PainWeek

ADVANCED EDUCATION

CERTIFICATION SERIES

CANNABINOIDS

Pharmaceutical & Commercial Cannabinoid Products

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Faculty Disclosure

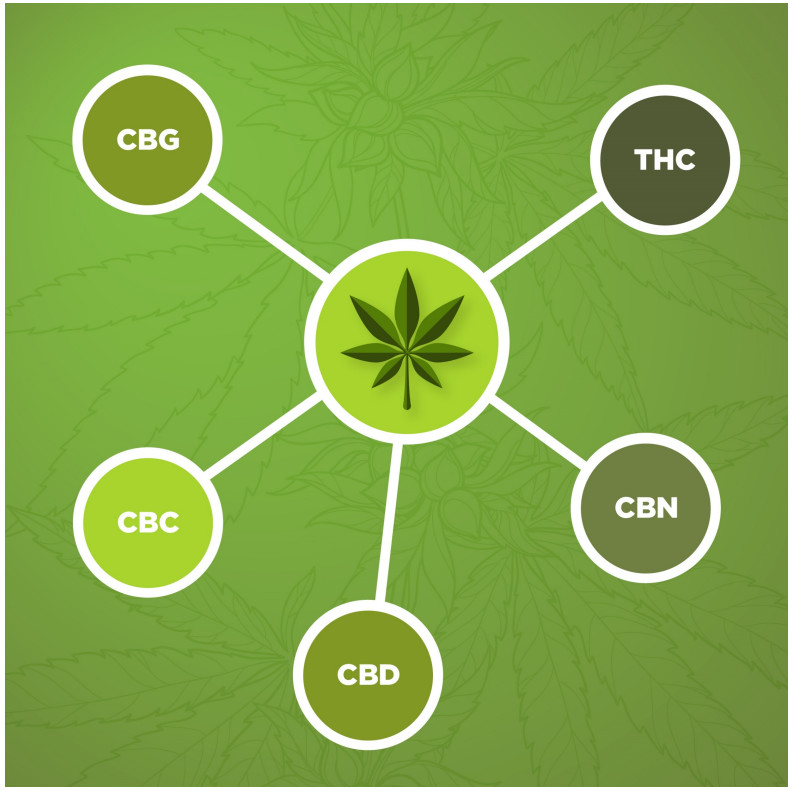
- Consulting Fee: HealthXL, Speranza
- Other: Expert Witness—Cardinal Health

This presentation was not a part of the presenter's official duties at the WVU and does not represent the opinion of WVU

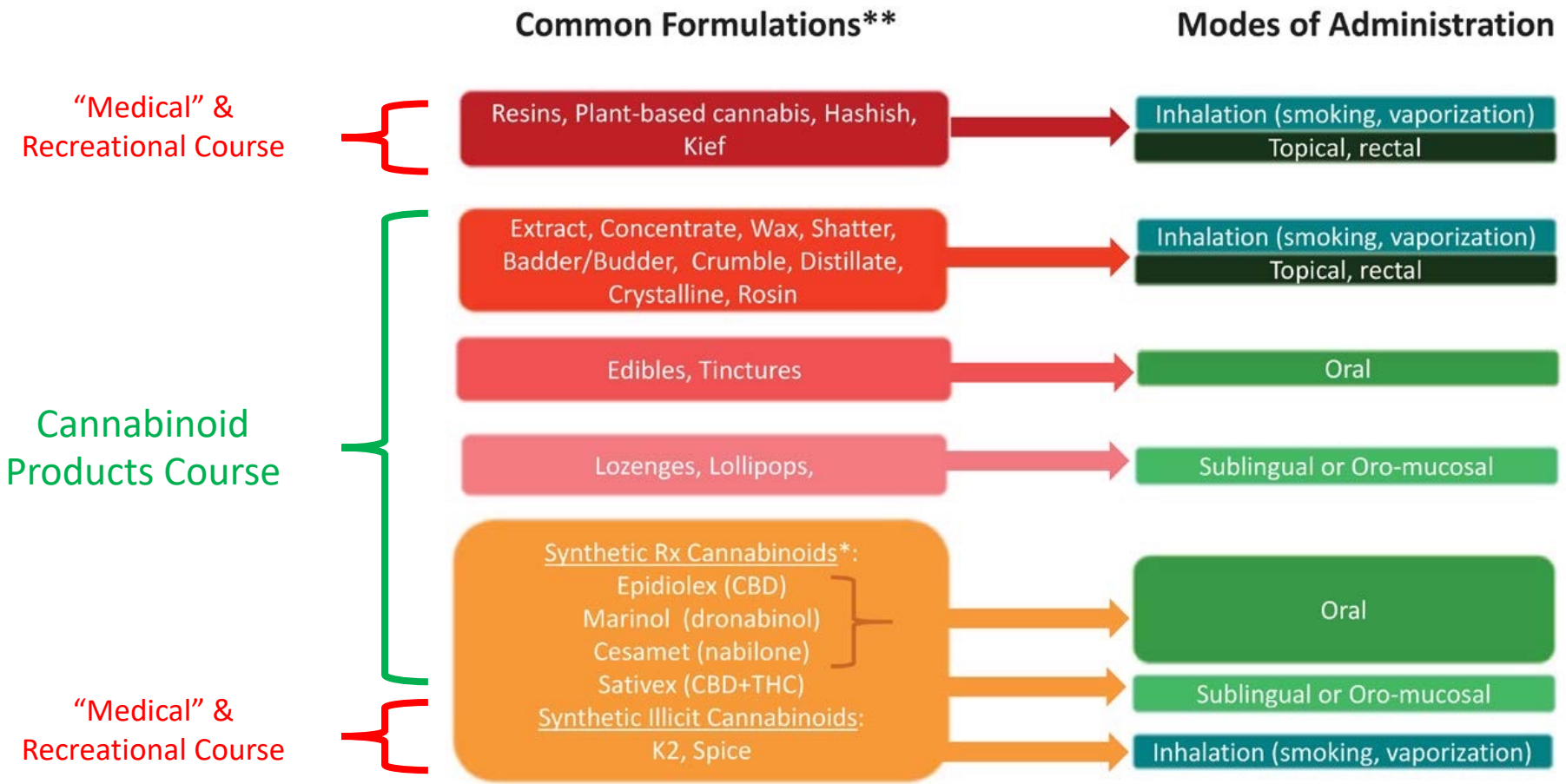
Learning Objectives

- Explain how to differentiate various CBD and THC products based on pharmacological properties.
- Identify practical CBD and THC dosing with an air of caution to the reality that products are not universally regulated for actual content.
- Recall mechanisms of action of novel cannabinoids currently being studied.

Cannabinoids



Cannabis Formulations & Administrations



Robert L. Page. Circulation. Medical Marijuana, Recreational Cannabis, and Cardiovascular Health: A Scientific Statement From the American Heart Association, Volume: 142, Issue: 10, Pages: e131-e152

Cannabinoids

Endo-Cannabinoids

Phyto-Cannabinoids

Synthetic Cannabinoids

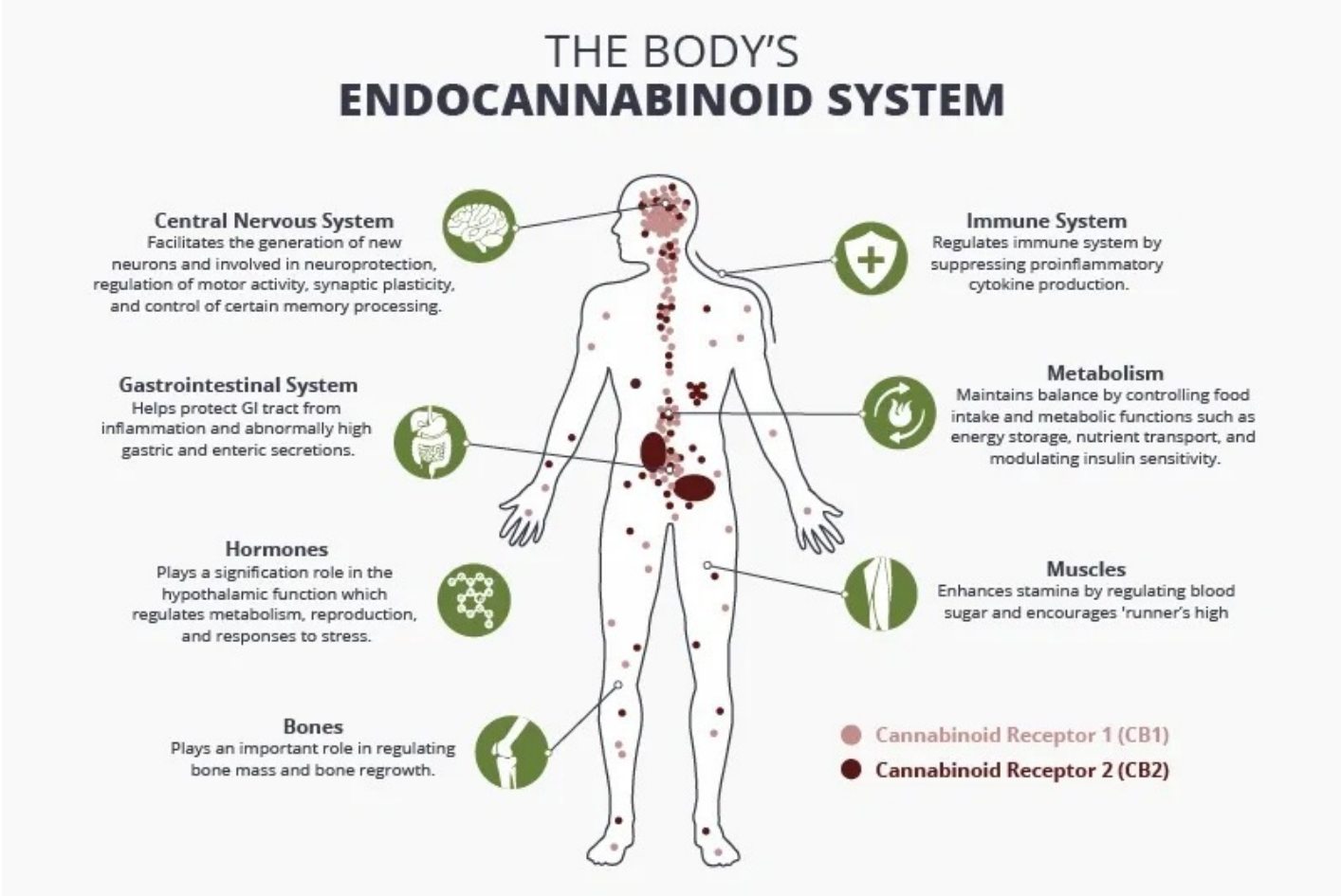
Cannabinoids

Endo-Cannabinoids

Phyto-Cannabinoids

Synthetic Cannabinoids

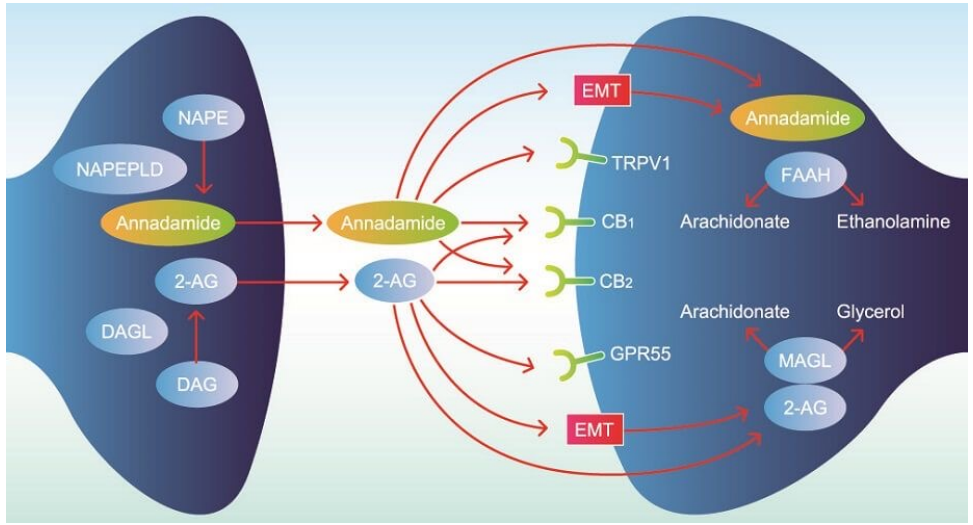
Endocannabinoid System

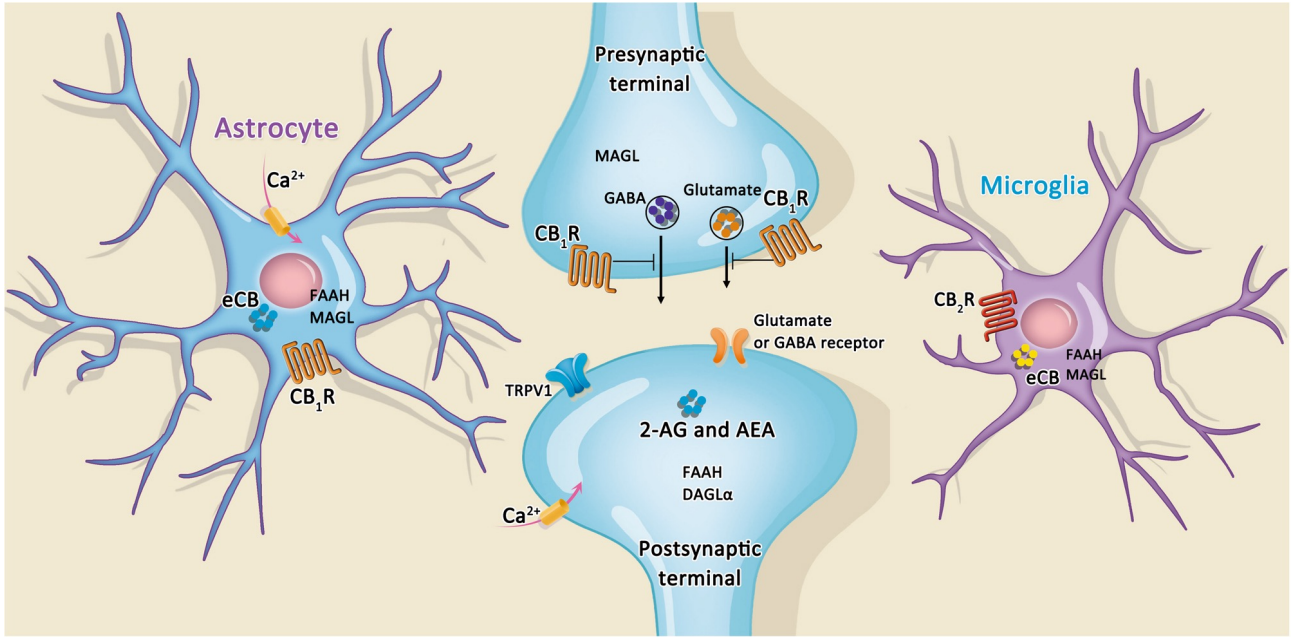


summitreleaf.com/2020/05/04/the-endocannabinoid-system/.

Endocannabinoid System

Pre/Post Synaptics, Astrocytes, and Microglia





biologydictionary.net/endocannabinoid-system/.
Yin. *Acta Pharmacol Sin.* 2019;40:336-341.

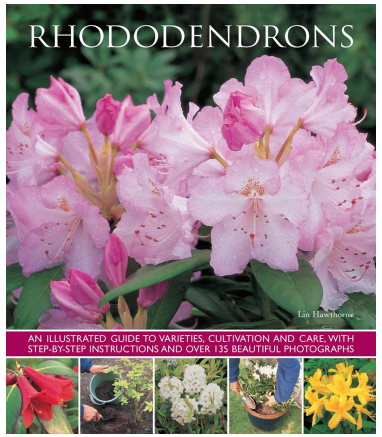
Cannabinoids

Endo-Cannabinoids

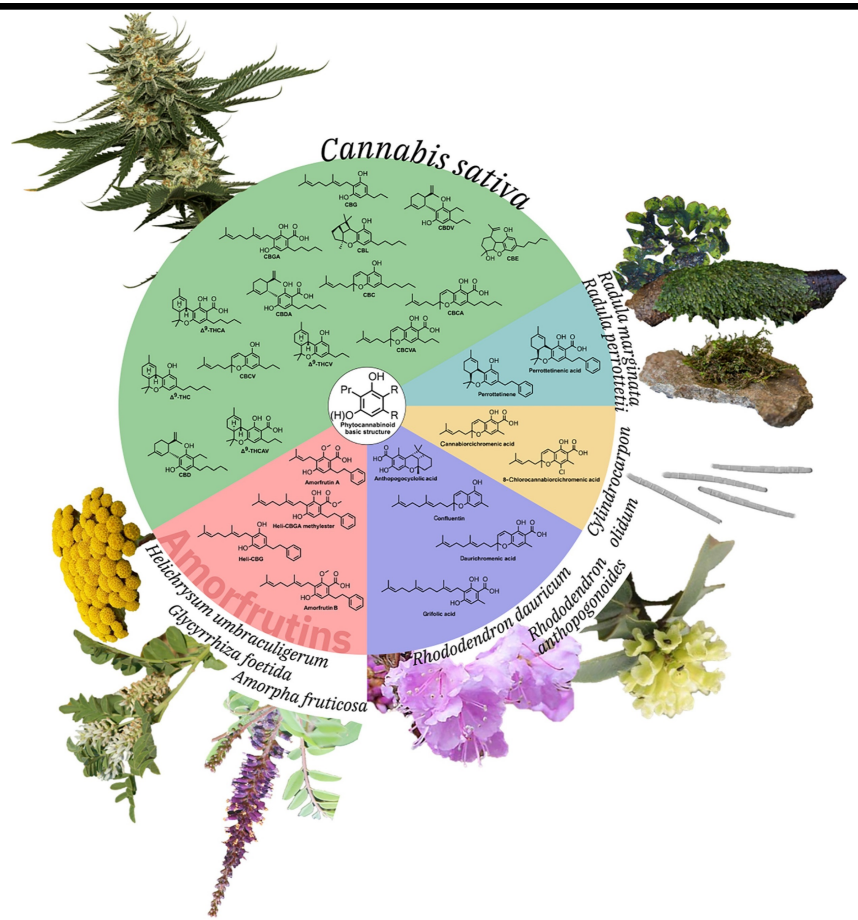
Phyto-Cannabinoids

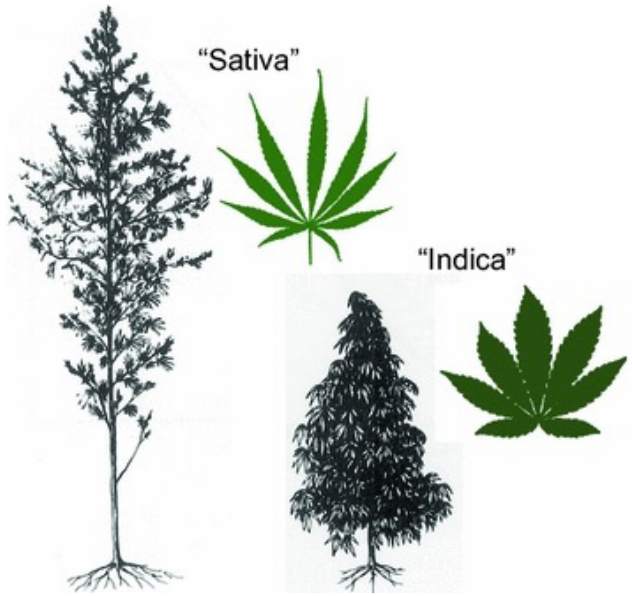
Synthetic Cannabinoids

Cannabinoid Natural Sources



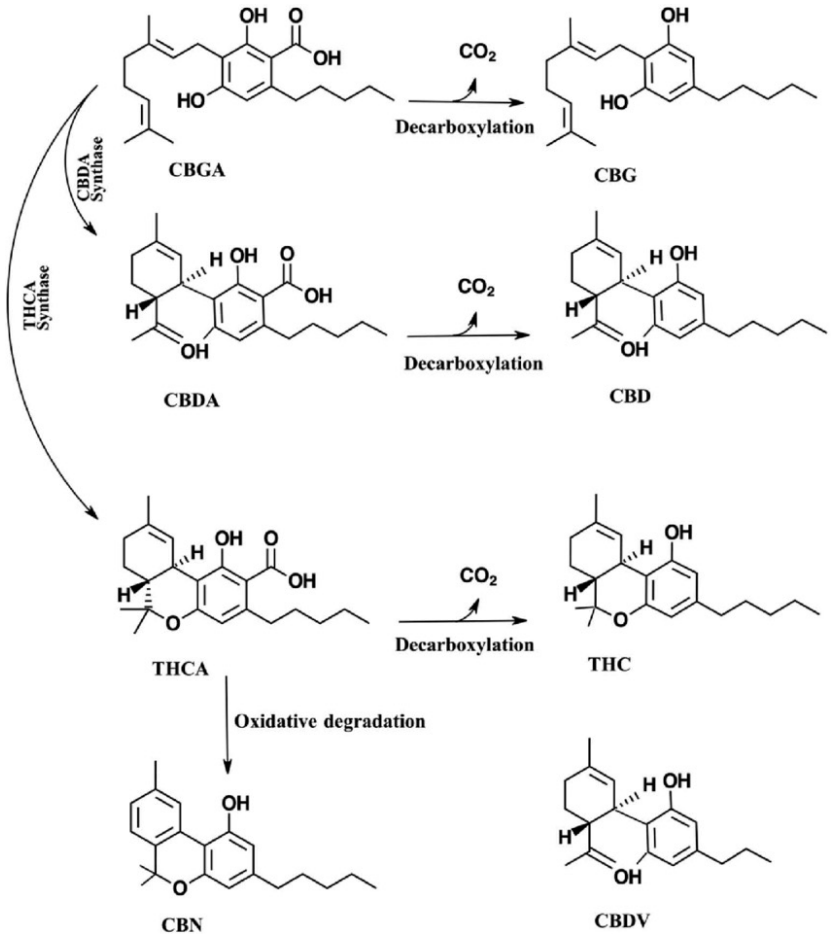
Echinacea





Trends in Plant Science 2020 25985-1004.
Gertsch J. *Br J Pharmacol*. 2010;160:523-529.

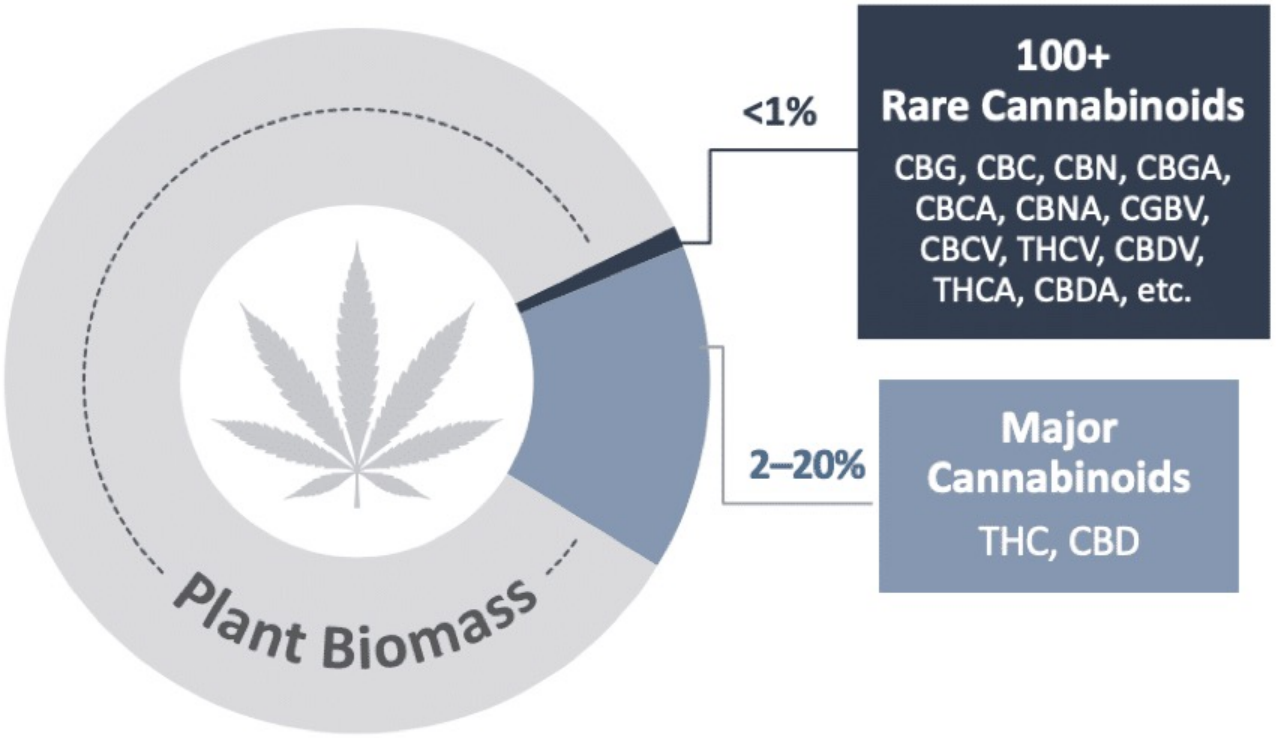
Cannabis Biosynthesis and Conversion of Cannabinoids



- CBGA: cannabigerolic acid
- CBG: cannabigerol
- CBDA: cannabidiolic acid
- CBD: cannabidiol
- THCA: tetrahydrocannabinolic acid
- THC: tetrahydrocannabinol
- CBN: cannabinol
- CBDV: cannabidivarin

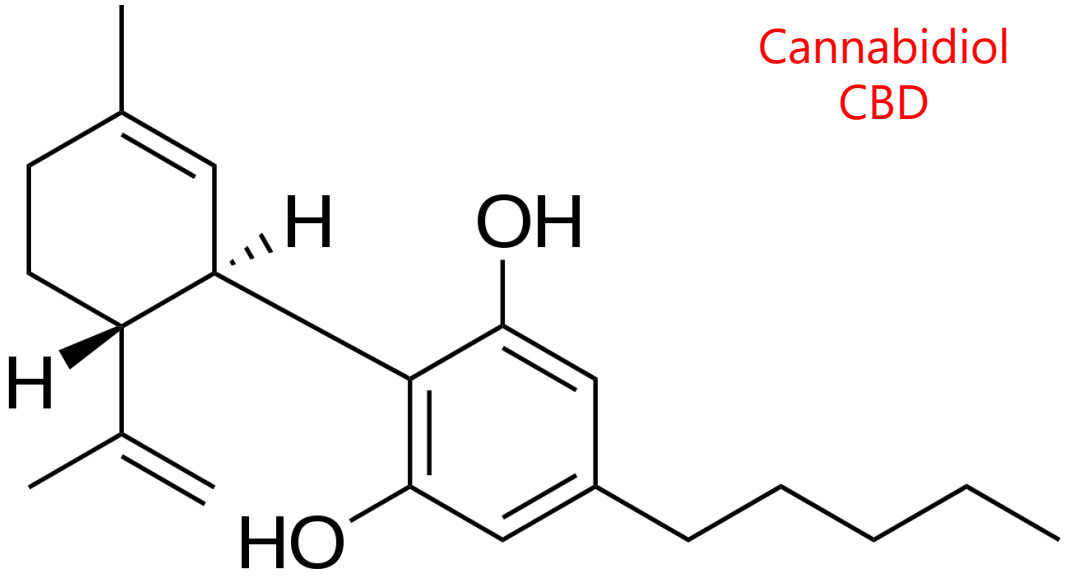
www.researchgate.net/figure/Major-cannabinoids-present-in-Cannabis-sativa-L-Biosynthesis-and-conversion-pathways_fig1_332566538.

A Pot Full of Cannabinoids

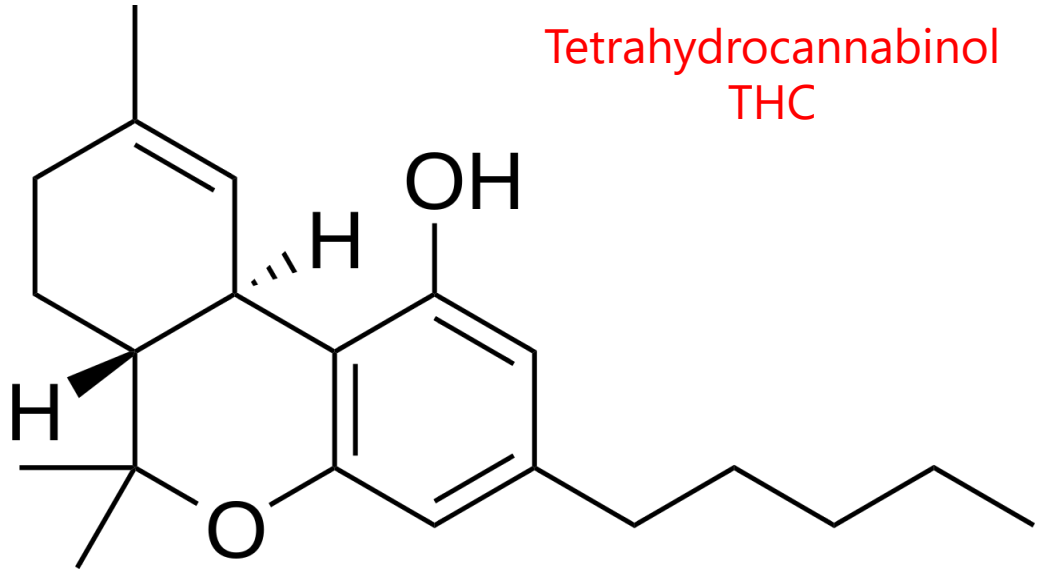


www.inmedpharma.com/media-news/cannabinol-101-the-science-of-cannabinol-cbn/.

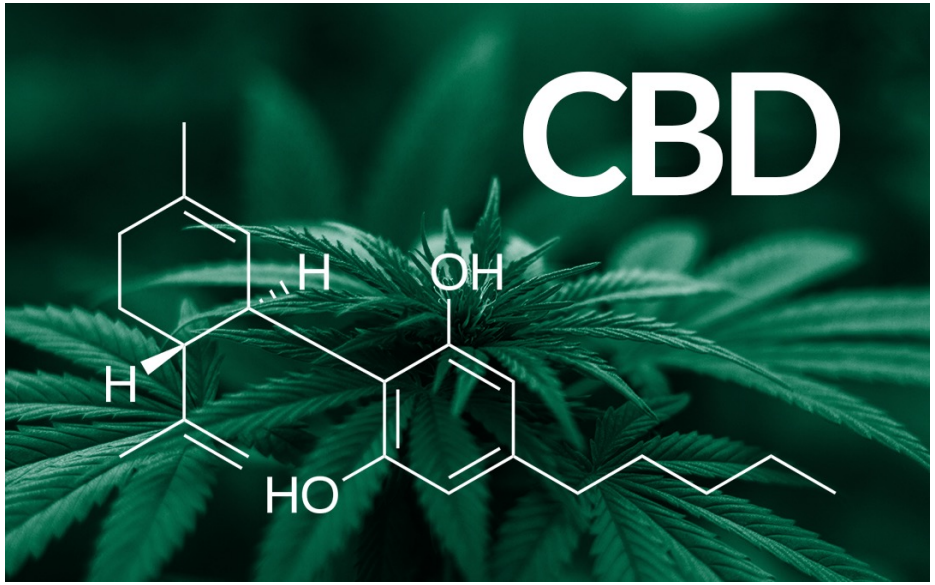
Major Phytocannabinoids: CBD and THC



Cannabidiol
CBD



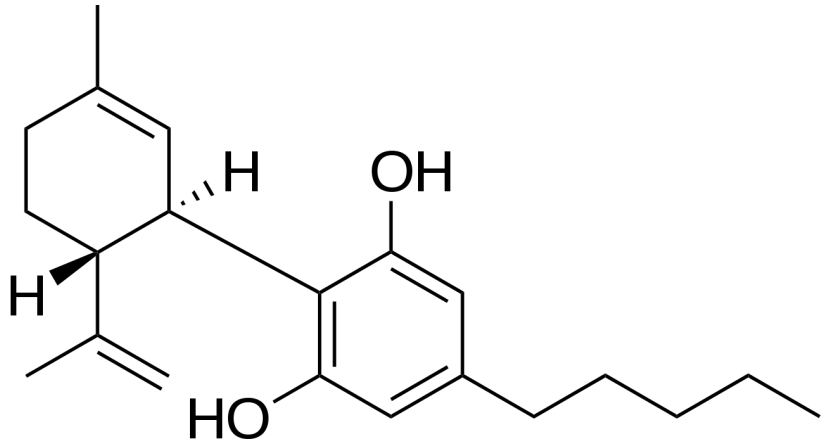
Tetrahydrocannabinol
THC



CBD

Cannabidiol (CBD)

- Discovered in 1940
- 40% of plant cannabinoid extract
- Mechanisms of action
  - Indirect CB1 antagonist
  - GPR18 partial agonist and GPR55 antagonist
  - PPARγ agonist
  - $5HT_{1A}$ agonist
  - Mu & delta opioid modulator
- May reduce THC clearance



- Bioavailability: oral (6%) and inhalation (11% to 45%)
- t ½: 18 to 32 hours

➢CBD derived from hemp (with ≤0.3% THC) is legal to sell as a cosmetics ingredient, but cannot be sold under federal law in food or dietary supplements

Horn. Drug Interactions with Marijuana. *Pharmacy Times*. Dec 2014. Kathmann. *Naunyn Schmied Arch Pharmacol*. 2006;372:354-361. Huestis. *Chem Biodivers*. 2007;4(8):1770-1804. Huestis. *Chem Biodivers*. 2009;4(8):1770-1804. Akpan. PBS News. Jul 12, 2019.

CBD Products

Origin

- China
  - 70% of USA's hemp comes from China
- Unregulated?
- Similar to prescription medications?

Trust in contents

- 26 of 84 (31%) samples of CBD oils, tinctures, and vaporization liquids contained the CBD amount reported on the label
- 58 of 84 (69%) samples of CBD oils, tinctures, and vaporization liquids DID NOT contain the CBD amount reported on the label

Bonn-Miller. *JAMA*. 2017;318(17):1708-1709.

Shopping for CBD: Consumer Reports

1. Be able to state why you want to utilize CBD
2. Decide what form of CBD is preferred
3. Consider amount of THC in product (euphoria)
4. For Hemp products, ask for growth location
5. Ask for lab testing results and frequency/amount
6. Prefer products that list CBD amount
7. Be familiar with other terms on label
8. Avoid products making sweeping health benefit claims
9. Be careful with vaping products containing propylene glycol (becomes formaldehyde)

www.consumerreports.org/cbd/how-to-shop-for-cbd/.

Shopping for CBD: Certificate of Analysis (Example)

CERTIFICATE OF ANALYSIS

Product:	**Broad Spectrum Hemp Extract (BSHE) 60ct Vegan Soft Gel**
Lot No:	**190506**
Source Lot No:	C19058
SKU#:	6118
Date of Manufacture:	March 26th, 2019
Best Before Date	March 26th, 2021
Ingredients:	Broad Spectrum Hemp Extract (*Cannabis Sativa*) (aerial parts). Organic Hemp Seed Oil, Modified corn starch, Glycerin, Carrageenan, Purified water

Test	Analytical Result	Specification	Testing Method
PROFILE			
CBD (total)	**14 mg/Soft gel**	12-18 mg/soft gel	HPLC (LOQ <50 ppm)
CBD	**4.030 %**	*Report only*	HPLC (LOQ <50 ppm)
CBDA	**0.008 %**	*Report only*	HPLC (LOQ <50 ppm)
CBC	**0.012 %**	*Report only*	HPLC (LOQ <50 ppm)
CBCA	**ND**	*Report only*	HPLC (LOQ <50 ppm)
CBG	**< LOQ**	*Report only*	HPLC (LOQ <50 ppm)
CBGA	**ND**	*Report only*	HPLC (LOQ <50 ppm)
CBN	**ND**	*Report only*	HPLC (LOQ <50 ppm)
Δ9 THC (total)	**0.005 %**	< 0.01%	Calculated
Δ9 THC	**0.005 %**	*Report only*	HPLC (LOQ <50 ppm)
THCA	**ND**	*Report only*	HPLC (LOQ <50 ppm)

TERPENES			
(-)-alpha-Bisabolol	**61 mg/100g**	*Report only*	HS-GC or GS-MS
Camphene	**< 1.0 mg/100g**	*Report only*	HS-GC or GS-MS
(1S)-(+)-3-Carene	**< 1.0 mg/100g**	*Report only*	HS-GC or GS-MS
beta-Caryophyllene	**19 mg/100g**	*Report only*	HS-GC or GS-MS
p-Cymene	**< 1.0 mg/100g**	*Report only*	HS-GC or GS-MS
Eucalyptol	**2.8 mg/100g**	*Report only*	HS-GC or GS-MS
alpha-Humulene (alpha-Caryophyllene)	**5.7 mg/100g**	*Report only*	HS-GC or GS-MS
(-)-Isopulegol	**< 1.0 mg/100g**	*Report only*	HS-GC or GS-MS
(R)-(+)-Limonene	**< 1.0 mg/100g**	*Report only*	HS-GC or GS-MS
Linalool	**< 1.0 mg/100g**	*Report only*	HS-GC or GS-MS
beta-Myrcene	**1.3 mg/100g**	*Report only*	HS-GC or GS-MS
(E)-b-Ocimene	**< 0.60 mg/100g**	*Report only*	HS-GC or GS-MS
(Z)-b-Ocimene	**< 0.30 mg/100g**	*Report only*	HS-GC or GS-MS
alpha-Pinene	**< 1.0 mg/100g**	*Report only*	HS-GC or GS-MS
beta-Pinene	**< 1.0 mg/100g**	*Report only*	HS-GC or GS-MS
alpha-Terpinene	**< 1.0 mg/100g**	*Report only*	HS-GC or GS-MS
gamma-Terpinene	**< 1.0 mg/100g**	*Report only*	HS-GC or GS-MS
Terpinolene	**< 1.0 mg/100g**	*Report only*	HS-GC or GS-MS

manitobaharvest.com/blogs/hemp-resource-hub/how-to-read-a-cbd-certificate-of-analysis.

Shopping for CBD: Certificate of Analysis (Example)

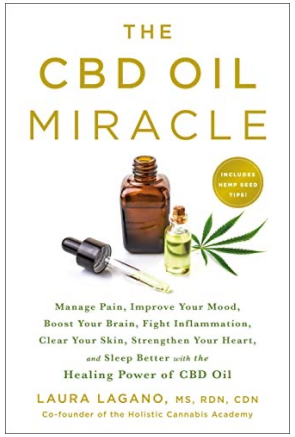
MICROBIOLOGICAL			
Standard Plate Count	**< 10 cfu/g**	< 10,000 cfu/g	AOAC 966.23
Total Coliforms	**< 10 cfu/g**	< 100 cfu/g	AOAC 991.14
Yeast & Mold	**< 20 cfu/g**	< 1,000 cfu/g	FDA BAM Chapter 18
E. coli	**< 10 cfu/g**	< 10 cfu/g	AOAC 991.14
Salmonella	**Negative**	Negative in 25g	AOAC 2004.03
MYCOTOXINS			
Aflatoxin	**< 20 ppb**	< 20 ppb	Calculated
Aflatoxin B1	**< 0.5 ppb**	*Report only*	UHPLC-MS/MS
Aflatoxin B2	**< 0.5 ppb**	*Report only*	UHPLC-MS/MS
Aflatoxin G1	**< 0.5 ppb**	*Report only*	UHPLC-MS/MS
Aflatoxin G2	**< 0.5 ppb**	*Report only*	UHPLC-MS/MS
Aflatoxin M1	**< 0.5 ppb**	*Report only*	UHPLC-MS/MS
Aflatoxin M2	**< 0.5 ppb**	*Report only*	UHPLC-MS/MS
Deoxynivalenol	**< 100 ppb**	*Report only*	UHPLC-MS/MS
T-2 Toxin	**< 10 ppb**	*Report only*	UHPLC-MS/MS
HT-2 Toxin	**< 100 ppb**	*Report only*	UHPLC-MS/MS
Fumonisin B1	**< 25 ppb**	*Report only*	UHPLC-MS/MS
Fumonisin B2	**< 25 ppb**	*Report only*	UHPLC-MS/MS
Ochratoxin A	**< 1 ppb**	*Report only*	UHPLC-MS/MS
Zearalenone	**< 30 ppb**	*Report only*	UHPLC-MS/MS

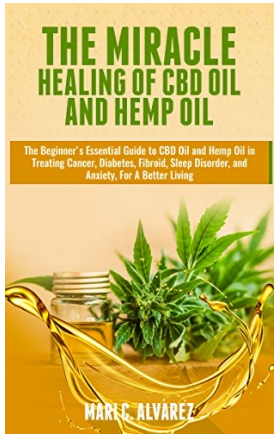
CHEMICAL			
Residual Solvents	**ND**	No detection	USP <467>
Pesticides	**ND**	No detection	AOAC 2007.01
Lead	**0.002 ppm**	< 0.5 ppm	ICP-MS/AOAC 993.14
Arsenic	**< 0.0009 ppm**	< 0.2 ppm	ICP-MS/AOAC 993.14
Cadmium	**< 0.002 ppm**	< 0.1 ppm	ICP-MS/AOAC 993.14
Mercury	**< 0.002 ppm**	< 0.1 ppm	ICP-MS/AOAC 993.14
Gluten	**< 3 ppm**	< 20 ppm	ELISA
ORGANOLEPTIC			
Appearance	**Conforms**	Soft gel	Visual
Size / Shape	**Conforms**	7.5 Oval	Visual
Gel color	**Conforms**	Clear	Visual
Fill color	**Conforms**	Green	Visual
PHYSICAL DOSAGE			
Average fill weight	**355 mg**	342-378 mg/sg	LAB-50-029
Average gross weight	**578 mg**	567-692 mg/sg	LAB-50-029
Rupture time	**2 minutes**	≤ 15 mins	QCU-50-013

*ND = Not detected.

manitobaharvest.com/blogs/hemp-resource-hub/how-to-read-a-cbd-certificate-of-analysis.

CBD Headline Endless Claims





CBD Delivery Methods and Products

- Inhaled
  - Smoked, vaped, hookah, etc
- Oral
  - Edibles, capsules, tablets, oils, tinctures, sprays, etc
- Topical
  - Creams, gels, ointments, etc

Huestis. *Chem Biodivers*. 2007;4(8):1770-1804.
MacCallum. *Eur J Intern Med*. 2018;pii:S0953-6205(18)30004-9.

CBD Products: Inhaled

- Onset: immediate
- Peak: 30 minutes
- 1st pass metabolism: bypassed
- Vape vs smoke preference

Huestis. *Chem Biodivers*. 2007;4(8):1770-1804.
MacCallum. *Eur J Intern Med*. 2018;pii:S0953-6205(18)30004-9.

CBD Products: Oral Tablets/Capsules/Edibles

- Onset 1 to 6 hours
- Duration 6 to 8 hours
- Patient counseling
  - Take with water
  - Take after meals
    - Food delays absorption
    - Fat increases peak concentration

Huestis. *Chem Biodivers*. 2007;4(8):1770-1804.
MacCallum. *Eur J Intern Med*. 2018;pii:S0953-6205(18)30004-9.

CBD Products: Oral Sprays

- Onset 15 minutes to 2 hours
- 1st pass metabolism: moderate/some
- Patient counseling
  - Sublingual absorption provides fastest effects

Huestis. *Chem Biodivers*. 2007;4(8):1770-1804.
MacCallum. *Eur J Intern Med*. 2018;pii:S0953-6205(18)30004-9.

Topical CBD Products in Pharmacies

www.cnbc.com/2019/03/20/cvs-has-started-selling-cannabis-based-products-in-8-states.html.
www.usatoday.com/story/money/2019/03/27/walgreens-sell-cbd-products-nearly-1-500-drugstores-report-says/3295939002/.
www.cnbc.com/2019/04/11/rite-aid-will-start-selling-cbd-products-in-2-states.html.
www.cnbc.com/2019/06/11/kroger-to-sell-cbd-products-in-nearly-1000-stores.html.

CBD Products: Topical

- Human skin cannabinoids absorption rate are very low
  - CBD > THC
- Higher CBD topical concentration aids local absorption
- Must apply topical CBD products generously
- May work peripherally, but not absorbed into bloodstream

Huestis. *Chem Biodivers*. 2007;4(8):1770-1804.
MacCallum. *Eur J Intern Med*. 2018;pii:S0953-6205(18)30004-9.

CBD Products

- Full spectrum
  - Created from plant; not manufactured synthetically
  - Contains other cannabinoids and trace amounts of THC
- Broad spectrum
  - Contains other cannabinoids but not THC
- CBD isolate
  - Chemical extraction of CBD from plant materials to remove THC, terpenes, chlorophyll, etc

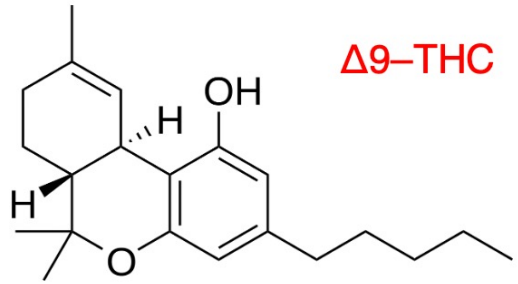
Cather. *Bayl Univ Med Cent*. 2020;33(3):376-379.

CBD Products

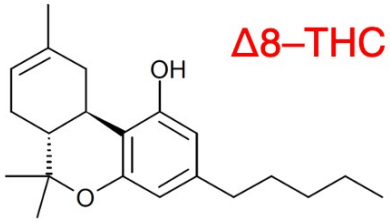
THC

Tetrahydrocannabinol (THC)

- Δ9–tetrahydrocannabinol
  - Δ8–tetrahydrocannabinol also exists
- Mechanism of action
  - CB1 partial agonist
- Highly lipophilic
  - Distributing rapidly to highly perfused tissues, and later to fat tissue



Δ9–THC

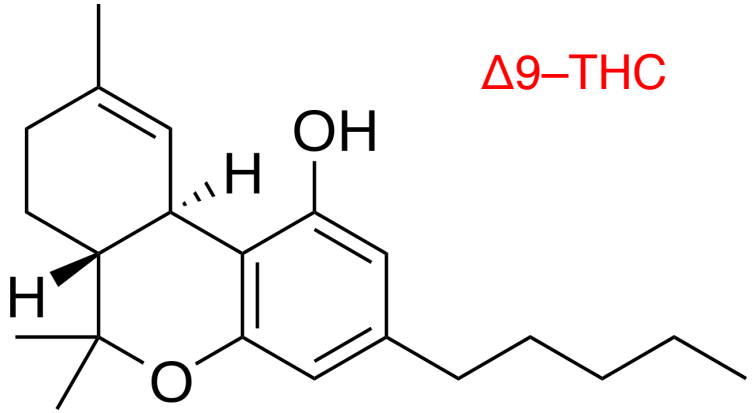


Δ8–THC

Horn. Drug Interactions with Marijuana. *Pharmacy Times*. Dec 2014.
Bridgeman. *P T*. 2017;42(3):180-188.

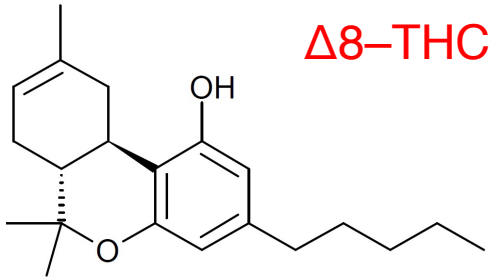
Tetrahydrocannabinol (THC)

- Inhalation
  - Immediate absorption
  - Peak 15 to 30 minutes
  - Taper off in 2 to 3 hours



Δ9–THC

- Oral ingestion
  - Delayed effects (30 minutes to 1 hour)
  - Peak 2 to 3 hours
  - Taper off in ~12 hours

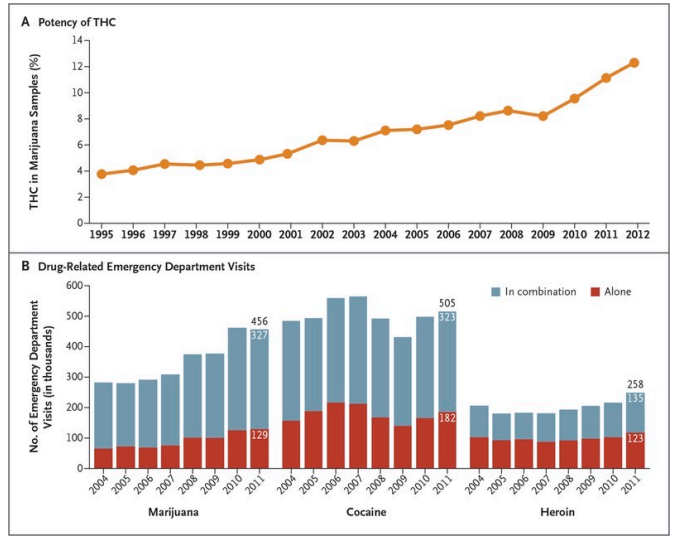


Δ8–THC

Horn. Drug Interactions with Marijuana. *Pharmacy Times*. Dec 2014.
Bridgeman. *P T*. 2017;42(3):180-188.

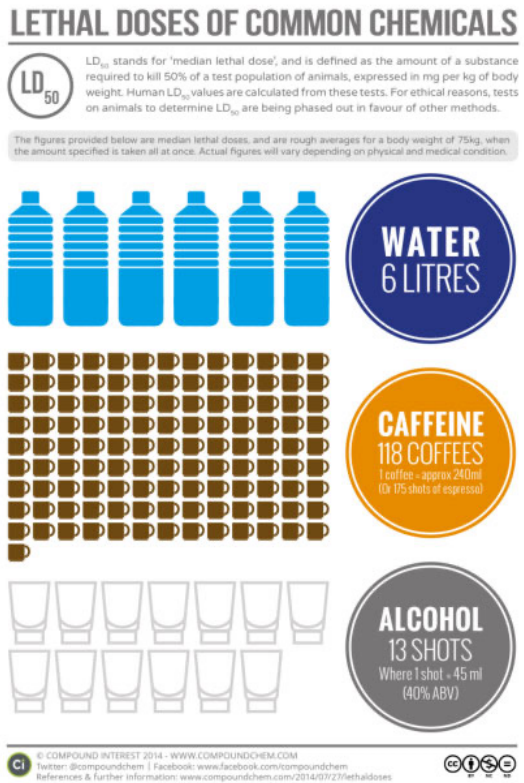
Marijuana THC Potency

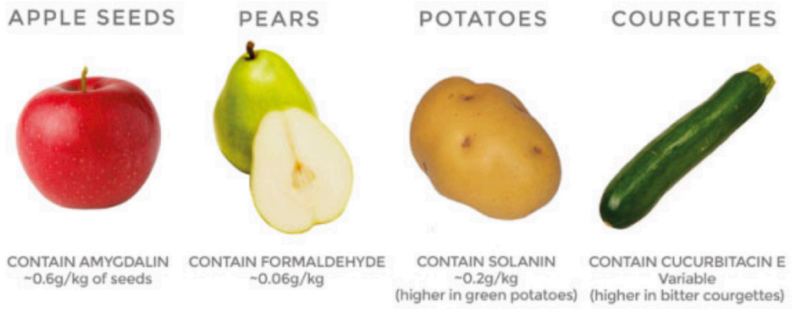
- Typical joint: 0.5 grams of marijuana
  - 1960's to 1980's joint (2% THC) → 10 mg THC per joint
  - 2020's joint (10% THC) → 50 mg THC per joint
  - 2020's extracts (90% THC) → 450 mg THC (relatively)
- One nabiximols spray: 2.7 mg THC and 2.5 mg CBD
- Cocaine: coca leaf vs crack
- Nicotine: FDA considering reducing tobacco nicotine concentrations
- Ethyl alcohol ABV: difference between beer/wine (4) and bourbon (40)
- Opioid MME factors: codeine (0.15) vs carfentanyl (10,000)

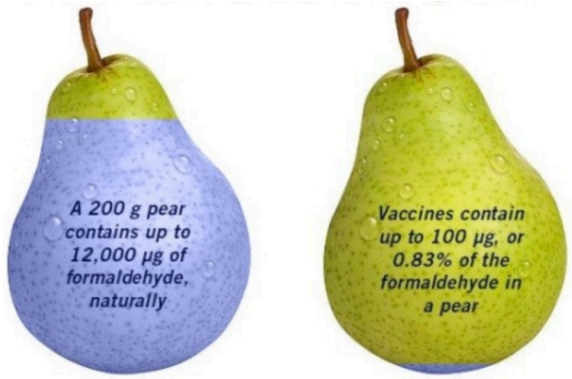


Volkow. *N Engl J Med.* 2014; 370:2219-2227.

It’s All About the Dosage, Baby!





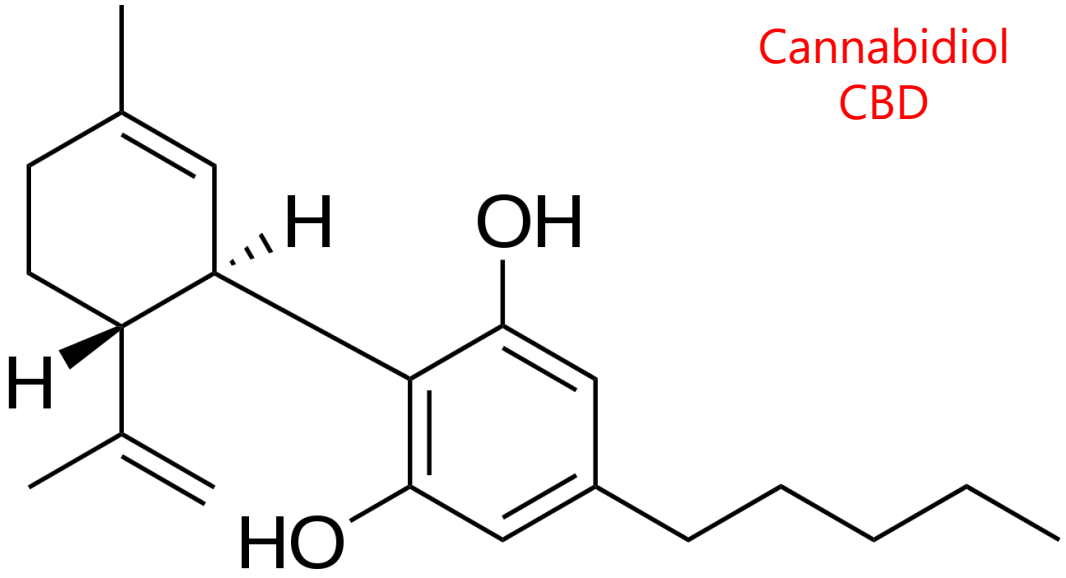


The amount of formaldehyde in a vaccine is so tiny that it doesn't even affect the naturally occurring levels of formaldehyde in a child's blood.

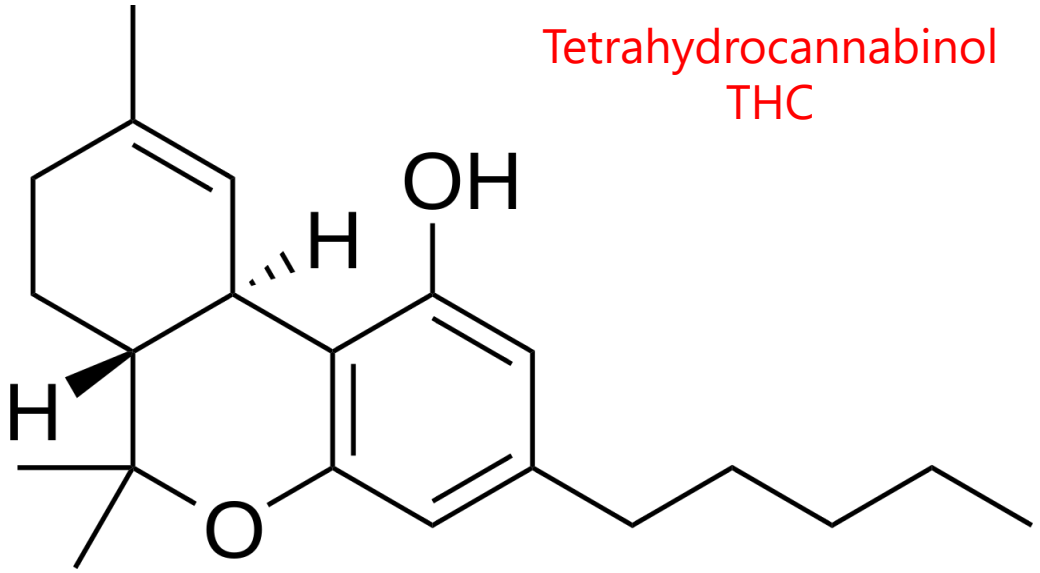
Paracelsus
“All things are poison and nothing is without poison; only the dose makes a thing not a poison."

www.chemicalsafetyfacts.org/dose-makes-poison-gallery/.

Major Phytocannabinoids: CBD and THC



Cannabidiol
CBD



Tetrahydrocannabinol
THC

Practical THC and CBD Dosage Considerations

- Condition severity
- Body weight
- Other medical conditions (kidney/liver function, etc)
- Consider similar pharmaceutical product dosages
- Formulation (administration route)
- Product potency (unregulated)

Guidance for the use of medicinal cannabis in the treatment of chronic non-cancer pain in Australia. Symonston (AU): Australian Government Department of Health, Therapeutic Goods Administration; 2017.

Cannabinoids

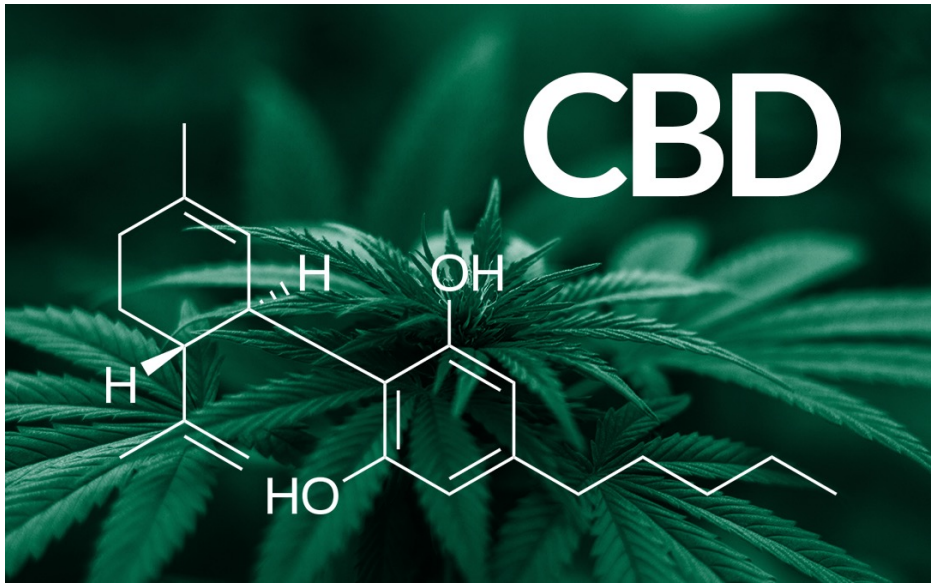
Endo-Cannabinoids

Phyto-Cannabinoids

Synthetic Cannabinoids

Synthetic Cannabinoids
CBD Derivatives

- Hydrogenated
- Dimethylheptyl (DMH)
- C4′-alkyl chain modifications
- Halogenated (Cl, Br, Fl, and I)
- Hydroxyl
- Diacetylated
- Quinones



Extensively covered in another cannabinoid certificate module

Synthetic Cannabinoids
THC Derivatives

- 1st Generation
  - Sterling-Winthrop Aminoalkylindoles (WIN-X)
  - John Williams Huffman (JWH-X)
  - Hebrew University (HU-X)
  - Charles Pfizer (CP-X)

- 2nd Generation
  - Alkyl derivatives
  - N-methylpiperidines
  - Benzoindoles

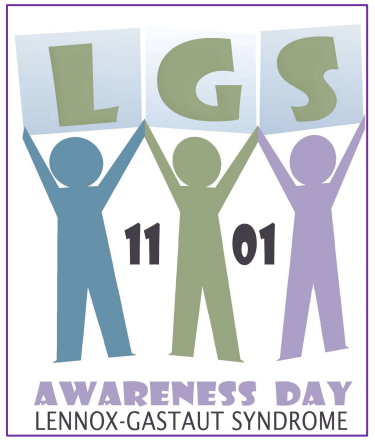
- 3rd Generation
  - Indoles
  - Indazoles

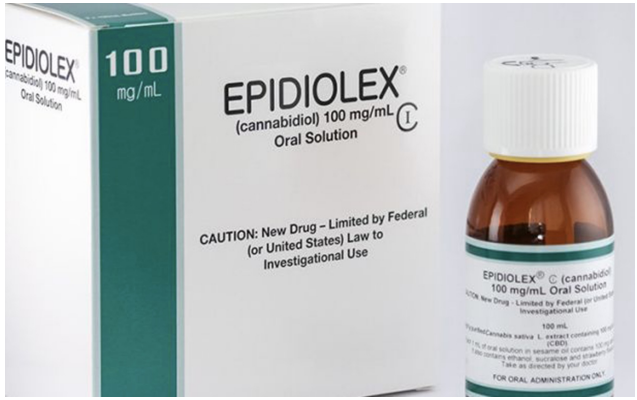
Extensively covered in another cannabinoid certificate module

Synthetic Cannabinoids
Cannabidiol (Epidiolex)

FDA approvals (>/= 2yo)

- Dravet syndrome
  - Severe myoclonic epilepsy of infancy (SMEI)
- Tuberous sclerosis
  - Rare disease that causes brain tumors/growths
    - Also skin, kidneys, eyes, heart, or lungs
  - Usually benign (noncancerous)
- Lennox-Gastaut syndrome (LGS)
  - Complex, rare, and severe childhood epilepsy
  - Multiple/concurrent seizure types
  - Cognitive dysfunction
  - Slow spike waves on electroencephalogram (EEG)
  - Presents typically in children aged 3 to 5 years of age
  - November 1st: International LGS Awareness Day

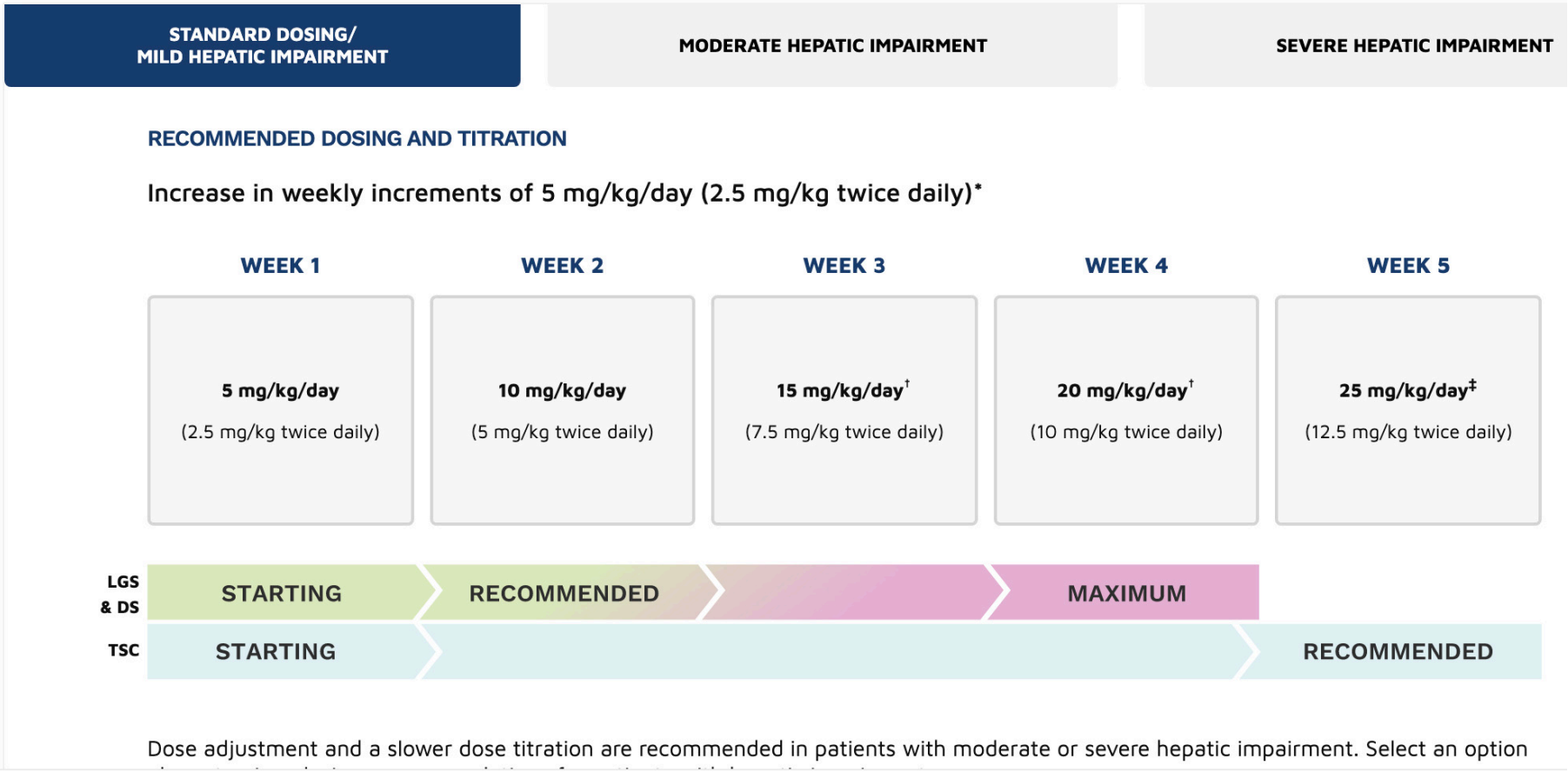




Clinical Pharmacology Online Database.
www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf.

Synthetic Cannabinoids

CBD (Epidiolex) Dosage



www.epidiolexhcp.com/dosing-and-calculator.

Synthetic Cannabinoids

CBD (Epidiolex) Dosage

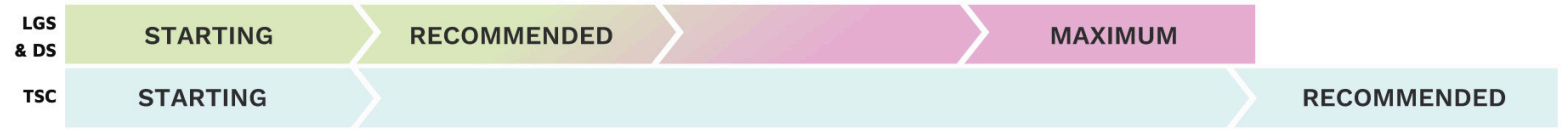
STANDARD DOSING/ MILD HEPATIC IMPAIRMENT	MODERATE HEPATIC IMPAIRMENT	SEVERE HEPATIC IMPAIRMENT

Because of an increase in exposure to EPIDIOLEX, dose adjustment and slower titration are recommended in patients with moderate or severe hepatic impairment. Consider not initiating EPIDIOLEX in patients with evidence of significant liver injury. Dose adjustments are not required in patients with mild hepatic impairment.

REVIEW ADDITIONAL MONITORING CONSIDERATIONS →

RECOMMENDED DOSAGE AND TITRATION — 1/2 STANDARD DOSING*

WEEK 1	WEEK 2	WEEK 3	WEEK 4	WEEK 5
2.5 mg/kg/day (1.25 mg/kg twice daily)	**5 mg/kg/day** (2.5 mg/kg twice daily)	**7.5 mg/kg/day** (3.75 mg/kg twice daily)	**10 mg/kg/day** (5 mg/kg twice daily)	**12.5 mg/kg/day** (6.25 mg/kg twice daily)



www.epidiolexhcp.com/dosing-and-calculator.

Synthetic Cannabinoids

CBD (Epidiolex) Dosage

STANDARD DOSING/ MILD HEPATIC IMPAIRMENT	MODERATE HEPATIC IMPAIRMENT	SEVERE HEPATIC IMPAIRMENT

Because of an increase in exposure to EPIDIOLEX, dose adjustment and slower titration are recommended in patients with moderate or severe hepatic impairment. Consider not initiating EPIDIOLEX in patients with evidence of significant liver injury. Dose adjustments are not required in patients with mild hepatic impairment.

REVIEW ADDITIONAL MONITORING CONSIDERATIONS →

RECOMMENDED DOSAGE AND TITRATION — 1/5 STANDARD DOSING*

WEEK 1	WEEK 2	WEEK 3	WEEK 4	WEEK 5
1 mg/kg/day (0.5 mg/kg twice daily)	**2 mg/kg/day** (1 mg/kg twice daily)	**3 mg/kg/day** (1.5 mg/kg twice daily)	**4 mg/kg/day** (2 mg/kg twice daily)	**5 mg/kg/day** (2.5 mg/kg twice daily)

LGS & DS	STARTING	RECOMMENDED		MAXIMUM	
TSC	STARTING				RECOMMENDED

www.epidiolexhcp.com/dosing-and-calculator.

Synthetic Cannabinoids

CBD (Epidiolex) Dosage

Rx

PATIENT Kierstin

EXAMPLE TITRATION PRESCRIPTION

EPIDIOLEX (cannabidiol)
100 mg/mL oral solution
Disp: 30-day supply

Take 1.4 mL PO BID for 7 days, then take 2.7 mL PO BID.

Weight: 54 kg
Diagnosis: Q85.1 tuberous sclerosis

REFILL _____ TIMES
DISPENSE AS WRITTEN ☑

DEA # _____
LIC. # _____

Rx

PATIENT Kierstin

EXAMPLE MAINTENANCE PRESCRIPTION

EPIDIOLEX (cannabidiol)
100 mg/mL oral solution
Disp: 30-day supply

Take 6.8 mL PO BID.

Weight: 54 kg
Diagnosis: Q85.1 tuberous sclerosis

REFILL 11 TIMES
DISPENSE AS WRITTEN ☑

DEA # _____
LIC. # _____

www.epidiolexhcp.com/dosing-and-calculator.

Synthetic Cannabinoids

THC Products (Oral Capsules/Liquid)

- Dronabinol (Marinol®) Capsules
- Syndros®: Liquid, C3
- FDA approvals
  - Chemo-induced N/V
  - Aids anorexia
- Off-label
  - Cancer anorexia
  - Intractable pruritus secondary to cholestatic liver disease

Clinical Pharmacology Online Database.
www.accessdata.fda.gov/drugsatfda_docs/label/2017/018651s029lbl.pdf.

Synthetic Cannabinoids

THC Products Dosages

Chemotherapy-Induced Nausea and Vomiting

- Oral capsules
  - 5 mg/m² PO 1 to 3 hr before and q2 to 4 hr after chemotherapy;
  - May be increased in 2.5 mg/m² increments to 15 mg/m²; not to exceed 4-6 doses/day
- Oral solution
  - Starting dose: 4.2 mg/m² PO 1-3 hr before chemotherapy, THEN q2 to 4 hr after chemotherapy for a total of 4-6 doses/day
  - Give 1st dose on empty stomach ≥30 mins before a meal; subsequent doses can be given without regard to meals
  - Calculate starting dose
    - Starting dose (mg) = Patient body surface area (BSA) in m² multiplied by 4.2 mg/m²
    - Round dose to the nearest 0.1 mg increment
    - To correspond with calibrated oral dosing syringe, dose may need to be rounded to nearest 0.1 mL increment
  - Dose titration
    - Titrate to clinical response during a chemotherapy cycle or subsequent cycles, based upon initial effect, as tolerated to achieve a clinical effect, in increments of 2.1 mg/m²
    - Maximum dosage: 12.6 mg/m² per dose for 4-6 doses/day
    - Adverse reactions are dose-related and psychiatric symptoms increase significantly at the maximum dosage

reference.medscape.com/drug/marinol-syndros-dronabinol-342047.

Synthetic Cannabinoids

THC Products Dosages

AIDs Anorexia

- Oral Capsules
  - 2.5 mg PO q12hr initially, taken right before meals; may be increased to max 20 mg/day or decreased to 2.5 mg at bedtime PRN
- Oral Solution
  - Starting dose
    - 2.1 mg PO BID, 1 hr before lunch and 1 hr before dinner (late day dosing may reduce CNS adverse reactions)
    - If CNS adverse reactions of feeling high, dizziness, confusion, and somnolence occur, they usually resolve in 1-3 days and usually do not require dosage reduction
    - If CNS adverse reactions are severe or persistent, reduce the dose to 2.1 mg/day 1 hr before dinner or in the evening at bedtime
  - Dose titration
    - If tolerated and further therapeutic required, increase dose gradually to 2.1 mg 1 hr before lunch & 4.2 mg 1 hr before dinner
    - Gradually increase dose to reduce the frequency of dose-related adverse reactions
    - Most patients respond to 2.1 mg BID, but the dose may be further increased to 4.2 mg 1 hr before lunch and 4.2 mg 1 hr before dinner, as tolerated to achieve a therapeutic effect
    - Maximum dosage: 8.4 mg BID

reference.medscape.com/drug/marinol-syndros-dronabinol-342047.

Synthetic Cannabinoids
CBD and THC (Nabiximols)

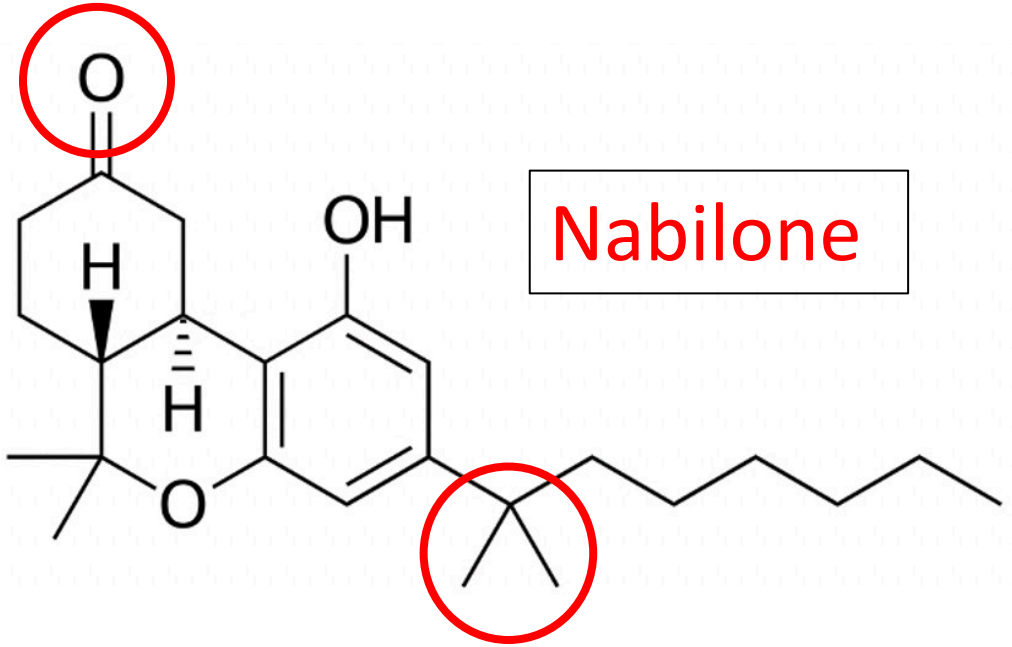
Approvals and trials
- Approved for MS spasticity in >2 dozen countries (Canada, Mexico, Europe, etc)
- Approved for MS neuropathic pain and cancer pain in Canada
- US Phase 3 clinical trials (MS spasticity and neuropathic pain)

Dosage
- Each 100-microliter spray contains:
  - 2.7 mg delta-9-tetrahydrocannabinol (THC)
  - 2.5 mg cannabidiol (CBD)
- Dose titration (sprays)
  - Starting with 1/day up to 12/day

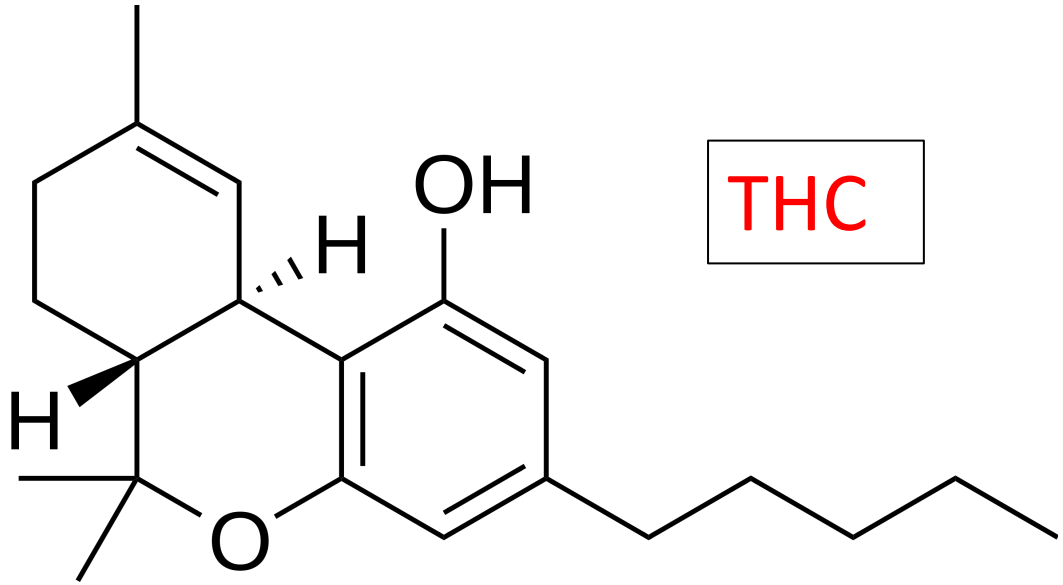
www.practicalpainmanagement.com/treatments/pharmacological/analgesics-future-potential-endocannabinoid-system.

Synthetic Cannabinoids

Nabilone



Nabilone

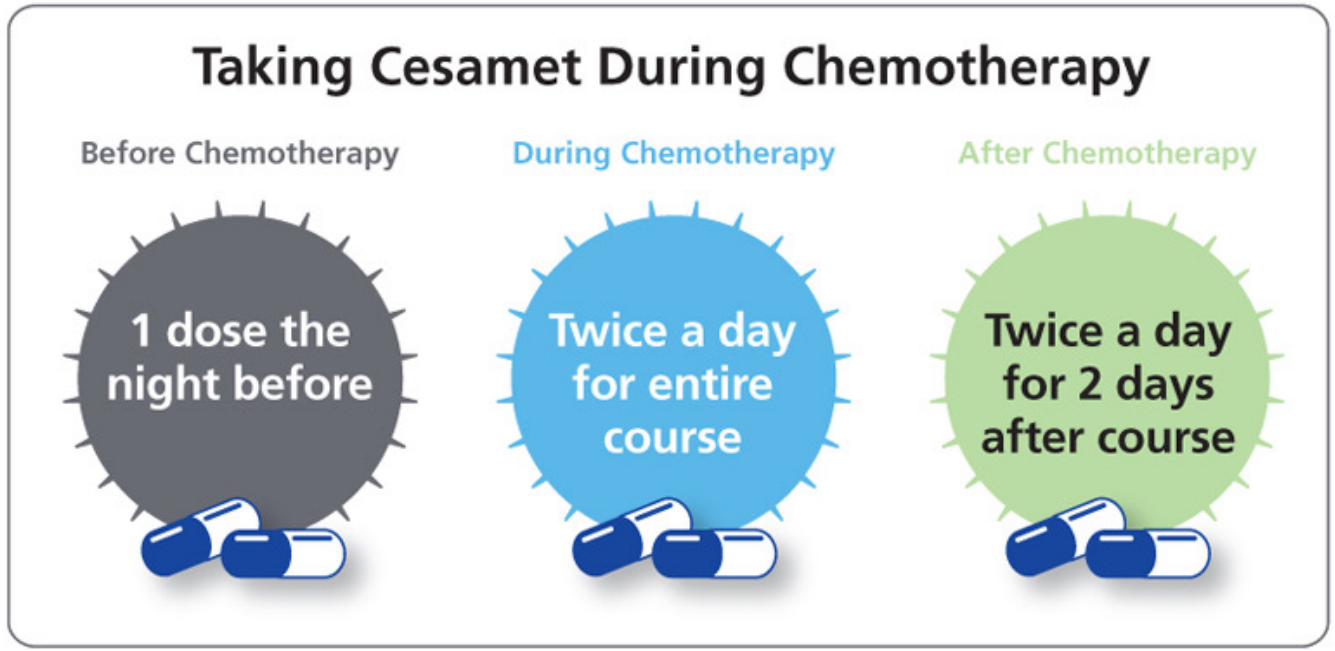


THC

www.sciencedirect.com/topics/neuroscience/nabilone.

Synthetic Cannabinoids
Nabilone (Cesamet)

Cesamet® capsules: C2, chemo-induced N/V (CINV)



Clinical Pharmacology Online Database.
pdf.hres.ca/dpd_pm/00007760.PDF.
www.accessdata.fda.gov/drugsatfda_docs/label/2006/018677s011lbl.pdf.

Cannabinoid Pharmaceutical Pipeline

https://softsecrets.com/us/2019/02/19/10-best-weed-pipes-on-the-market/

Cannabinoid Pharmaceutical Pipeline

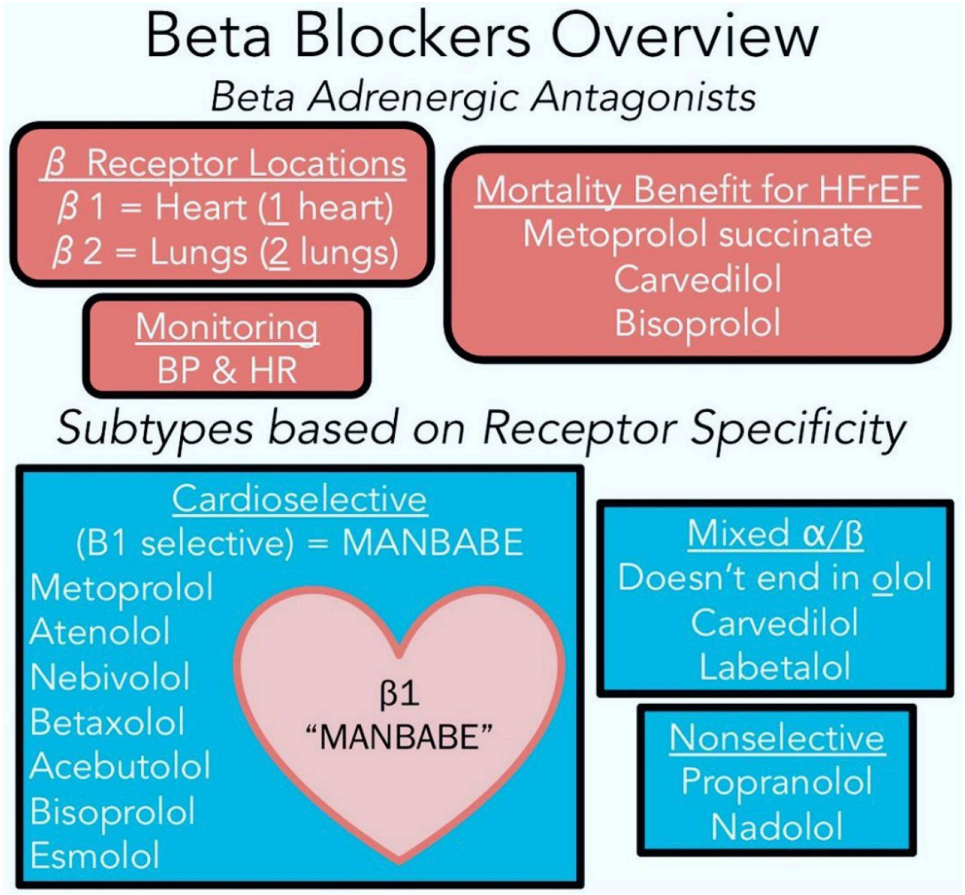
- CB2 agonists
- CB1/CB2 agonists (peripheral selective)
- CB1 inverse agonists
- TRPV1 antagonists
- FABP5 inhibitors
- MAGL inhibitors
- FAAH combo inhibitors

Endo-Cannabinoids

www.practicalpainmanagement.com/treatments/pharmacological/analgesics-future-potential-endocannabinoid-system.

Receptor Selectivity is Not New

Beta Blockers



www.grepmed.com/images/5947/cardioselective-nonselective-pharmacology-betablockers-cardiology-mnemonic-manbabe.

Endocannabinoid System

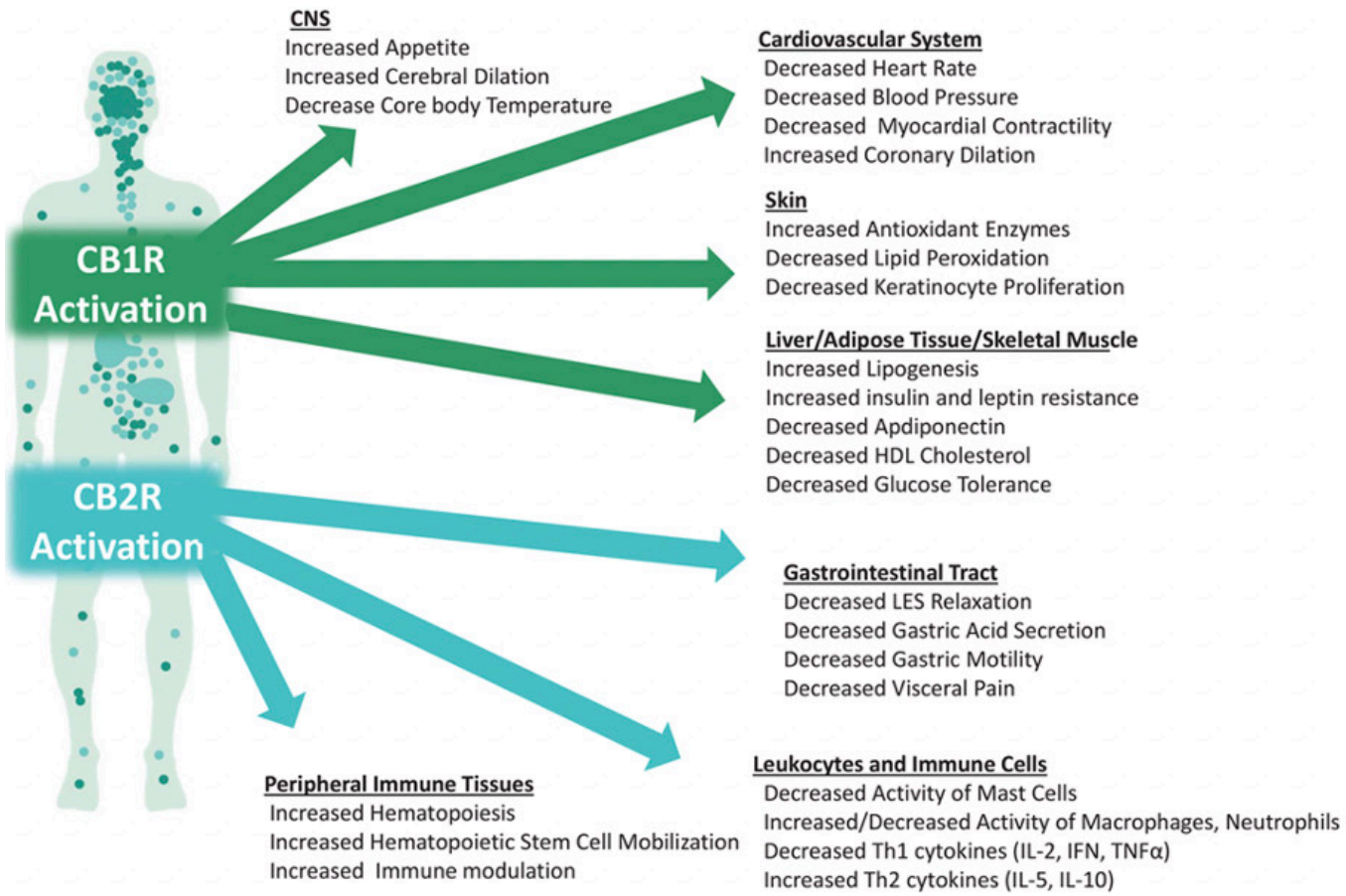
Cannabinoid Receptors (CB1/CB2)

CB1 receptors

- Primarily in CNS
- Also in connective tissue, gonads, glands, and organs
- Analgesia, euphoria, and anticonvulsive

CB2 receptors

- Primarily in immune system and GI tract
- Inflammation and digestion



Page. *Circulation*. 2020;142(10):e131-e152.

Cannabinoid Pharmaceutical Pipeline

CB2 Agonists

- APD371 (olorinab)
  - Phase IIb clinical trials for the treatment of visceral gastrointestinal pain
  - Statistically significant improvements in abdominal pain and generally well-tolerated

- JBT-101 (lenabasum)
  - An oral, small-molecule
  - Phase III trials for the treatment of systemic sclerosis and dermatomyositis
  - Phase II trials for systemic lupus erythematosus and cystic fibrosis
  - Not currently seeking specific indications to treat pain conditions
  - Phase II trial data has shown favorable safety data

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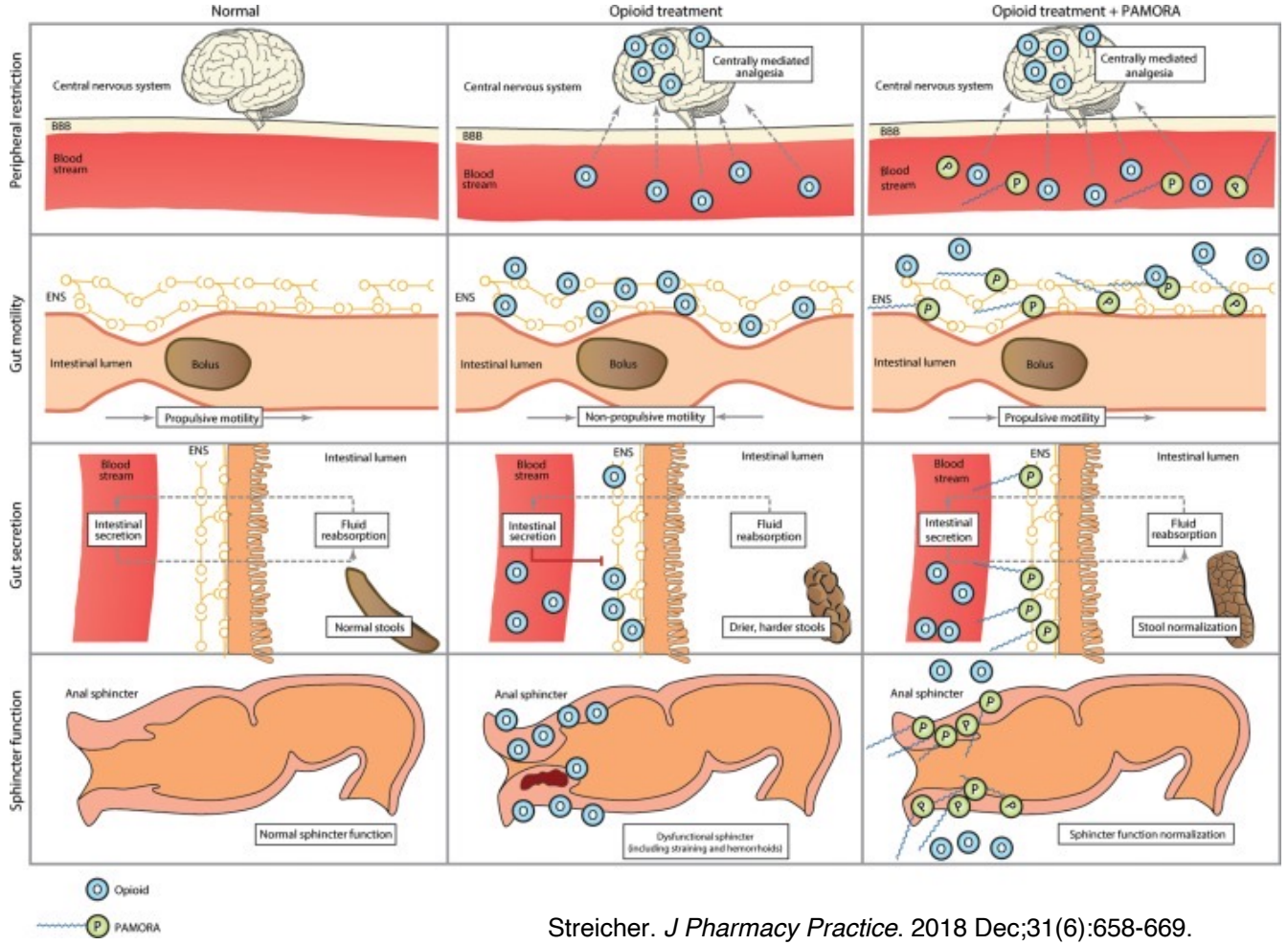
Peripheral Selectivity Is Not New

PAMORAs



Streicher. *J Pharmacy Practice*. 2018 Dec;31(6):658-669.

Cannabinoid Pharmaceutical Pipeline

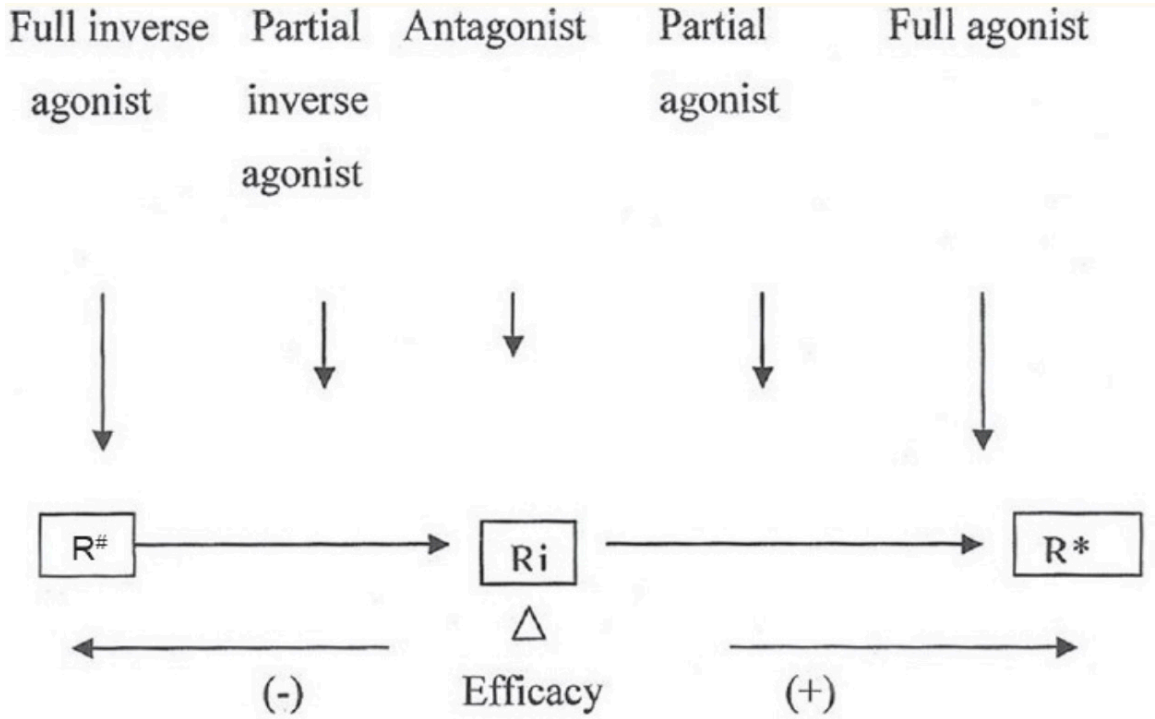
CB1/CB2 Agonists (Peripheral Selective)

- NEO1940/ART27.13
  - Potent agonist of CB1 and CB2 receptors with limited CNS penetration
  - Phase II trial planning for multimodal supportive care therapy for cancer patients and cancer-related anorexia
  - 5 phase I clinical studies demonstrated statistically significant and dose-proportional increases in body weight (efficacy outcome)

www.practicalpainmanagement.com/treatments/pharmacological/analgesics-future-potential-endocannabinoid-system.

Inverse Agonists Are Not New

- H_1 and H_2 antihistamines
- Naloxone induces opioid withdrawal
- Carvedilol in CHF
- Clozapine in psychosis
- Candesartan in cardiac hypertrophy
- Pimavanserin (ACP-103 study)
  - $5\text{-}HT_{2A}$, attenuates Parkinson's psychosis



Khilnani. *Indian J Pharmacol*. 2011;43(5):492-501.

Cannabinoid Pharmaceutical Pipeline

CB1 Inverse Agonists

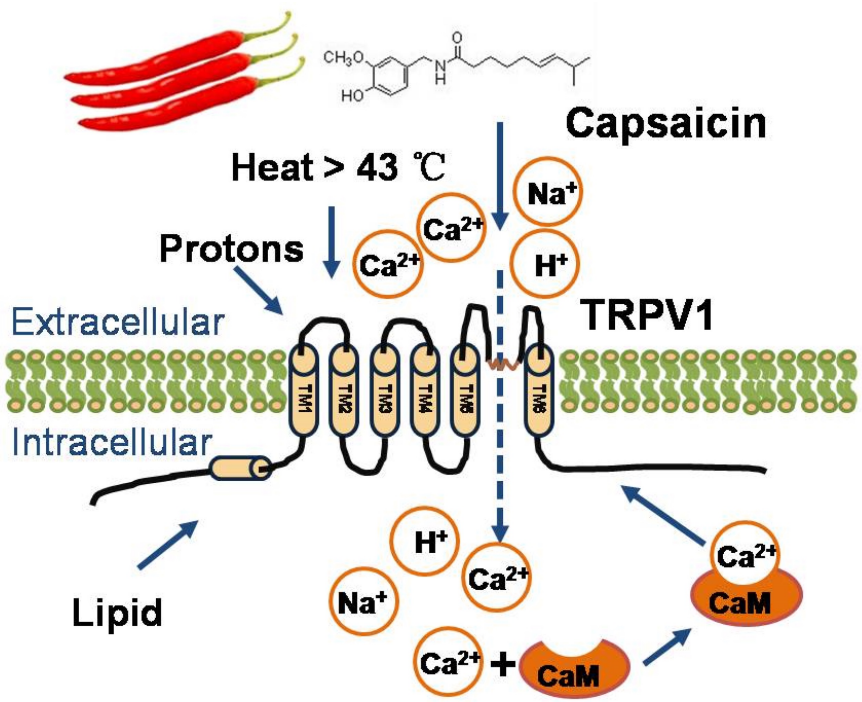
- CRB-4001
  - 2nd generation, peripherally-restricted, CB1 inverse agonist
  - Phase I studies (2019) for treatment of diseases with organ-specific fibrosis

www.practicalpainmanagement.com/treatments/pharmacological/analgesics-future-potential-endocannabinoid-system.

TRPVs

Transient Receptor Potential Subfamily V Member 1

- Transient receptor potential (TRP) family
- Activation
  - AEA and CBD
  - Temperature > 43ºC
  - Chilis (capsaicin)
  - Garlic
  - Spider venom
- Main functions
  - Detect and regulate heat
  - Pain
  - Itch
  - Inflammation



Sun. *Nutrients*. 2016;8(5):174.
www.practicalpainmanagement.com/treatments/pharmacological/analgesics-future-potential-endocannabinoid-system.

Cannabinoid Pharmaceutical Pipeline

TRPV Antagonist(s)

- NEO6860
  - Selective inhibitor of capsaicin-activated TRPV1 channels
  - Seeking indications for the treatment of osteoarthritis pain, neuropathic pain, and visceral pain/chronic pancreatitis
  - First generation TRPV1 antagonist programs had previously failed (including AMG517, SB-7054498, and MK2295) mainly due to their nonselective modes of channel antagonism, leading to the serious adverse effects of hyperthermia and impaired noxious heat sensation
  - In phase I trials, NEO6860 yielded analgesic effects without affecting body temperature or sensitivity to heat

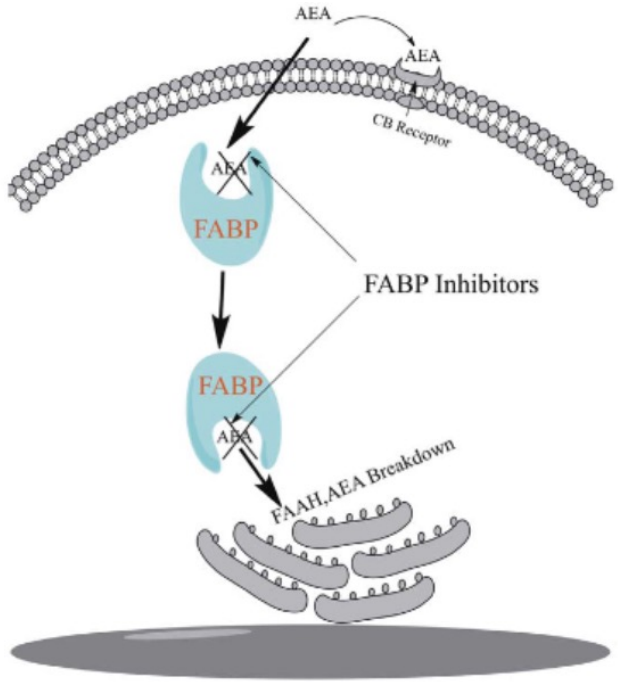
www.practicalpainmanagement.com/treatments/pharmacological/analgesics-future-potential-endocannabinoid-system.

Cannabinoid Pharmaceutical Pipeline

FABP5 Antagonist(s)

- ART26.12
  - Inhibits FABP5
  - Undergoing lead identification studies to create a compound with optimum design for potential indications of cancer and pain-related conditions

- FABP transports AEA to FAAH
  - FABP inhibitors attenuate FAAH's breakdown of AEA

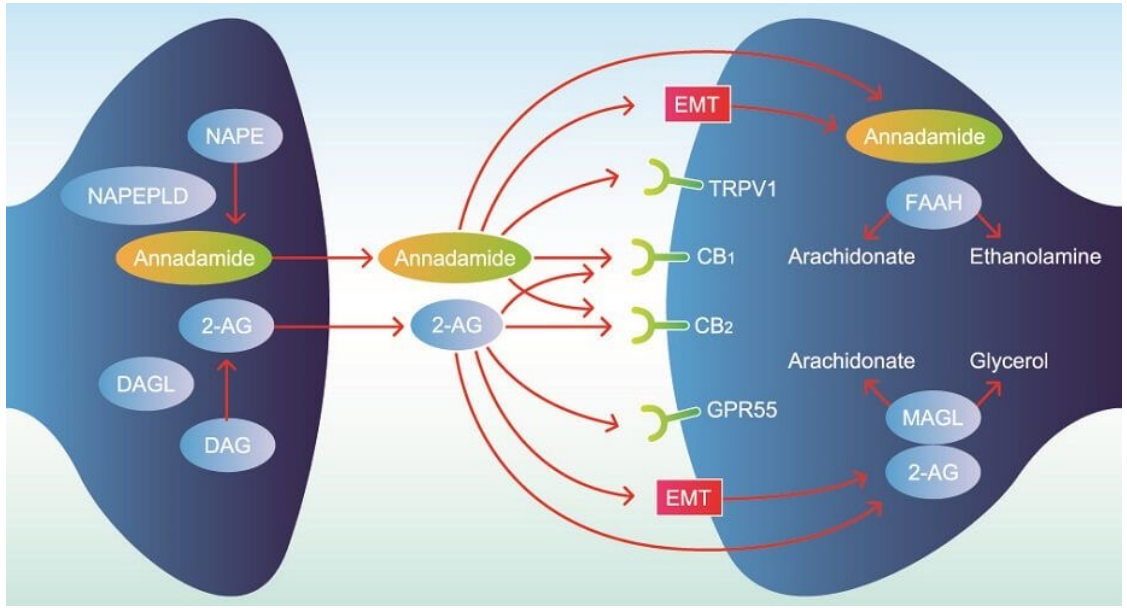


www.painresearchforum.org/news/51110-peripheral-gaba-relieves-trpv1-sensitization-thermal-hypersensitivity.
www.practicalpainmanagement.com/treatments/pharmacological/analgesics-future-potential-endocannabinoid-system.
Ramer. *Front Pharmacol*. 09 May 2019.
www.jbc.org/article/S0021-9258(19)81969-5/fulltext#figures.

Endocannabinoid System

Degrading Enzymes

- 2-AG is degraded to AA and glycerol by MAGL
- AEA is degraded to AA and ethanolamine ($EtNH_2$) by FAAH



biologydictionary.net/endocannabinoid-system/.
Ramer. *Front Pharmacol*. 09 May 2019

Cannabinoid Pharmaceutical Pipeline

Past MAGL and FAAH Inhibitor Failures

- Multiple FAAH selective inhibitors never made it past phase 2 trials
  - BIA10-2474, PF-04457845, JNJ-42165279, SSR-411298, V-158866, and URB597
  - Two postulated reasonings for failure
    1. Increasing synaptic concentrations of AEA allowed for increased activity on both CB1 receptors (desired effect) and TRPV1 channels (involved in nociception), thus overall analgesia was limited
    2. Blocking the FAAH metabolic pathway allowed for a higher percentage of AEA to metabolize via COX-2 into prostaglandins, leading to an increased pro-inflammatory effect

www.practicalpainmanagement.com/treatments/pharmacological/analgesics-future-potential-endocannabinoid-system.

Cannabinoid Pharmaceutical Pipeline

MAGL Inhibitor

- ABX-1431
  - Treatment of Tourette Syndrome and pain
  - Phase 1 trials showed Positive efficacy and well tolerated
  - Phase II Trials conducted

www.practicalpainmanagement.com/treatments/pharmacological/analgesics-future-potential-endocannabinoid-system.

Cannabinoid Pharmaceutical Pipeline

FAAH Combo Inhibitors

- OMDM-198
  - Dual inhibitor of FAAH and TRPV1
  - Shown efficacy in terms of reduction of osteoarthritic pain in rat models
  - No current human clinical trials of this compound in progress

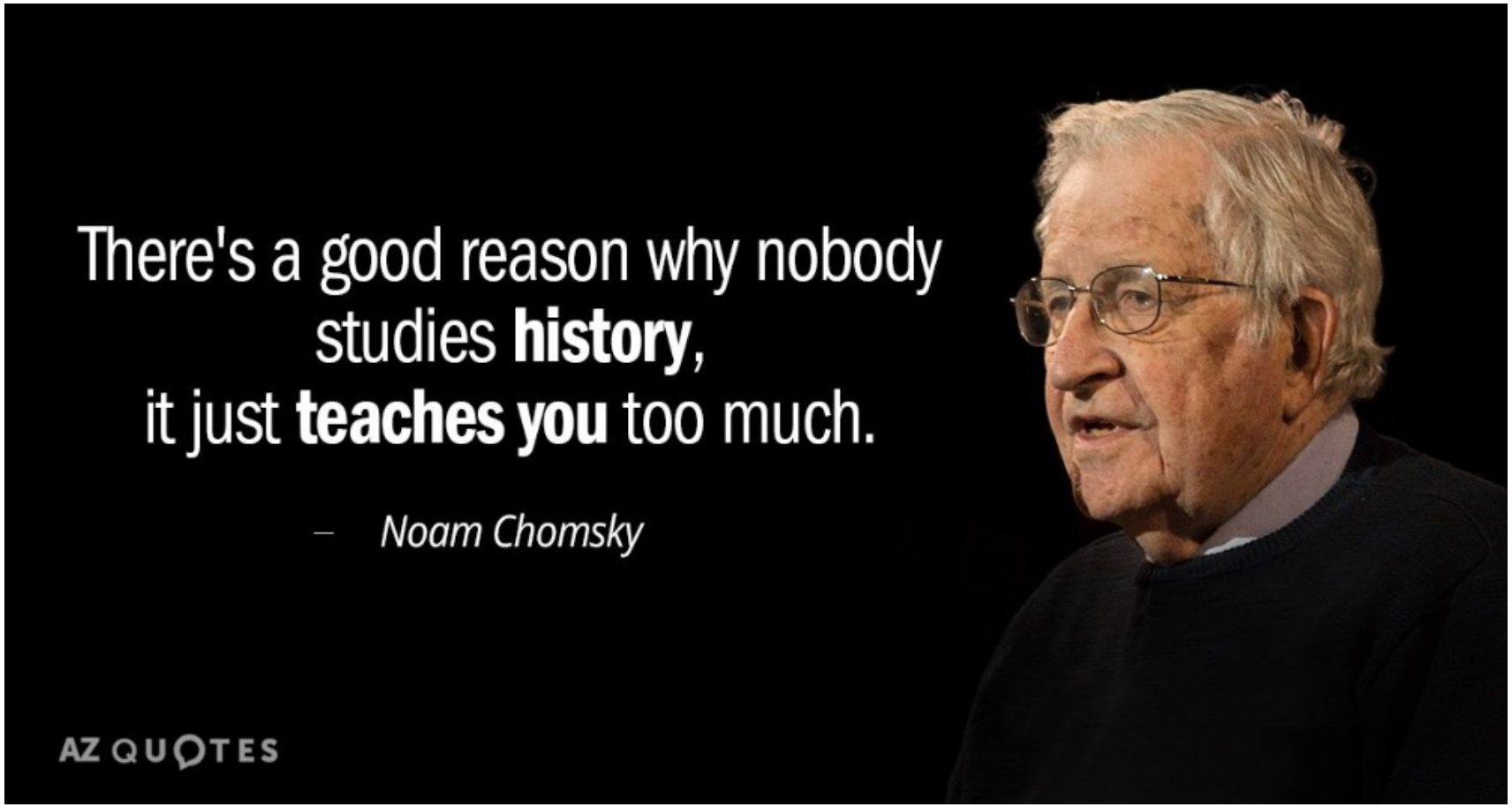
- ARN2508
  - Dual inhibitor of FAAH and COX-2
  - Has shown to increase plasma AEA levels and decrease prostaglandin and thromboxane A2 levels after IV administration
  - No current human clinical trials of this compound in progress

www.practicalpainmanagement.com/treatments/pharmacological/analgesics-future-potential-endocannabinoid-system.

From THC, to CBD, and BEYOND!!!

And the winner will be.....

Big Pharma or Big Tobacco?



PainWeek

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CANNABINOIDS

Pharmaceutical & Commercial Cannabinoid Products

Mark Garofoli, PharmD, MBA, BCGP, CPE