivars

- *Cannabis indica*
- Higher CBD content
- Relaxing, sedating, pain reducing
- Better at treating pain, inflammation, muscle spasms, epilepsy, glaucoma and insomnia

Fug-Berman A, Wood S, Kogan M, et al. *An Introduction to the Biochemistry & Pharmacology of Medical Cannabis*. Department of Health

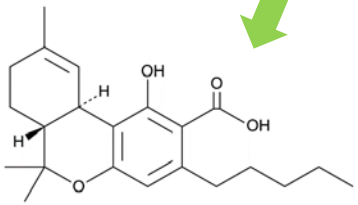
3 Main Cultivars

- *Cannabis ruderalis* (Higher CBD content)

Fug-Berman A, Wood S, Kogan M, et al. *An Introduction to the Biochemistry & Pharmacology of Medical Cannabis*. Department of Health

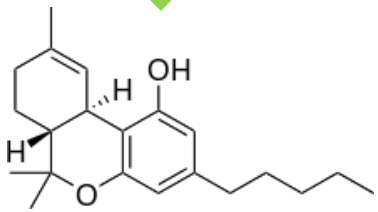
Cannabis Pharmacology

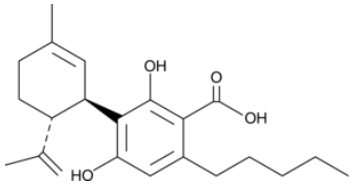
Tetrahydrocannabinolic acid-A (THCA-A)



Heat

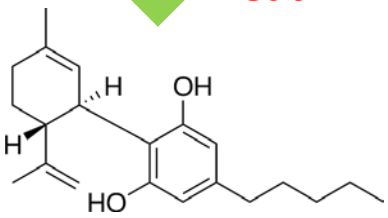
Tetrahydrocannabinol (THC)





Heat

Cannabidiolic acid (CBDA)



Cannabidiol (CBD)

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Endogenous Cannabinoid Agonists

- Anandamide (AEA)
- 2-arachidonoylglycerol (2-AG)

Fug-Berman A, Wood S, Kogan M, et al. *An Introduction to the Biochemistry & Pharmacology of Medical Cannabis*. Department of Health

Endogenous Cannabinoid Agonists

- Originate from cell membranes
- Not stored in synaptic vesicles
- Cleaved into arachidonic acid and:

  Ethanolamine (AEA)

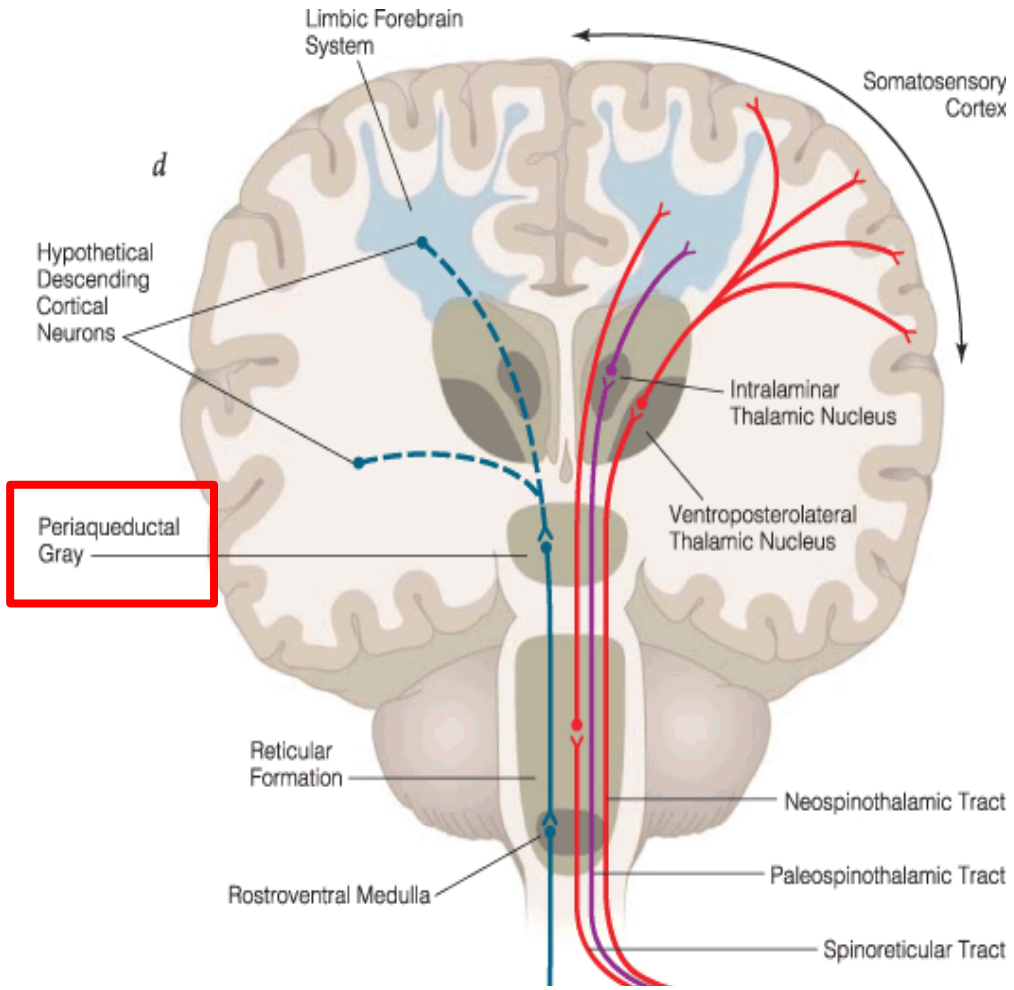
  Glycerol (2-AG)
- Arachidonic acid linked to prostaglandins

Fug-Berman A, Wood S, Kogan M, et al. *An Introduction to the Biochemistry & Pharmacology of Medical Cannabis*. Department of Health

Neural Distribution of CB1 Receptors

Brain CB1 Receptors:

- Periaqueductal gray
- Raphe nuclei
- Central-medial thalamic nuclei

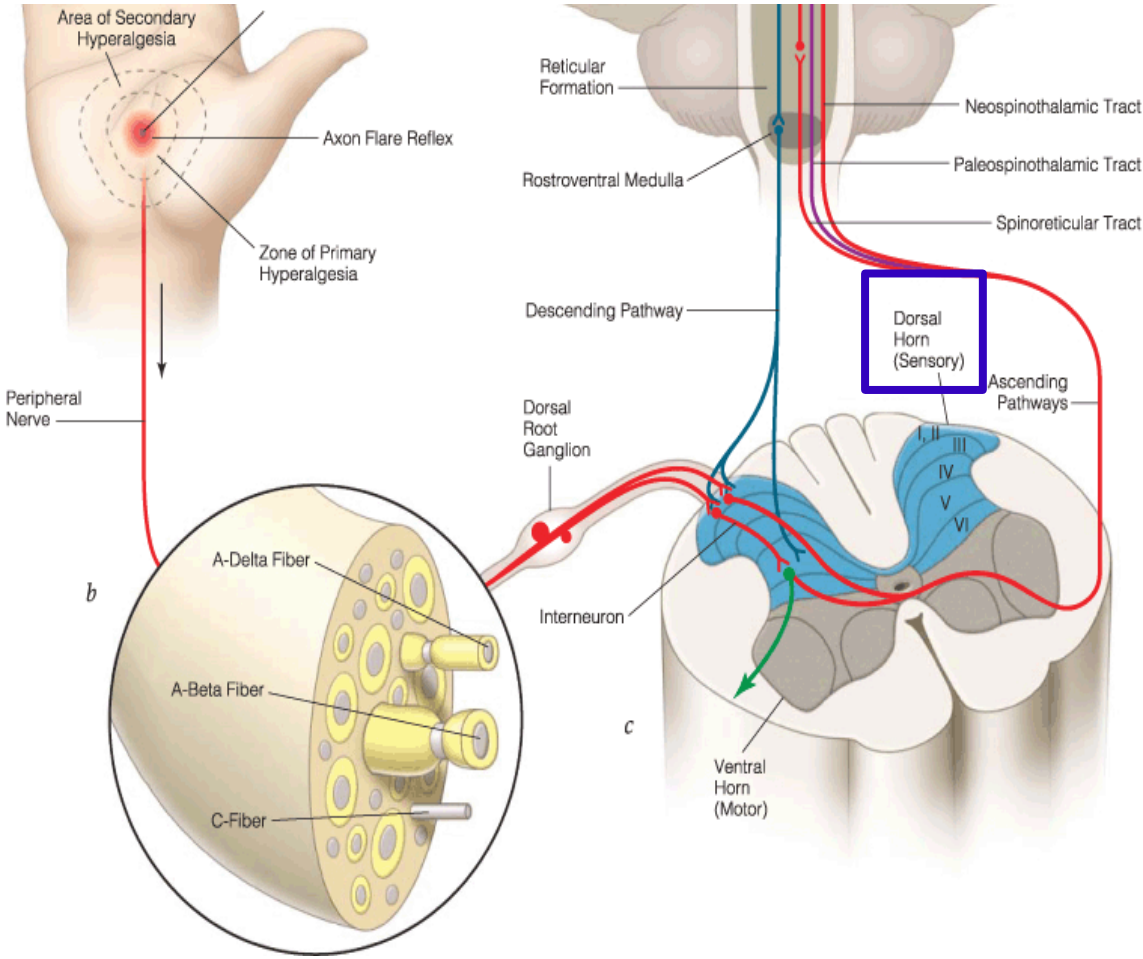


Daniel D. Federman, M.D., Elizabeth G. Nabel, MD, eds. 2012. ACP Medicine. Hamilton, Ontario & Philadelphia, PA. Decker Publishing Inc. ISSN 1547-1659.

Bushlin I, Rozenfeld R, and Devi LA. Cannabinoid-opioid interactions during neuropathic pain and analgesia. *Current Opinion in Pharmacology.* 2010;10-80-86

Neural Distribution of CB1 Receptors

CB1 Receptors are Also Found Within the Superficial **Dorsal Horn** of the Spinal Cord



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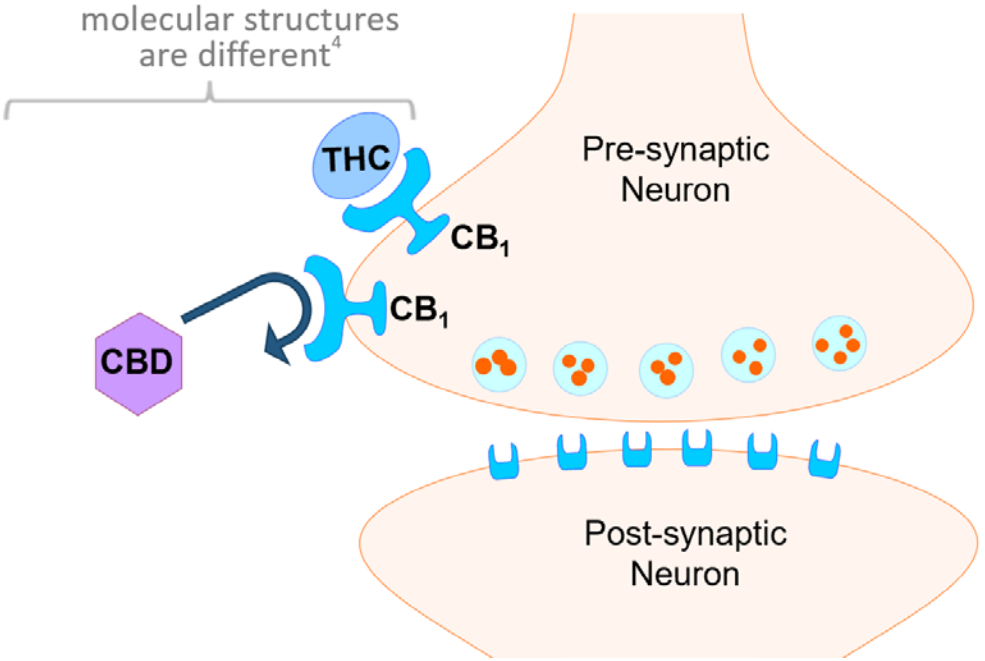
Distinct Cannabinoid Mechanisms

- THC potently binds CB_1 receptors in the CNS resulting in its euphoric effects [1-3]
- CBD has very poor affinity for CB_1 receptors and lacks euphoric effects[1,2,5]



1. Perucca E. J Epilepsy Res 2017;7(2):61-76; 2. Rosenberg EC et al. Neurotherapeutics 2015;12:747–768; 3. Grotenhermen F. Cannabinoids 2006;1(1):10-14; 4. Di Marzo V et al. Nat Rev Drug Dis 2004;3:771-784; 5. Pertwee RG. Br J Pharmacol 2008;153:199–215.

Neural Effects of CB1 Receptors

- Activation of CB1 Receptors Produces:

  Anti-nociception

  Hypothermia and Sedation

  Hypotension

  Inhibition of Intestinal Motility

  Motor depression

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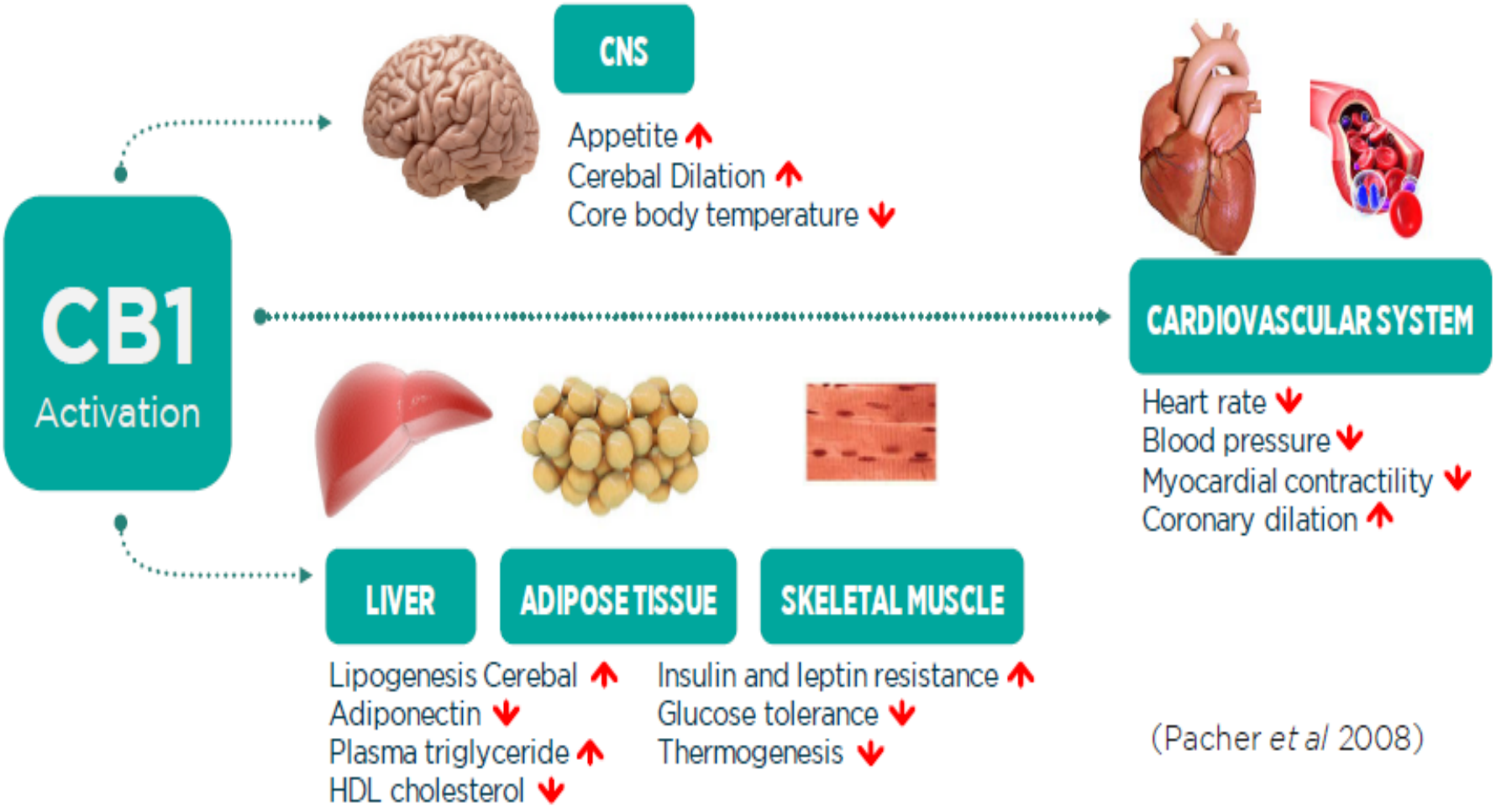
CB1 Receptors Beyond the CNS



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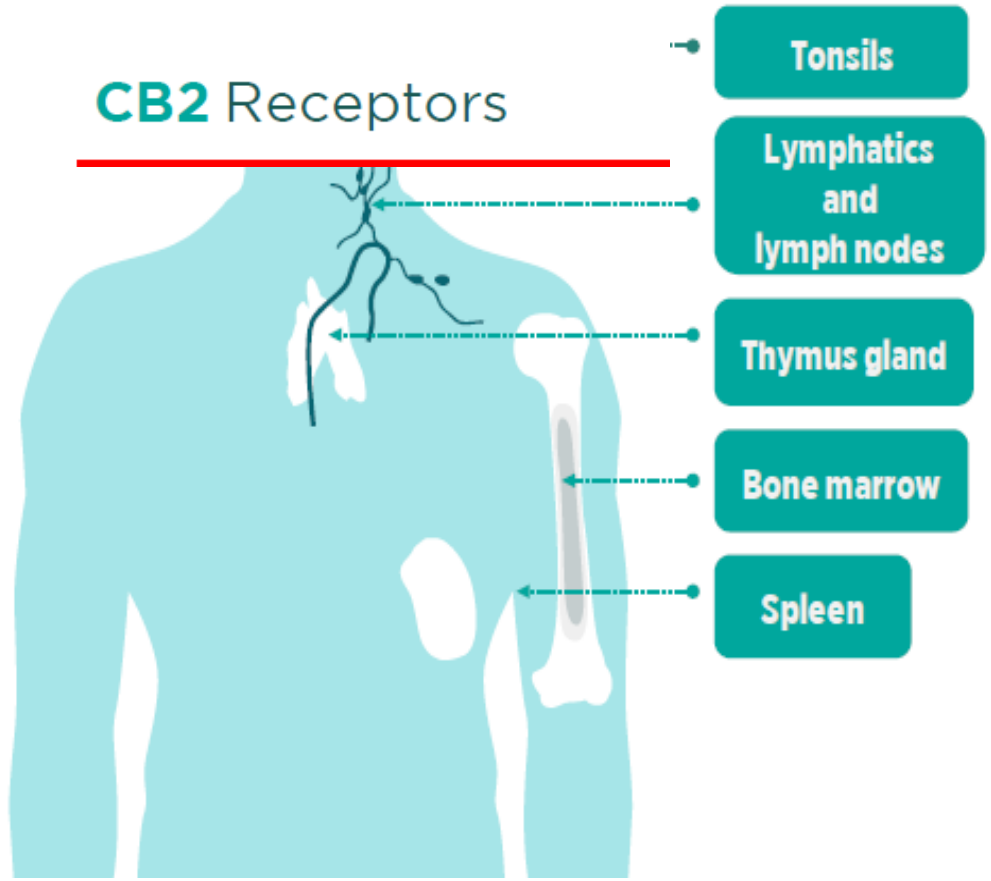

- CB2:

  Mainly expressed in the immune system and hematopoietic cells

  Immuno-modulation effects

Fug-Berman A, Wood S, Kogan M, et al. *An Introduction to the Biochemistry & Pharmacology of Medical Cannabis*. Department of Health

Signal Transduction Pathways

- CB1 receptors are G-protein coupled receptors that couple to $G_{\alpha i}$ and inhibit cAMP production
- Activate MAP kinases
- Inhibit calcium channels and activate of potassium channels

Bushlin I, Rozenfeld R, and Devi LA. Cannabinoid-opioid interactions during neuropathic pain and analgesia. *Current Opinion in Pharmacology.* 2010;10-80-86

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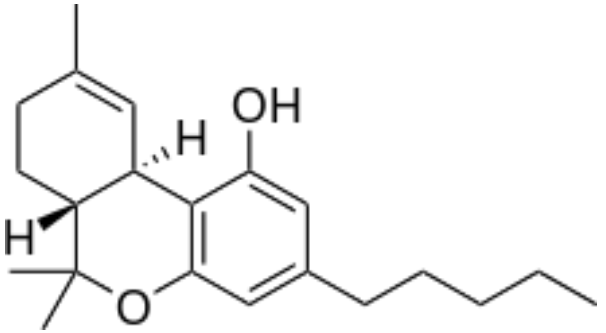
THC



- CB1 >>> CB2 partial agonist

  ↑ appetite, cerebral dilation

  ↓ core temperature, heart rate, myocardial contractility

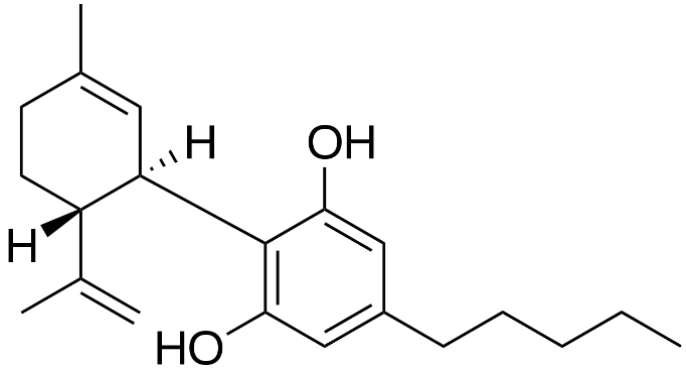
- Psychoactive

  11-OH-THC 4x more potent

- Lipophilic
- Anti-inflammatory, neuro-protective
- Anti-nausea, analgesia

Fug-Berman A, Wood S, Kogan M, et al. *An Introduction to the Biochemistry & Pharmacology of Medical Cannabis*. Department of Health

CBD



- Non-psychoactive
- Inhibits formation of 11-OH-THC
  Mitigates psychoactive effects of THC
  Enhances therapeutic effects of THC
- Inhibits adenosine uptake
- Inhibits release of pro-inflammatory cytokines
- Potent CYP2D6 and CYP3A1 inhibitor
- **Meta-analysis suggests clinical improvement in seizure frequency for certain seizure disorders**

Fug-Berman A, Wood S, Kogan M, et al. *An Introduction to the Biochemistry & Pharmacology of Medical Cannabis*. Department of Health

Pharmacokinetics

- Inhalation

  Onset of ~90 seconds with peak at 3-10 minutes

  Easier to titrate

  Cleared in 3 hours

  Similar carcinogens and bronchial irritants as cigarette smoking

MacCallum CA, and Russo EB. Practical considerations in medical cannabis administration and dosing. *European Journal of Internal Medicine*. 2017; 49(2018):12-19

Pharmacokinetics

- Oral

  Onset of 90 minutes with peak at 1-6 hours

  Half life is 20-30 hours

  Low and erratic GI bioavailability with first past metabolism

    50% of the THC is metabolized before entering systemic circulation

  “Start low and go slow”

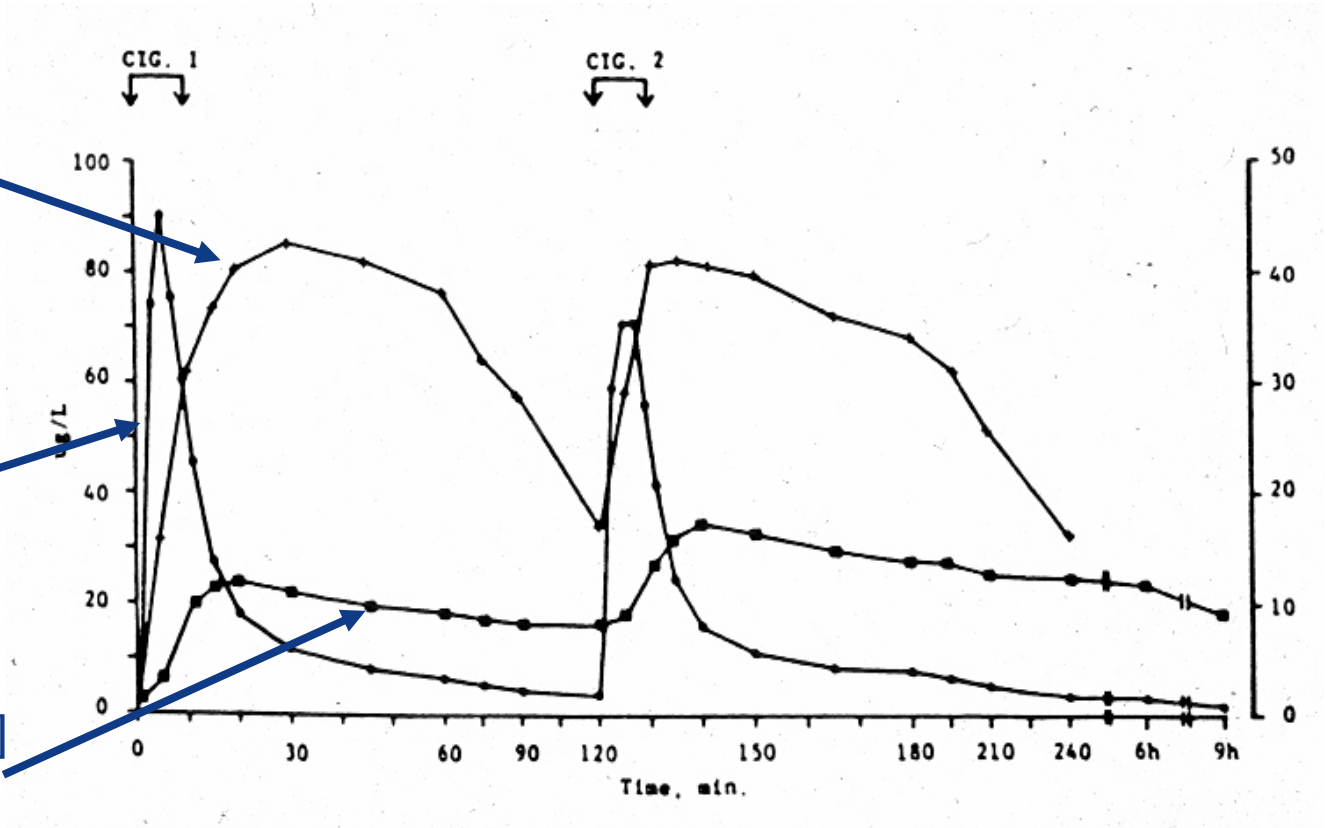
MacCallum CA, and Russo EB. Practical considerations in medical cannabis administration and dosing. *European Journal of Internal Medicine*. 2017; 49(2018):12-19

Blood Cannabinoids vs “high” (After Smoking 2 Marijuana Joints)

“high”

[THC]
active

[THCCOOH]
Non-active



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Drug Interaction Concerns

- Interactions may exist between medical marijuana and other drugs
- CYP2C9 and 3A4 play a significant role in the primary metabolism of THC

  3A4 inhibitors will ↑ THC concentrations
- CYP2C19 and 3A4 are responsible for CBD metabolism

Bridgeman MB and Abazia, DT. Medicinal Cannabis: History, Pharmacology, and Implications for the Acute Care Setting. *Pharmacology and Therapeutics*. 2017;42(3):180-188

Routes of Administration

- Common:

  Inhalation: Smoking and vaporization

  Edibles

- Others

  Topical

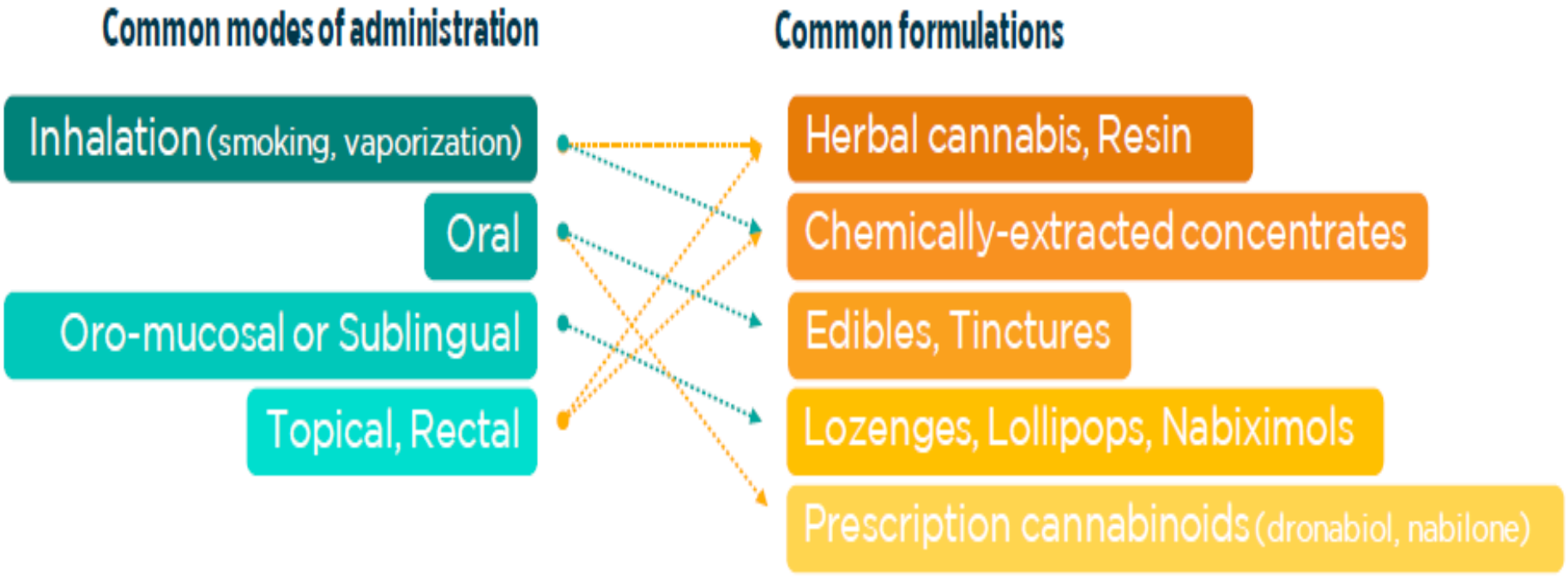
  Rectal

  Oral: Oro-mucosal/sublingual

Dosage Forms

- Herbal/joints
- Chemically-extracted concentrates
  Has varying amounts of THC
- Resin
- Edibles, tinctures, oils
- Lozenges, lollipops
- Prescription oral products

Common Forms and Routes of Administration



Fug-Berman A, Wood S, Kogan M, et al. *An Introduction to the Biochemistry & Pharmacology of Medical Cannabis*. Department of Health

Quality Control Concerns

- May be contaminated with harmful fungi and bacteria (McPartland, et. al.)
- Pesticides may leave residues (Sullivan, et. al.)

- Quality control standards for cultivation, drying, packaging, and analytical testing

  Should be more strictly enforced

McPartland JM and Pruitt PL. Medical marijuana and its use by the immunocompromised. *Altern Ther Health Med.* 1997; 3(3):39-45

Sullivan N, Elzinga, and Raber JC. Determination of Pesticide Residues in Cannabis Smoke. *Journal of Toxicology.* 2013; 2013:1-6

Chemical Extraction Concerns

- Extraction processes may leave behind residual solvents
- E-cigarette formulations often contain propylene glycol

  Carbonyls (e.g. formaldehyde) may form when vaporizing
- Extraction may remove medically beneficial terpenoids

Fug-Berman A, Wood S, Kogan M, et al. *An Introduction to the Biochemistry & Pharmacology of Medical Cannabis*. Department of Health

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CBD Purification Concerns

- Positive marijuana tests for CBD users
- Quality control

  Sensitivity and specificity of assays for testing purposes
- 0.3% vs 0.1% THC content

Current U.S. FDA Approved Drugs

- Dronabinol (Marinol) – May 1985

  THC (2.5, 5, or 10mg) - $200

  Chemo related nausea/vomiting

  AIDS-associated anorexia

Dronabinol, nabilone, and cannabidiol monographs. Lexi-Comp, Inc. (Lexi-Drugs™). Lexi-Comp, Inc.; October 8, 2018

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Current U.S. FDA Approved Drugs

- Nabilone (Cesamet) – December 1985

  THC (1mg) – $2,000

  Chemo related nausea/vomiting

Dronabinol, nabilone, and cannabidiol monographs. Lexi-Comp, Inc. (Lexi-Drugs™). Lexi-Comp, Inc.; October 8, 2018

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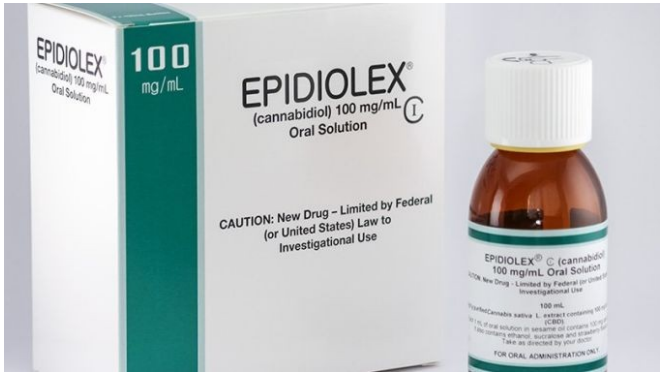
Current U.S. FDA Approved Drugs

- Cannabidiol (Epidiolex) – June 2018

  CBD (100 mg/mL; 100 mL) – $14.82 per 1 mL

  Lennox-Gestault Syndrome

  Dravet Syndrome



Dronabinol, nabilone, and cannabidiol monographs. Lexi-Comp, Inc. (Lexi-Drugs™). Lexi-Comp, Inc.; October 8, 2018

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Products Outside the U.S.

- Nabiximols (Sativex) – THC/CBD

  Oro-mucosal Spray

  Multiple Sclerosis and Cancer Pain

Products Outside the U.S.

- Canasol:

  Available in Jamaica

  Ophthalmic Drops

Disadvantages of THC Only Products

- Lack constituents that mitigate side effects:

  CBD

  Terpenoids

- Harmful effects more likely in the elderly and frail

Disadvantages of THC Only Products

- Dronabinol Adverse Effects

  Lethargy and Dizziness

  Anxiety and Paranoia

  Seizure risk

  Depersonalization

- Additional Nabilone Adverse Effects:

  Dry mouth

Clinical Applications

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Substantial Evidence For…

- MM is effective for

  Treatment of chronic pain in adults

  Chemotherapy-induced nausea and vomiting

  Improving **patient-reported** spasticity symptoms in multiple sclerosis

National Academies of Sciences, Engineering, and Medicine. 2017. *The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research.* Washington, DC: The National Academies Press. doi:10.17226/24625.

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Synergy with Opiate Use

- Cannabinoids act as opioid sparing agents

  Lower Doses

  Fewer Side Effects

Elikottil J, et al. The Analgesic Potential of Cannabinoids. *J Opioid Manag.* 2009

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Synergy with Opiate Use

- MM use associated with

  64% Decrease in Opioid Use (n=118)

  Decreased Number of Medications

  Fewer Side Effects

  Improved Quality of Life (45%)

Boehnke KF, et al.. Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients With Chronic Pain. *The Journal of Pain*. 2016

CBD Decreases Inflammation in Multiple Sclerosis

- Modified the deleterious effects of inflammation
- CBD decreased the transmigration of blood leukocytes to decrease inflammation
- Improves MS associated motor deficits

Mecha M, et al. Cannibidiol provides long-lasting protection against deleterious effects of inflammation in a viral model of MS. *Neurobiol Dis* 2013 2011:59C:141-150

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Neuropathic Pain

- A single inhalation of 25 mg smoked cannabis of three times daily for 5 days

  Reduced pain intensity

  Improved sleep

  Well tolerated

- Neuropathic pain reduction was modest compared to gabapentin and pregabalin

Ware MA, Wang T, Shapiro S, et al. Smoked cannabis for chronic neuropathic pain: a randomized control trial. *Canadian Medical Association Journal*. 2010; 182(14):E694-E701

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Glaucoma

- Recent review by the American Society of Glaucoma indicated that marijuana does lower intraocular pressure for 3-4 hours requiring frequent administration

- ASG does NOT recommend for treatment of glaucoma due to the short duration of effectiveness

Jampel H. J Glaucoma. 2010 Feb; 19(2):75-6

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Anti-emesis

- Systematic review and meta-analysis found cannabinoids were superior to conventional drugs
- Chemotherapy-induced nausea and vomiting

  Dronabinol: Statistically and clinically more effective than neuroleptics

  Nabilone: Clinically but not statistically more effective

Machado Rocha FC, et al. Therapeutic use of Cannabis sativa on chemotherapy-induced nausea and vomiting among cancer patients: systematic review and meta-analysis. *Eur J Cancer Care(Engl)*. 2008 Sep;17(5):431-43.

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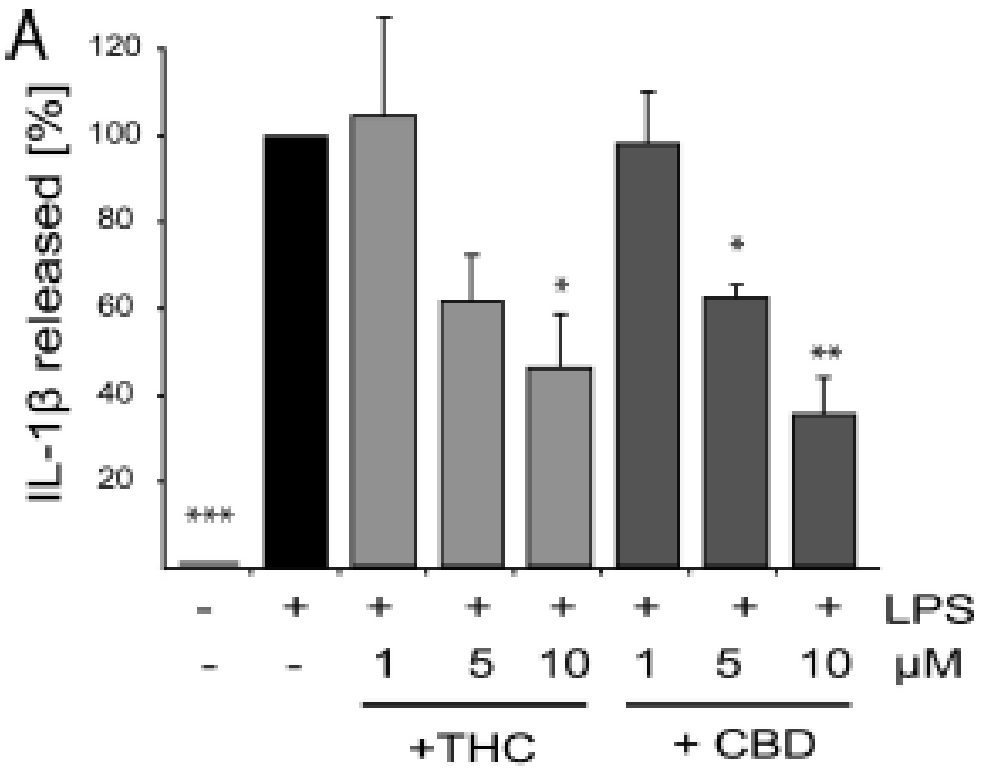
THC/CBD Decreases Inflammation



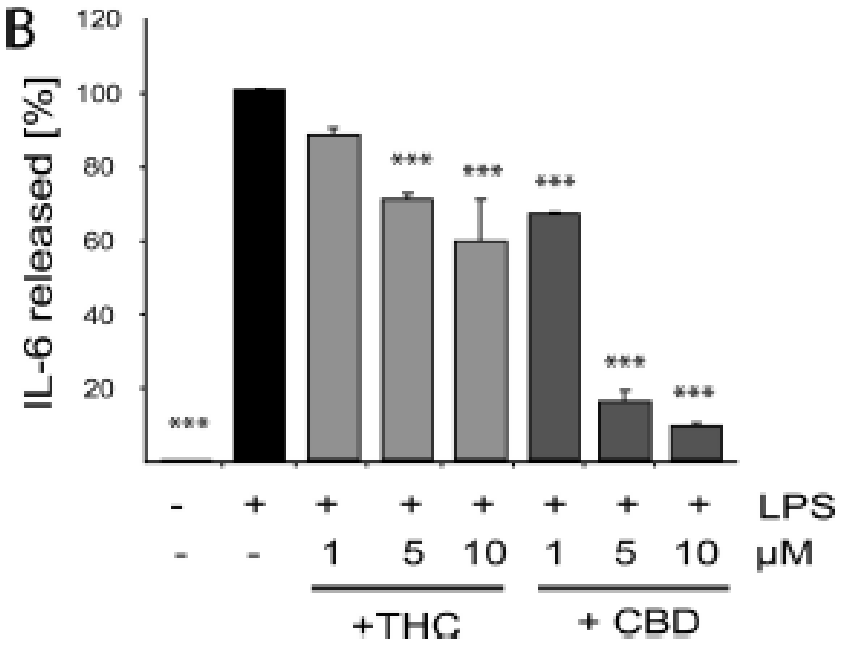


FIGURE 1. **THC and CBD inhibit the LPS-induced release of IL-1β and IL-6 from BV-2 cells.** Cells were preincubated for 2 h with the indicated concentrations of THC or CBD and then activated for 4 h with 100 ng/ml LPS. Cell-free media were then collected, and the release of IL-1β (*A*) and IL-6 (*B*) was measured using ELISA. The percentage compared with LPS applied alone (marked as 100%) is expressed as the mean ± S.E. of three independent experiments. One-way ANOVA was used as follows: IL-1β, $F(7,16) = 10.21$, $p < 0.001$ and IL-6 $F(7,16) = 81.8$, $p < 0.0001$. Bonferroni post hoc test: *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$ show significant differences from LPS-treated cells.

Kozela E, et al. Cannabinoids THC and CBD differentially inhibit lipo-polysaccahride-activated NK-kappaB and interferon-beta proinflammatory pathways in microglial cells. *J Biol Chem*. 2010 Jan 15;285(3):1616026

THC/CBD Decreases Inflammation

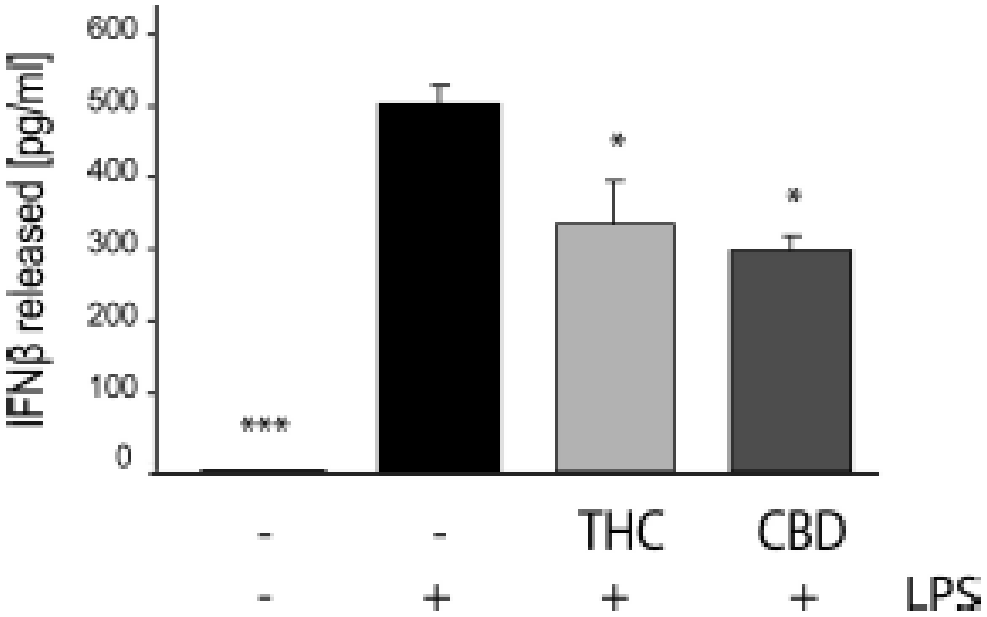


FIGURE 2. **THC and CBD decrease the LPS-induced release of IFNβ from BV-2 cells.** Cells were pretreated for 2 h with THC or CBD (both at 10 μM) and then activated for 4 h with 100 ng/ml LPS. Cell-free media were then collected and subjected to ELISA for IFNβ. Each *bar* represents the mean (in pg/ml) ± S.E. from three independent experiments. One-way ANOVA was used as fol-

Kozela E, et al. Cannabinoids THC and CBD differentially inhibit lipo-polysaccahride-activated NK-kappaB and interferon-beta proinflammatory pathways in microglial cells. *J Biol Chem*. 2010 Jan 15;285(3):1616026

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Adverse Effects

- Addiction risk increases
- Mental illness risk with early exposure
- Cognitive development deficits
- Development of respiratory problems

Volkow ND, Rubed DB, Compton WM, et al. Adverse Health Effects of Marijuana Use. *The New England Journal of Medicine.* 2014:2219-2227

Review Article of Adverse Effects

Effect	Overall Level of Confidence*
Addiction to marijuana and other substances	High
Abnormal brain development	Medium
Progression to use of other drugs	Medium
Schizophrenia	Medium
Depression or anxiety	Medium
Diminished lifetime achievement	High
Motor vehicle accidents	High
Symptoms of chronic bronchitis	High
Lung cancer	Low

- Possible gateway drug
- Motor vehicle accidents increase 2-fold after marijuana use
- E.R. visits have increased yearly due to marijuana use

Volkow ND, Rubed DB, Compton WM, et al. Adverse Health Effects of Marijuana Use. *The New England Journal of Medicine.* 2014:2219-2227

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Risk Factors for MM Use Problems

- Using MM at Earlier Ages
- Increases in Frequency of MM Use
- Male Sex
- Cigarette Smoking
- **Stimulant Treatment for ADHD is NOT a Risk Factor**

National Academies of Sciences, Engineering, and Medicine. 2017. *The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research.* Washington, DC: The National Academies Press. doi:10.17226/24625.

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MM as a Possible Gateway Drug

- Moderate evidence suggests a relationship between MM use and other substance use disorders:

  Alcohol

  Tobacco

  Other illicit drugs

National Academies of Sciences, Engineering, and Medicine. 2017. *The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research.* Washington, DC: The National Academies Press. doi:10.17226/24625.

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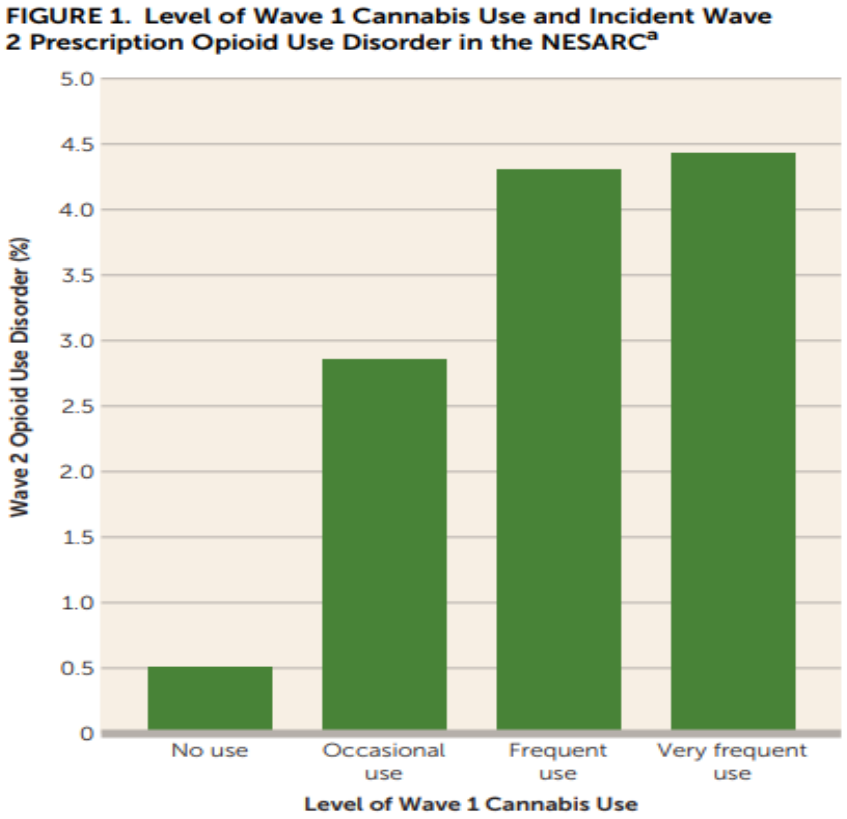
Cannabis Use and Risk of Prescription Opioid Use Disorder in the U.S.

Cannabis use appears to increase risk of developing non-medical prescription opioid use and opioid use disorder



Olfson M, et al. Cannabis Use and Risk of Prescription Opioid Use Disorder in the United States. *Am J Psychiatry.* 2018175(1):47-53

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Federal Law

- Marijuana is a Schedule I under the Controlled Substances Act of 1970

  Recreational or Medical

- According to the DEA, Schedule I means:

  “No Currently Accepted Medical Use”

  “High Potential for Abuse”

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Hemp Farming Act: Proposed 2018

- Redefines Hemp to include all derivatives, extracts, and cannabinoids with THC ≤ 0.3%
- Hemp removed from the CSA

  THC and derivatives remain Schedule I
- State may cultivate hemp independent of federal research programs if passed

Corroon J, Knight R. Regulatory Status of Cannabidiol in the United States: A Perspective. *Cannabis Cannabinoid Res.* 2018 Sep 27;3(1):190-194

Further Information

Epilepsy & Behavior 70 (2017) 288–291

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/yebeh

The legal status of cannabis (marijuana) and cannabidiol (CBD) under U.S. law

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ABSTRACT

In the United States, federal and state laws regarding the medical use of cannabis and cannabinoids are in conflict and have led to confusion among patients, caregivers, and healthcare providers. Currently, cannabis is legal for medical purposes in 50% of the states, and another seventeen states allow products that are high in cannabidiol (CBD) and low in THC (tetrahydrocannabinol) for medical use. Many of these artisanal products are sold in dispensaries or over the internet. However, none of these products has been approved by the Food and Drug Administration (FDA). Understanding how federal laws apply to clinical research and practice can be challenging, and

Further Information

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PERSPECTIVE Open Access

Regulatory Status of Cannabidiol in the United States: A Perspective

Jamie Corroon[1,2,*] and Rod Kight[3]

Abstract

Cannabidiol (CBD) is 1 of > 100 cannabinoids found in *Cannabis sativa* L. (*Cannabis spp.* or *Cannabis*). Despite its complex and rapidly evolving regulatory status in the United States, projected retail sales of CBD products—hemp, cannabis and pharmaceutical—are as high as $1.9 billion by 2020. CBD products can currently be purchased online, over the counter, and at cannabis-specific dispensaries throughout most parts of the country, despite the fact that CBD is presently deemed a Schedule I controlled substance by the U.S. Drug Enforcement Administration and renounced as a dietary supplement ingredient by the U.S. Food and Drug Administration

Summary- Medical Marijuana

- THC is primary psychoactive component of cannabis with higher affinity for CB1 and CB2 receptors
- CBD is the non-psychoactive component that can mitigate the THC side effects
- Quality Control Concerns- MM and CBD

Summary- Medical Marijuana

- CB1 receptors are found in the CNS
- CB2 receptors are found in the immune system
- There are many routes of administration and many dosage forms with different pharmacokinetic parameters

Summary- Medical Marijuana

- MM has demonstrated benefit in chemotherapy-induced nausea and vomiting and chronic pain and spasticity symptoms in multiple sclerosis

- MM remains federally illegal, and the DOJ reserves the right to enforce law at any time

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