Cannabinoid Use for Pain Management

Christopher D. Verrico, PhD

Assistant Professor

Departments of Psychiatry and Pharmacology

Baylor College of Medicine

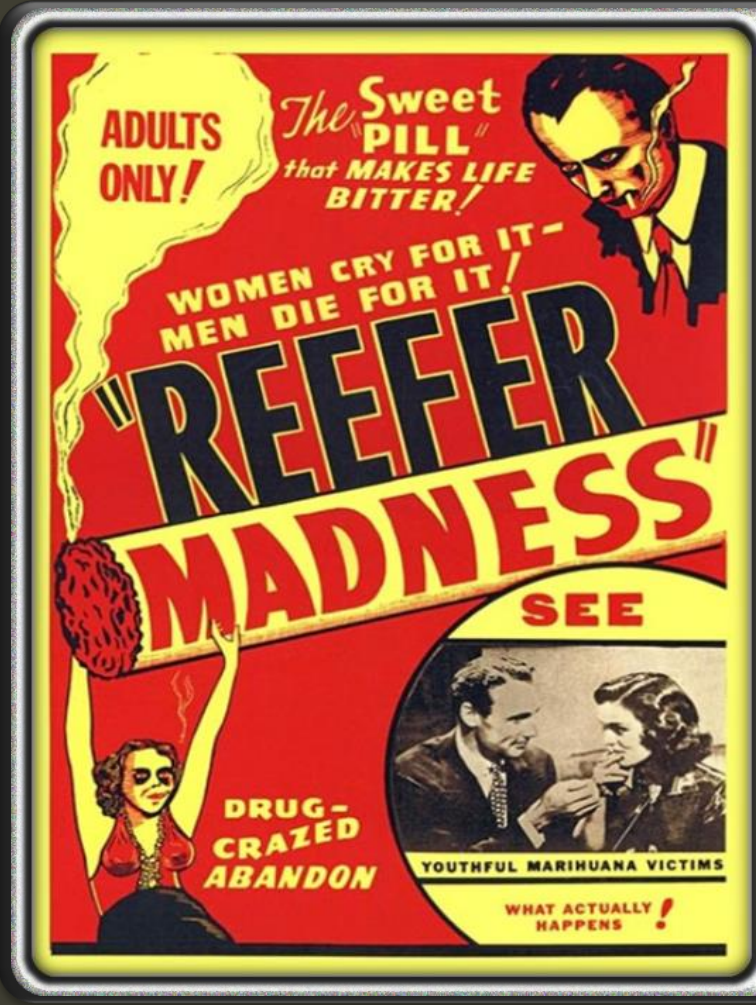
Disclosure Information for Christopher D. Verrico

1. Under ACCME guidelines, I have received an honorarium from Ascension Health for giving this presentation.

AND

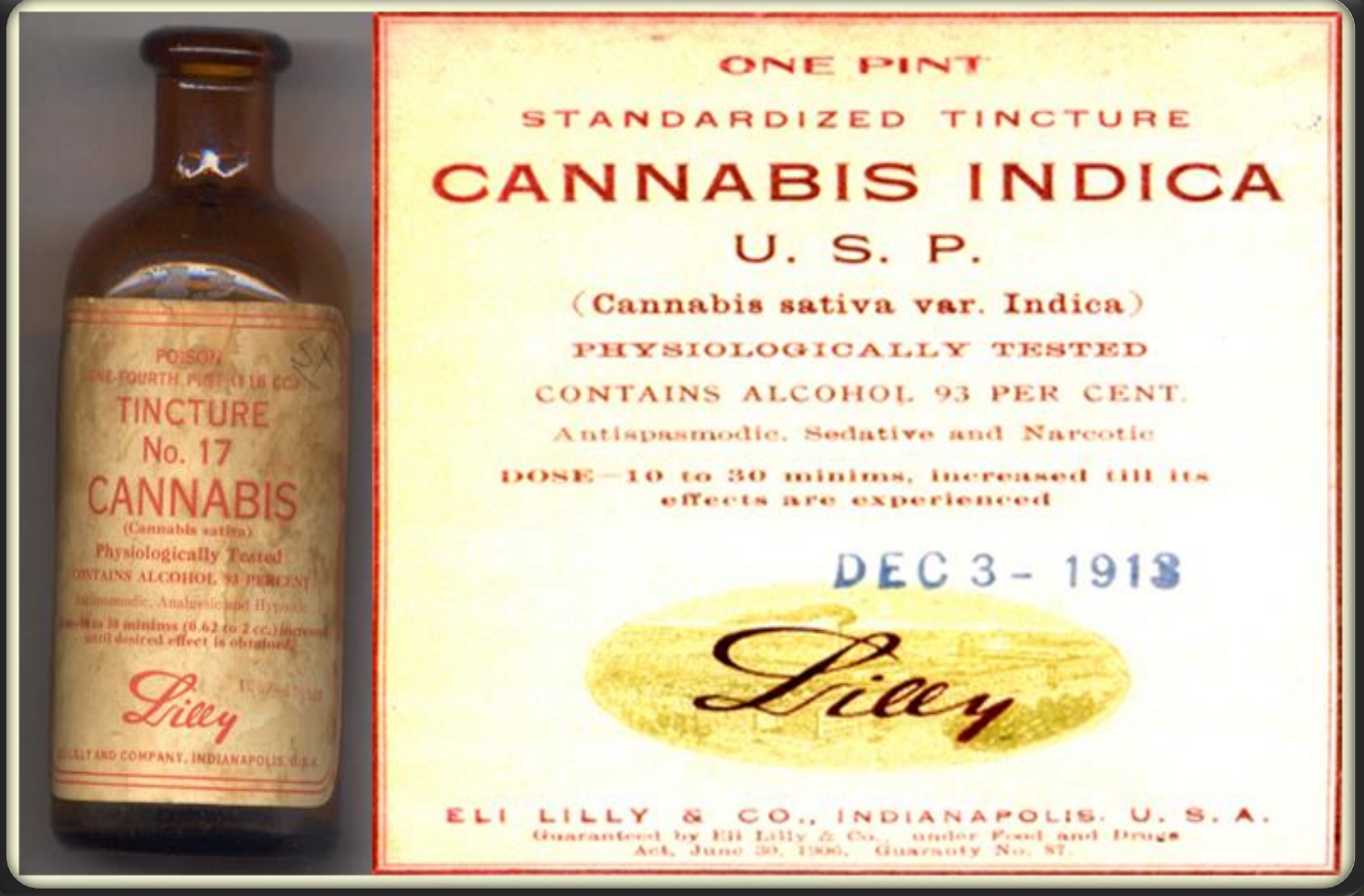
2. I intend to reference the following off-label or investigational use of drugs or products in my presentation: cannabis, dronabinol (Marinol, Syndros), cannabidiol (Epidiolex), nabilone (Cesamet).

What comes to mind when you think of a marijuana?

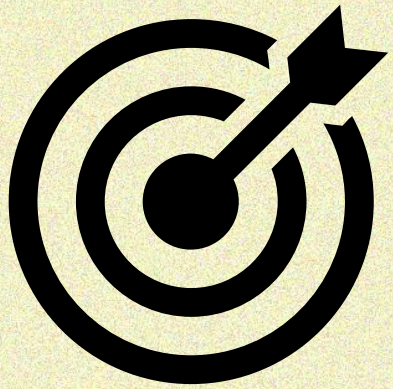


What comes to mind when you think of a marijuana?

What comes to mind when you think of a marijuana?



OBJECTIVES

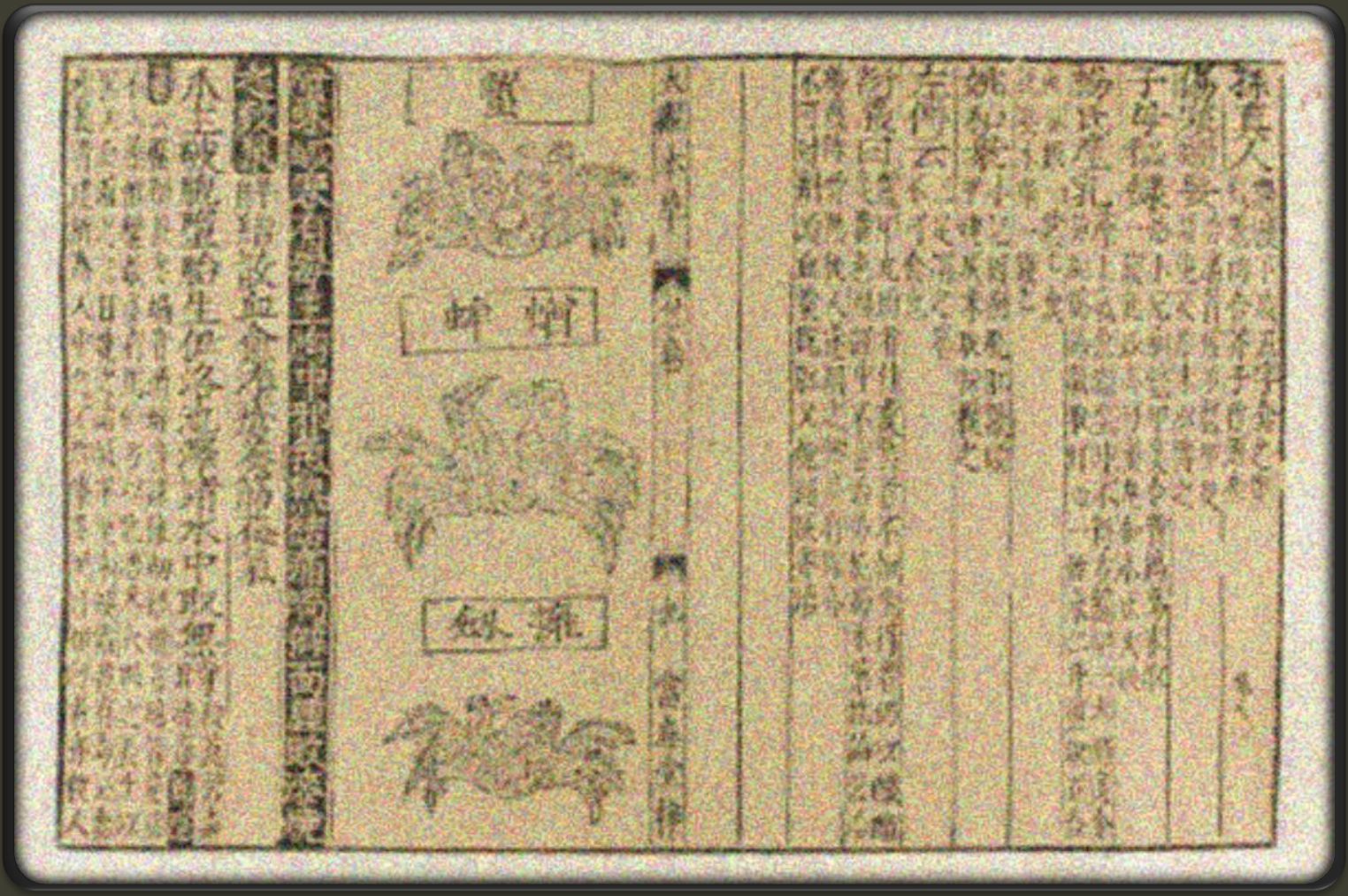


- Endogenous (Endo)cannabinoid system
  - Describe at least 3 unique characteristics of the endocannabinoid system
- Potential therapeutic properties of medicinal cannabis and cannabinoids
  - Describe at least 3 potential therapeutic purposes and clinical indications of cannabinoids.
  - Identify the cannabis-based pharmaceuticals currently available in the US market and abroad.
- Compare & contrast cannabinoids with opioids

1500 BC

EARLIEST WRITTEN REFERENCE

The use of cannabis for medicinal purposes predates recorded history; the earliest written reference is found in Chinese Pharmacopeia, the Rh-Ya, in the 15th century BC



1843

FIRST SCIENTIFIC ASSESSMENT

William O'Shaughnessy, scientifically assessed and publicized the therapeutic value of cannabis

PROVINCIAL MEDICAL JOURNAL

And Retrospect of the Medical Sciences.

No. 123.] LONDON, SATURDAY, FEBRUARY 4, 1843. [PRICE SIXPENCE. Stamped Edition Sevenpence.

ON THE PREPARATIONS
OF THE
INDIAN HEMP, OR GUNJAH,*
(*Cannabis Indica*)

Their Effects on the Animal System in Health, and their Utility in the Treatment of Tetanus and other Convulsive Diseases.

By W. B. O'Shaughnessy, M.D., Bengal Army,
Late Professor of Chemistry and Materia Medica in the Medical College of Calcutta.

[Concluded from p. 347.]

Experiments by the Author—Inferences as to the Action of the Drug on Animals and Man.

twenty minutes was ridiculously drunk; in four hours his symptoms passed away, also without harm.

Expts. 3, 4, and 5.—Three kids had ten grains each of the alcoholic extract of *gunjah*. In one no effect was produced; in the second there was much heaviness, and some inability to move; in the third a marked alteration of countenance was conspicuous, but no further effect.

Expt. 6.—Twenty grains were given, dissolved in a little spirit, to a dog of very small size. In a quarter of an hour he was intoxicated; in half an hour he had great difficulty of movement; in an hour he had lost all power over the hinder extremities, which were rather stiff but flexible; sensibility did not seem to

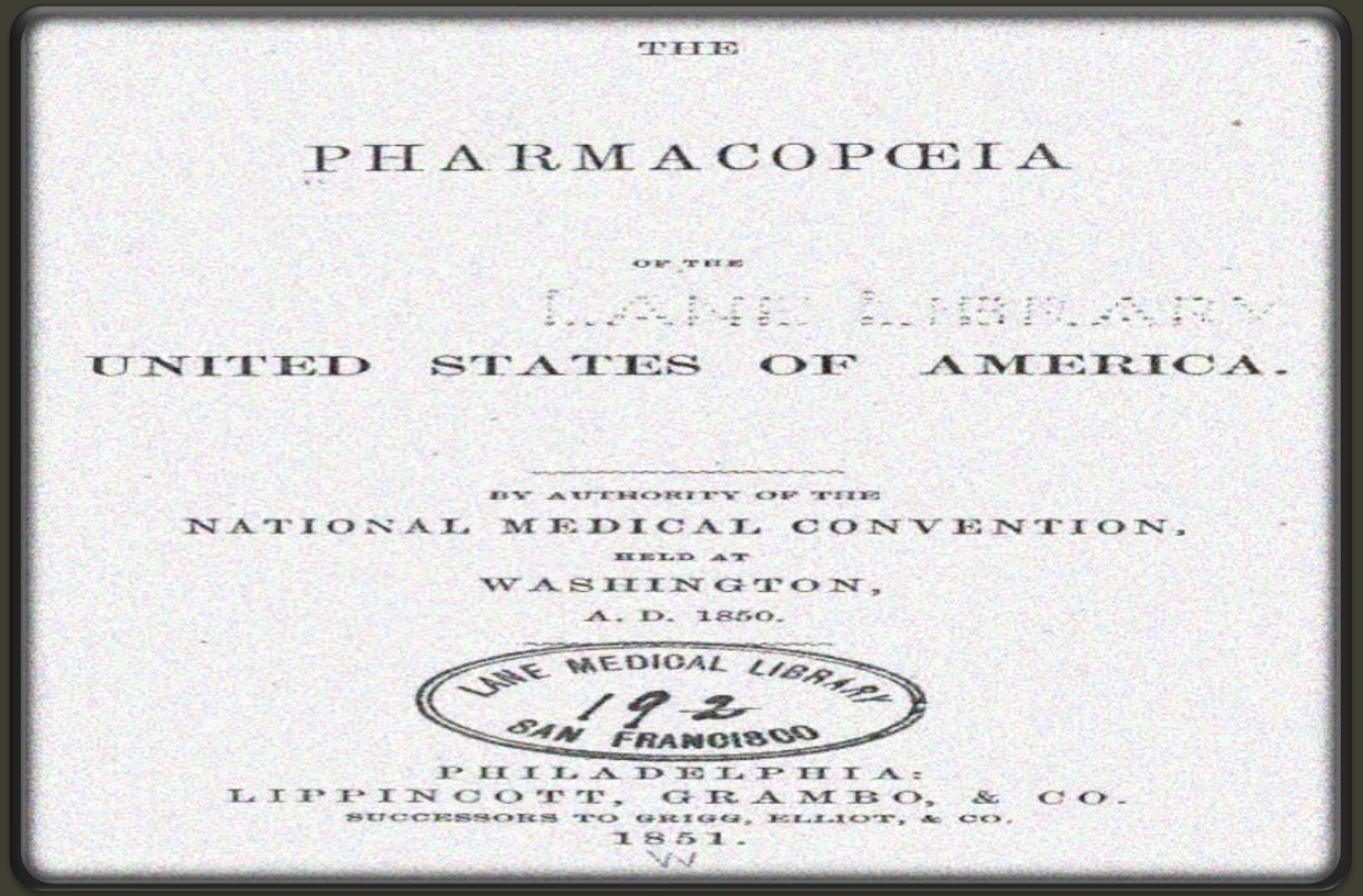
1851

ADDED TO US PHARMACOPOEIA

Added to the 3rd edition of the U.S. Pharmacopoeia

Listed for numerous afflictions, including tetanus, rabies, alcoholism

Subsequent editions expanded definition & medical uses



THE

PHARMACOPŒIA

OF THE

UNITED STATES OF AMERICA.

BY AUTHORITY OF THE

NATIONAL MEDICAL CONVENTION,

HELD AT

WASHINGTON,

A. D. 1850.

PHILADELPHIA:

LIPPINCOTT, GRAMBO, & CO.

SUCCESSORS TO GRIGG, ELLIOT, & CO.

1851.

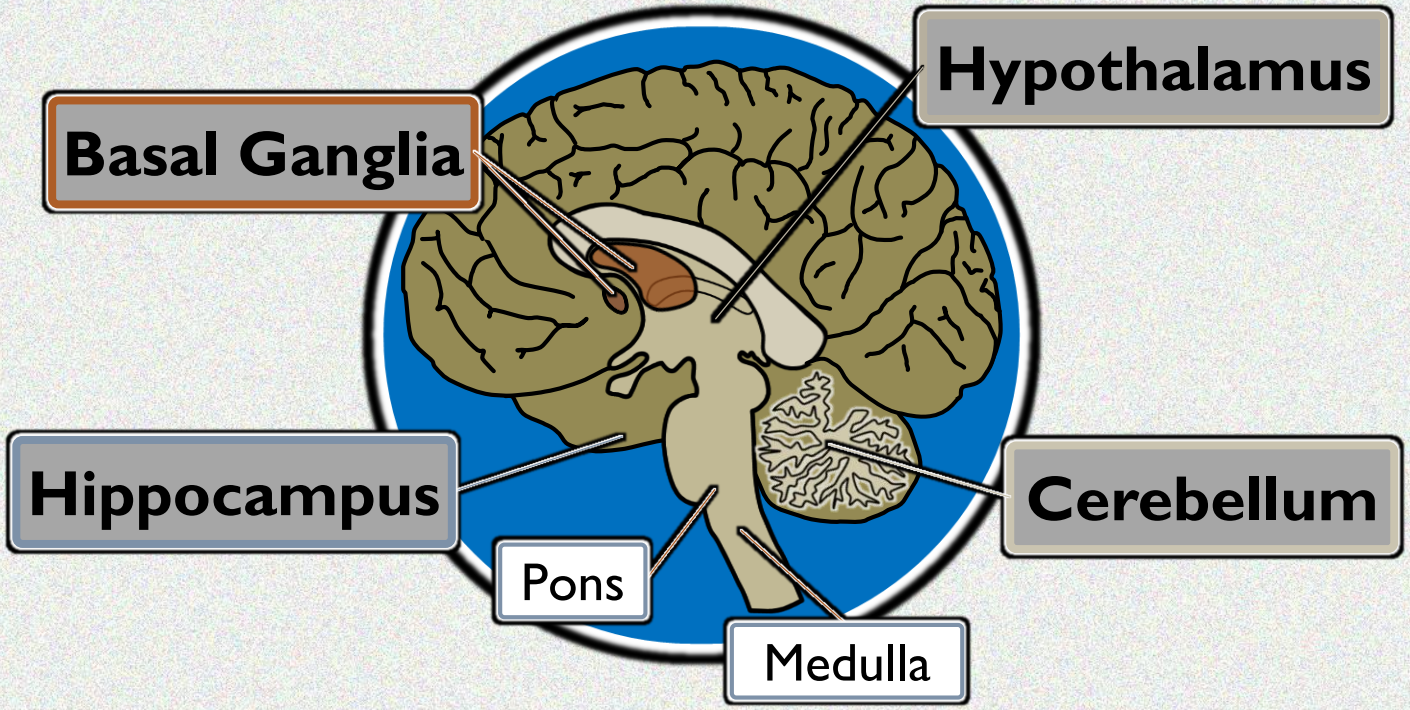
The Endocannabinoid System

- Cannabinoid Receptors
  - CB1
  - CB2
- Endocannabinoids
  - AEA
  - 2-AG
- Enzymes
  - FAAH
  - MGL

Cannabinoid Receptors

- Cloned and sequenced in 1990

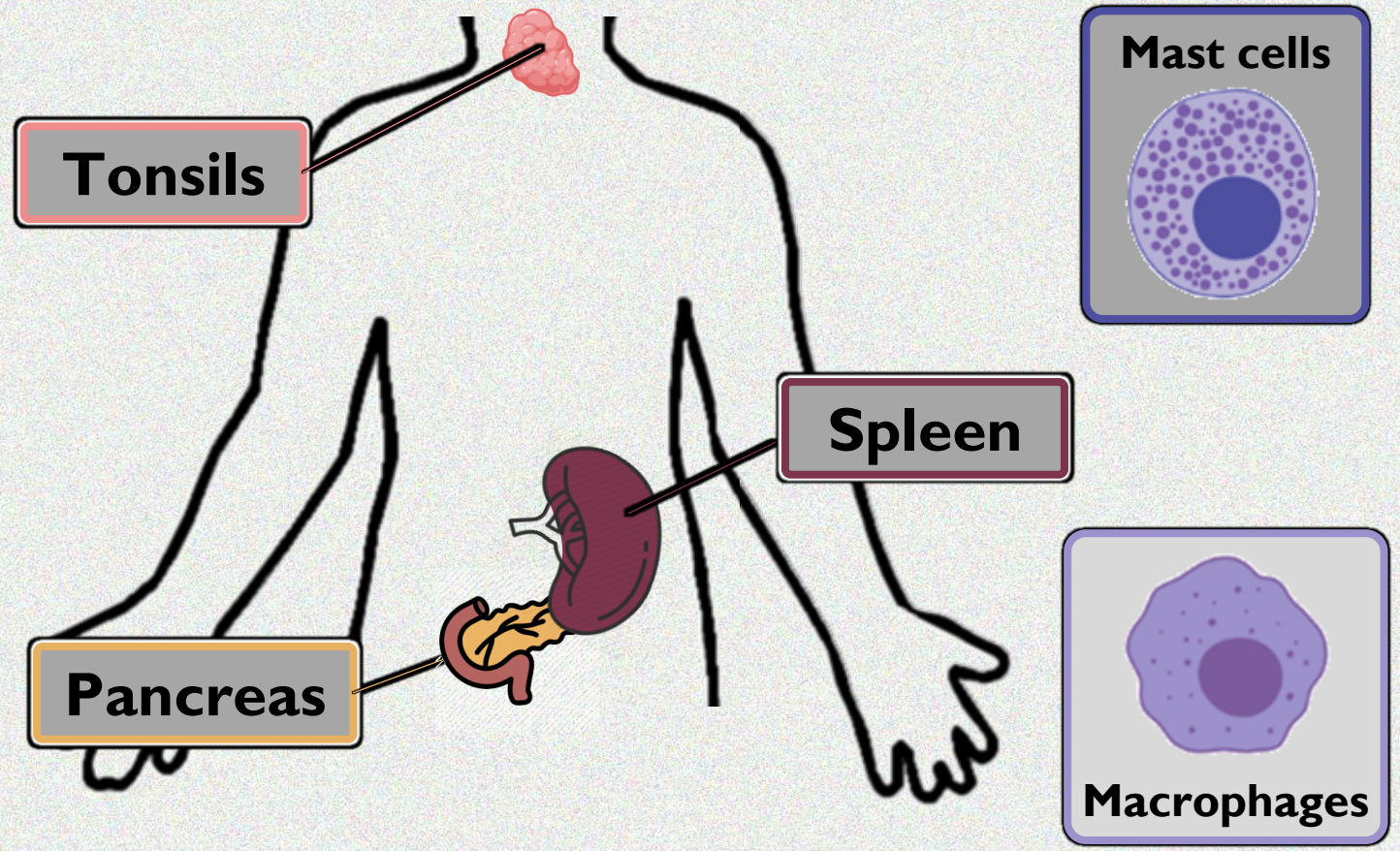
CB1



Cannabinoid Receptors

- Cloned and sequenced in 1990

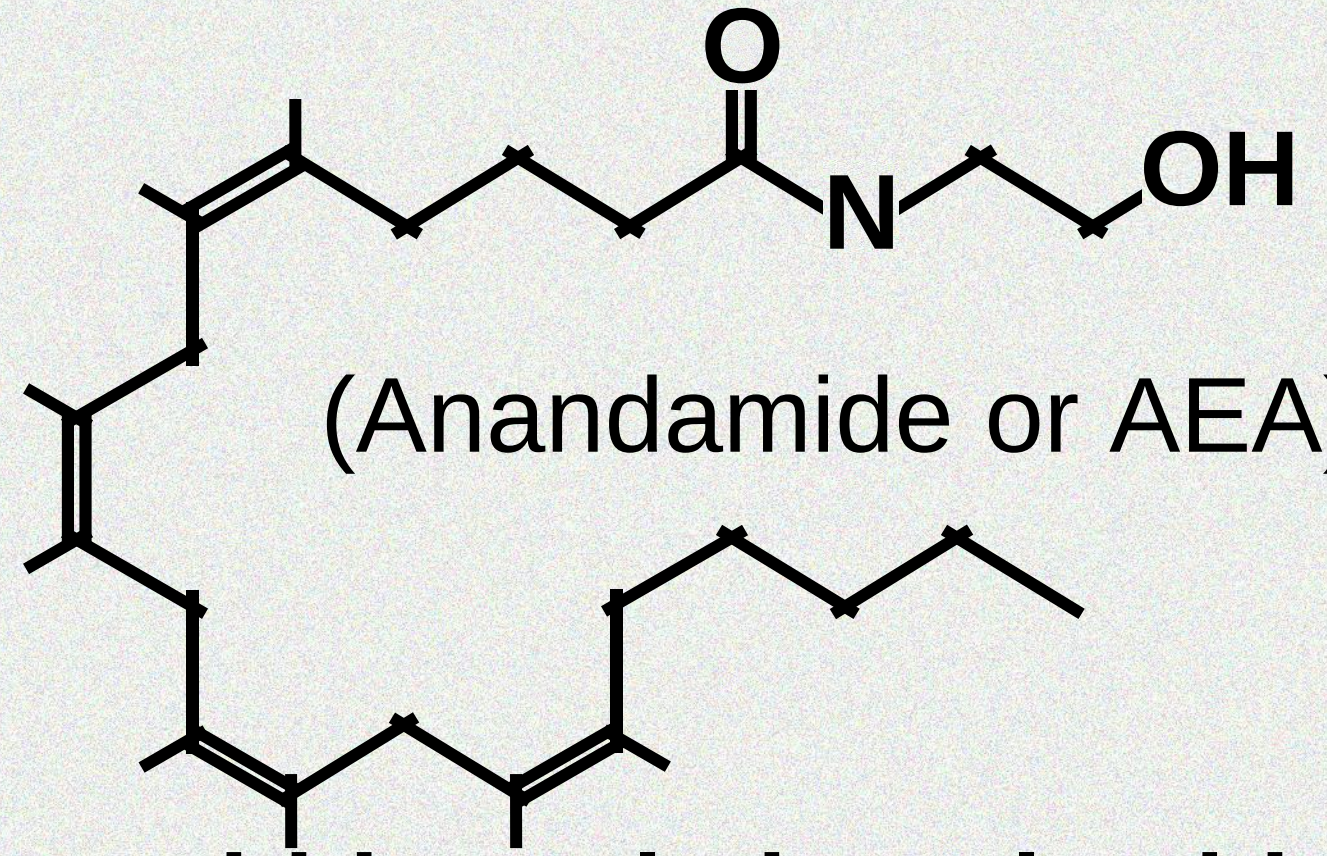
CB2



Endocannabinoids

- Endogenous ligands for the cannabinoid receptors.

AEA



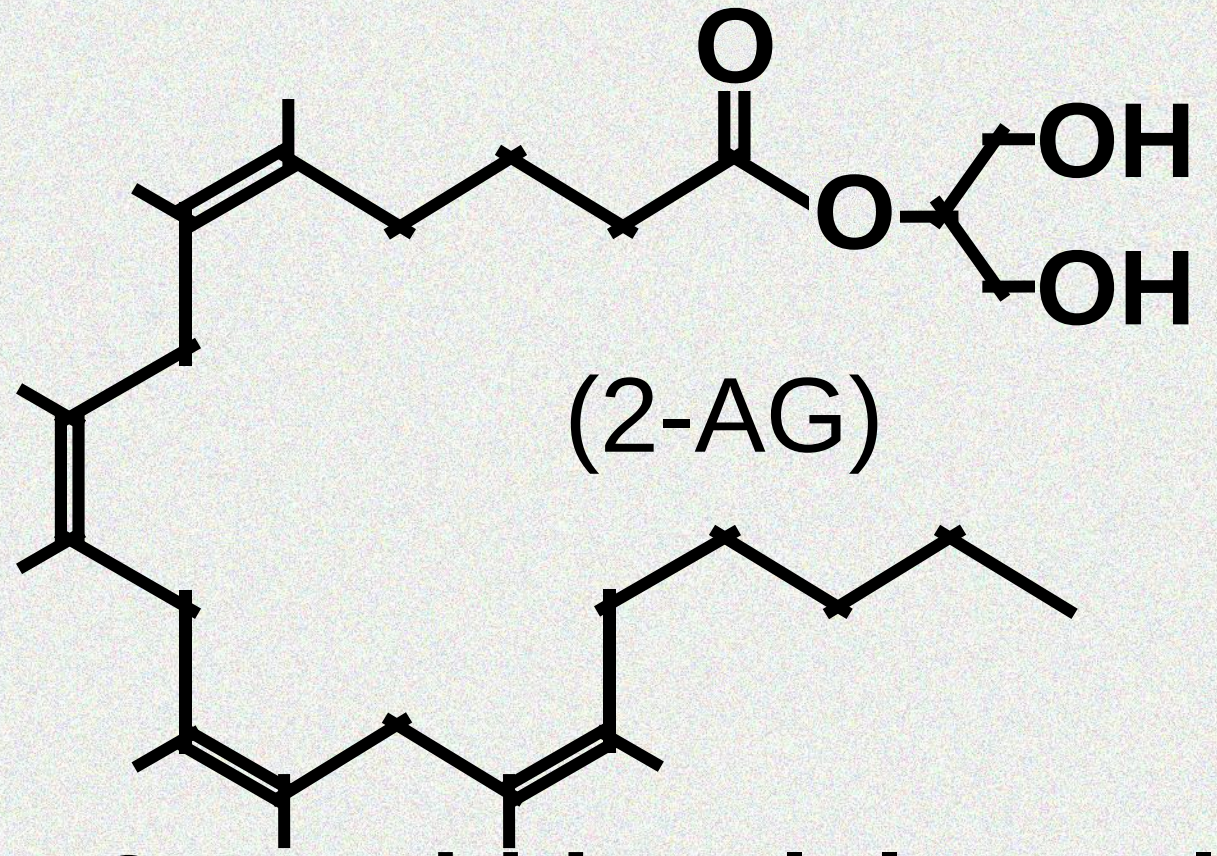
(Anandamide or AEA)

Arachidonoylethanolamide

Endocannabinoids

- Endogenous ligands for the cannabinoid receptors.

2-AG

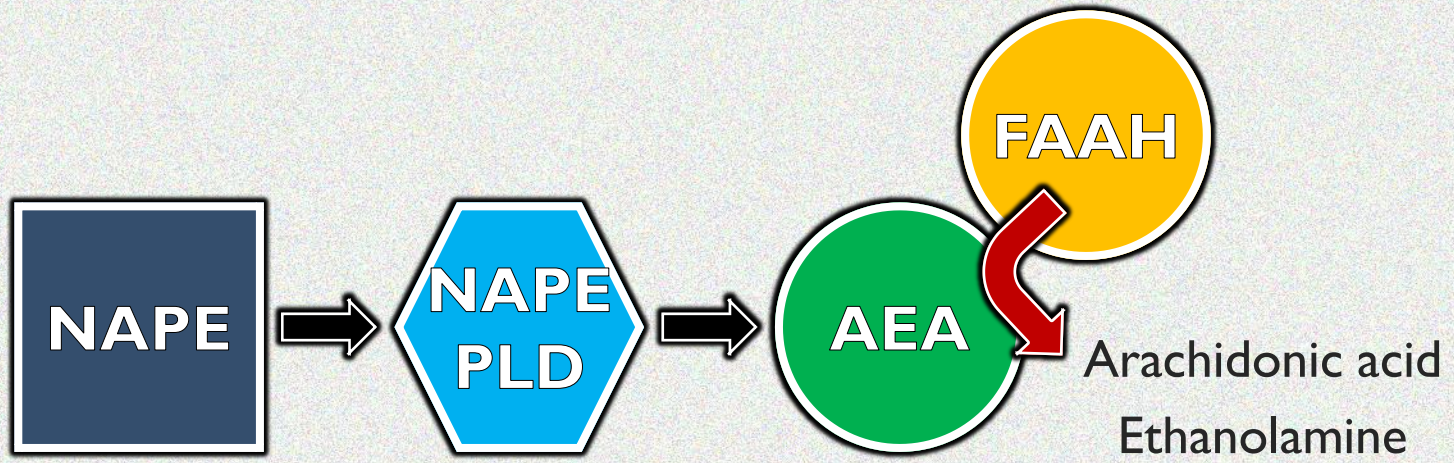


2-Arachidonylglycerol

Intracellular Enzymes

- Endocannabinoid synthesis and degradation

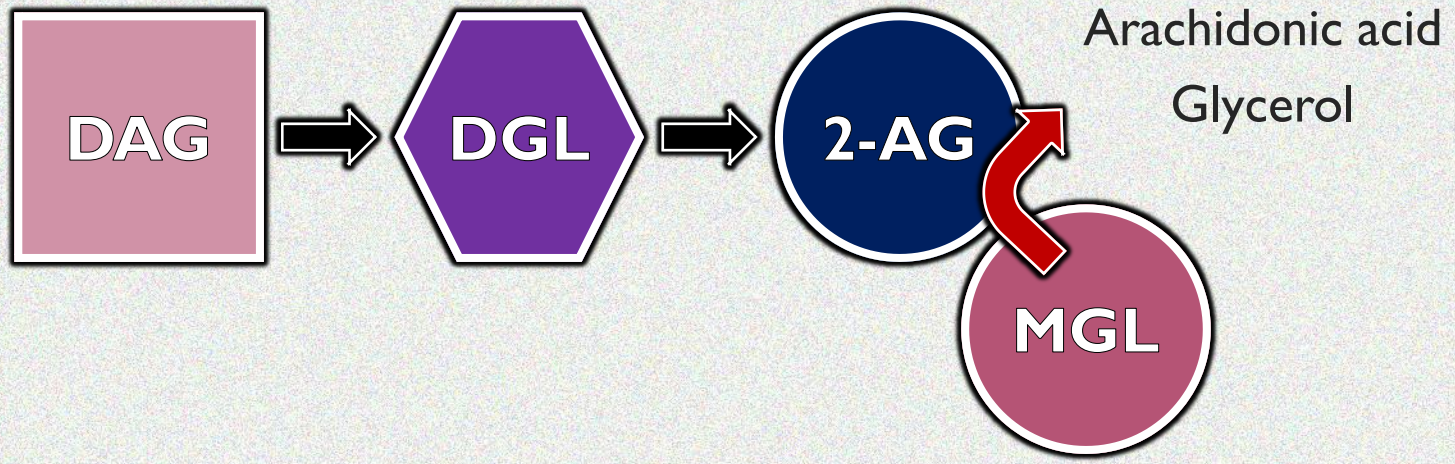
FAAH



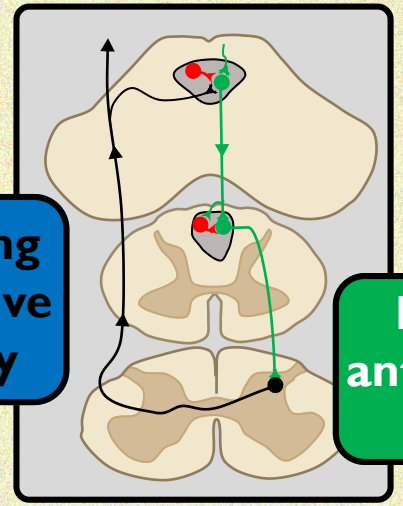
Intracellular Enzymes

- Endocannabinoid synthesis and degradation

MGL

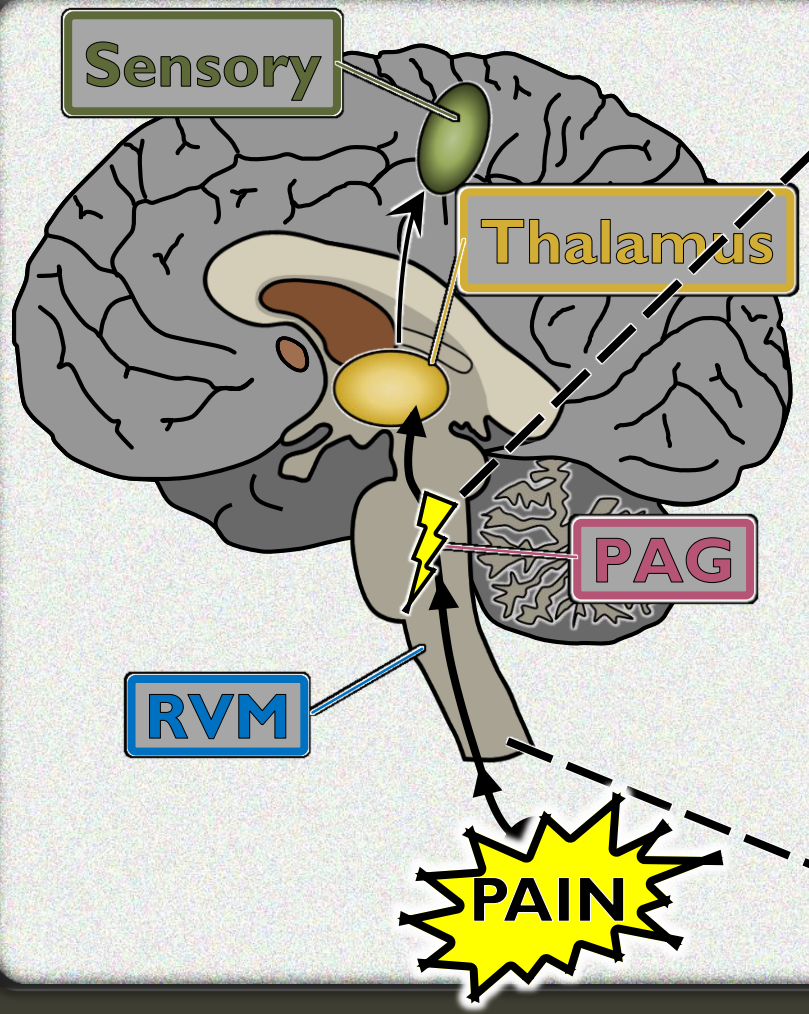


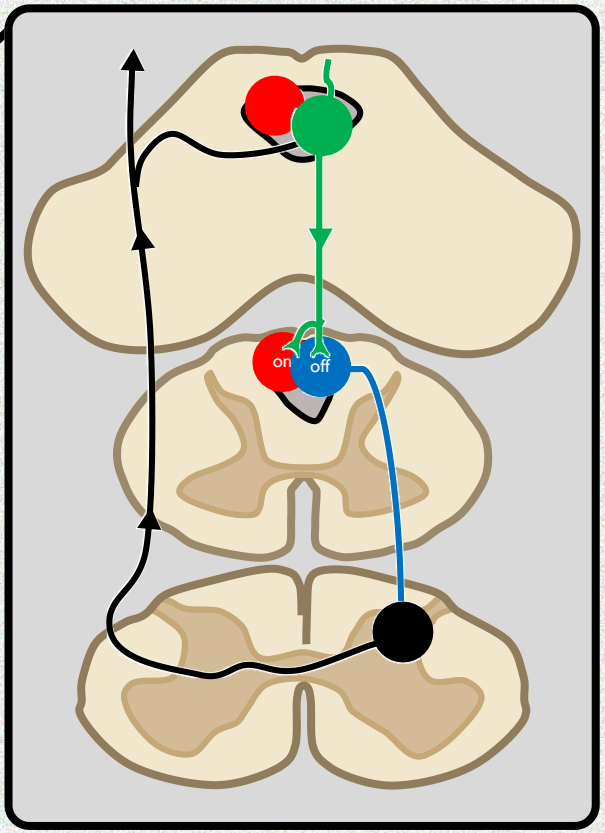
Endocannabinoids & Pain



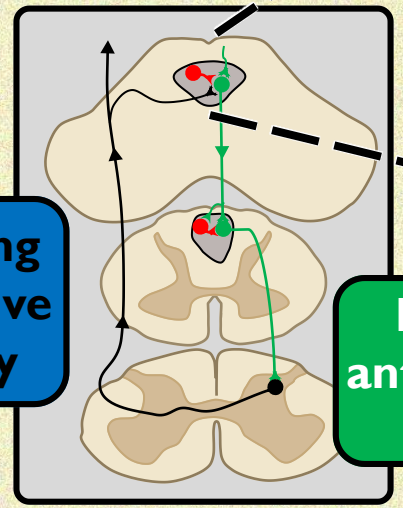
Ascending nociceptive pathway

Descending anti-nociceptive pathway





Endocannabinoid *de novo* Synthesis



Ascending nociceptive pathway

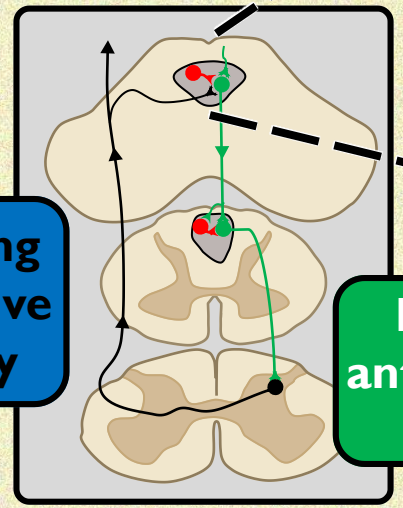
Descending anti-nociceptive pathway

1. Strong depolarization opens Ca^{2+} channels

2. Ca^{2+} influx induces the production of diacylglycerol (DAG)

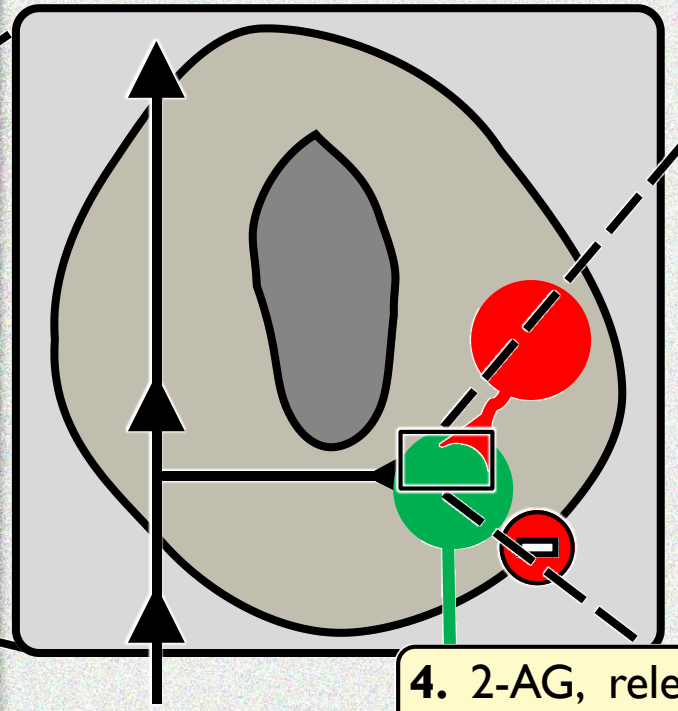
3. DAG is hydrolyzed to 2-AG by DAG lipase-α (DAGL-α)

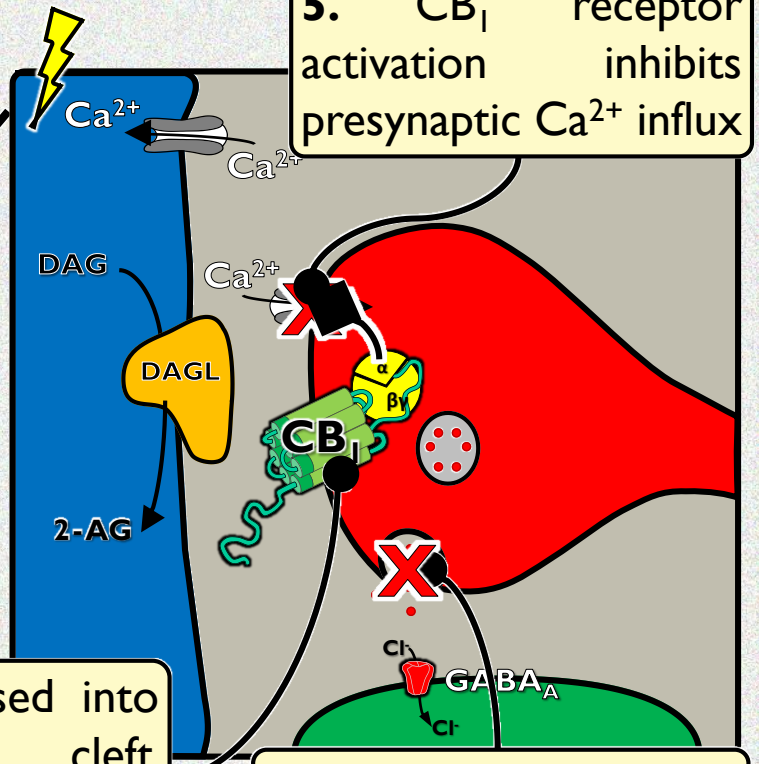
Endocannabinoid Retrograde Signaling



Ascending nociceptive pathway

Descending anti-nociceptive pathway





5. CB_1 receptor activation inhibits presynaptic Ca^{2+} influx

4. 2-AG, released into the synaptic cleft, actives CB_1 receptors on GABA interneurons

6. Suppressing GABA release and disinhibiting anti-nociceptive signals

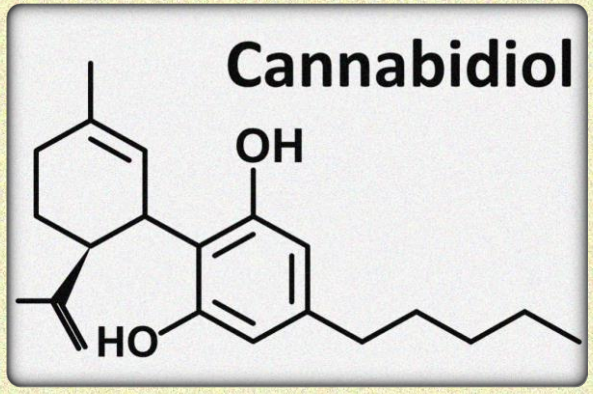
Phyto- & Synthetic Cannabinoids

Synthetic Cannabinoids - based on the chemical structure of THC or other ligands which bind to cannabinoid receptors .

Phytocannabinoids - Over 100, 21-carbon-containing terpenophenolic compounds (cannabinoids) unique to cannabis plant

- Only two that have been well characterized pharmacologically

CBD



- Full, weak, agonist at the transient receptor potential vanilloid type 1 (TRPV1).

- NOT psychoactive, but rather can potentially inhibit THC's effects in 3 ways:
  1. CBD has a slight affinity for CB receptors, and it signals receptors as an antagonist or reverse agonist.
  2. May modulate signal transduction by perturbing the fluidity of neuronal membranes, or by remodeling G-proteins that carry intracellular signals downstream from CB receptors.
  3. Potently inhibits CYP 3A11 metabolism, thus it blocks the hydroxylation of THC to its 11-hydroxy metabolite.
     - The 11-hydroxy metabolite is four times more psychoactive than un-metabolized THC and four times more immunosuppressive

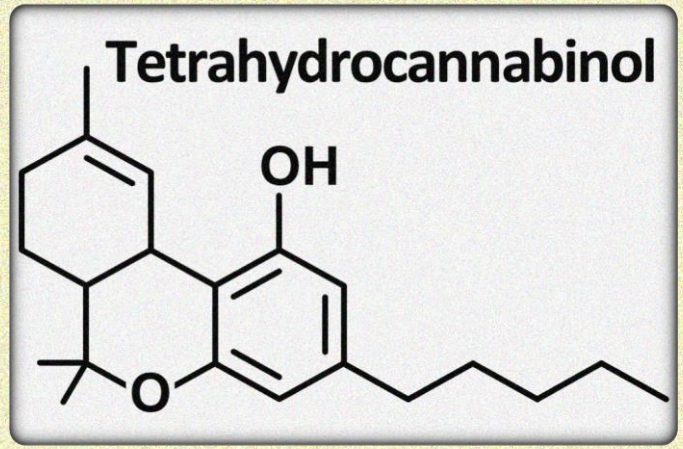
Other Medicinal Effects

Seizures associated with Lennox-Gastaut syndrome or Dravet syndrome

Epidiolex

- CBD botanical extract
- Dose: 2.5 mg/kg (~700 mg/day)
- Cost: $1.20 / 10 mg
- Dosage: 2.5 mg/kg BID
- FDA approved:
  - June 2018
- Schedule V
- AEs: somnolence, decreased appetite, diarrhea, transaminase elevations, insomnia, sleep disorder, and infections

Δ^9-TETRAHYDRO-CANNABINOL (THC)



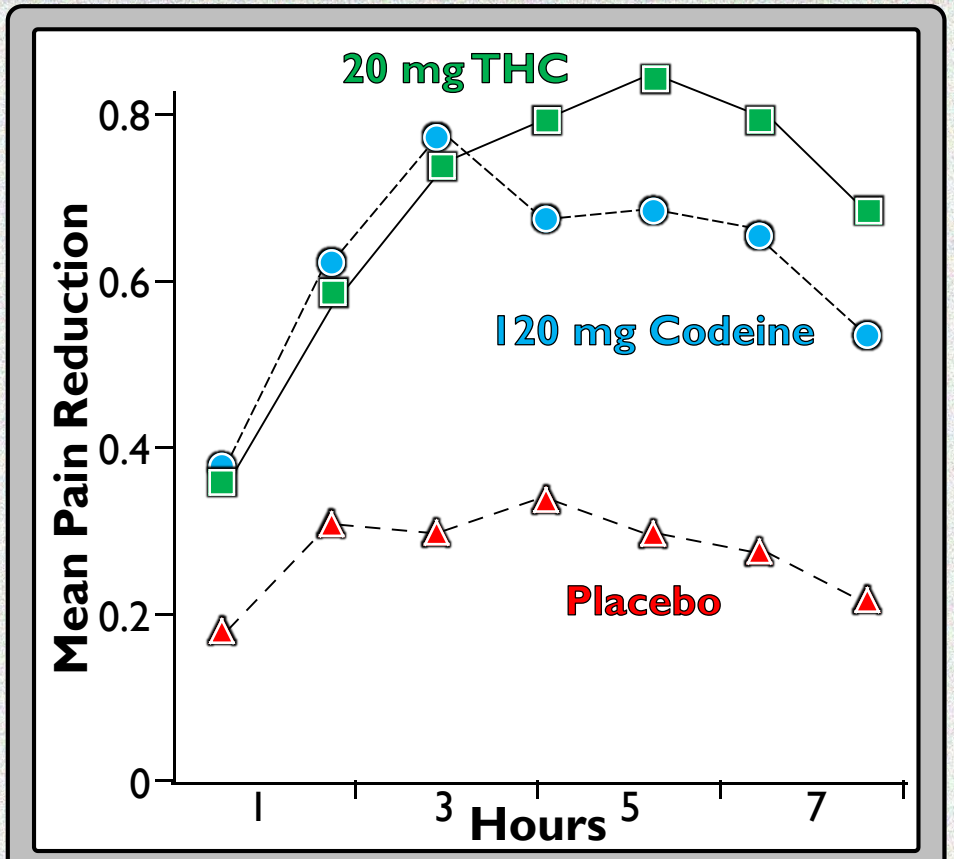
- Partial agonist at the CB1 and CB2 receptors, analogous to the endocannabinoid AEA.
- Responsible for the psychoactive effects of cannabis.
  - These effects are the most frequently mentioned reason for discontinuation of medicinal cannabis use among patients

THC is an analgesic, antispasmodic, & muscle relaxant

- 20 times the anti-inflammatory power of aspirin and twice that of hydrocortisone.

THC & Pain

- The analgesic effects of THC were first evaluated in humans in the 70's
- 20 mg THC was as effective as 120 mg codeine for reducing cancer pain



Mean hourly pain reduction following THC, codeine, and placebo. Adapted from Noyes *et al.* (1975a).

Other Medicinal Effects

Appetite Stimulation/Nausea

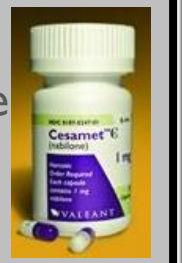
- Inhalation better than oral, but some people find smoking nauseating
- Tolerance develops

Marinol

- Generic name: Dronabinol
- Synthetic THC stereoisomer
- Dose: 2.5, 5, & 10 mg/capsule
- Cost: $6/2.5 mg
- Dosage: 2.5 mg BID
- FDA approved:
  - 1985: antiemetic
  - 1992: cachexia
- Schedule III
- AEs: dysphoria, vertigo, disorientation, somnolence

Cesamet

- Generic name: Nabilone
- Racemic mixture of synthetic THC analogue
- Dose: 1 mg/capsule
- Cost: $20/1 mg capsule
- Dosage: 1 mg TID
- FDA approved:
  - 2006: antiemetic
- Schedule II
- AEs: vertigo, somnolence, dysphoria, dry mouth, ataxia



Other Medicinal Cannabinoids

Although not approved for use in the US, in Canada nabiximols is approved as adjunctive treatment for symptomatic relief of spasticity in patients with multiple sclerosis (MS).

Sativex

- **Generic name**: Nabiximols
- Whole plant extract
- **Dose**: 2.7 mg THC and 2.5 mg CBD per 100 µL spray
- **Cost**: $2.50/spray
- **Dosage**: 6-12 sprays per day
- **FDA approved**:
  - NO, Phase 3
- **AEs**: dizziness, drowsiness, constipation or diarrhea, fatigue, memory or concentration problems, & dry mouth

Randomized Clinical Trials

Evidence of Cannabis or Cannabinoid Efficacy for Chronic Pain

Relief from chronic pain is by far the most cited condition by patients for using cannabis, with 87%-94% of medical marijuana users reporting use to relieve chronic pain (Kondrad & Reid, 2013).

Neuropathic Pain: A recent meta-analysis that included RCTs for dronabinol, nabilone, or THC/CBD in patients with moderate to severe (≥ 4 on a 0–10 NRS) chronic neuropathic pain of (including MS) concluded that cannabinoids produced a significant reduction of pain intensity after a minimum of 2 weeks following initiation of treatment (Meng et al., 2017).

Cancer Pain: THC/CBD has been considerably studied in patients with cancer pain. It has been conditionally approved in Canada and some European countries for the treatment of cancer-related pain. Currently, it is in Phase III trials for cancer pain.

Musculoskeletal Pain: Of 118 studies included in a systematic review relevant to general musculoskeletal pain, 85 (72%) indicated that cannabinoid treatment was effective, 17 (14%) demonstrated mixed effectiveness, 11 (9%) indicated that it was not effective, and 5 studies (4%) demonstrated inconclusive or unclear findings.

Research Summary

- The NASEM (2017) evaluated more than 10,000 scientific abstracts and established that there is "*conclusive or substantial evidence*" for the use of cannabis in treating chronic pain in adults.

- In adults with chemotherapy-induced nausea and vomiting, oral cannabinoids are effective antiemetics.
- In adults with chronic pain, treatment with cannabis or cannabinoids increases the likelihood of clinically significant reductions in pain symptoms.
- In adults with MS-related spasticity, short-term use of oral cannabinoids improves patient-reported spasticity symptoms.
- For these conditions, the effects of cannabinoids are modest; for all other conditions evaluated there is inadequate information to assess their effects.

Randomized Clinical Trials

Evidence of Efficacy for Cannabis or Cannabinoids

Substantial Evidence of Efficacy:

1. Chronic pain in adults (cannabis)
2. As antiemetics in the treatment of chemotherapy-induced nausea and vomiting (oral)
3. For improving patient-reported MS spasticity symptoms (oral)

Moderate Evidence of Efficacy:

1. Improving short-term sleep outcomes in individuals with sleep disturbance associated with OSA syndrome, fibromyalgia, chronic pain, and MS (cannabinoids, primarily nabiximols)

Limited Evidence of Efficacy:

1. Increasing appetite and decreasing weight loss associated with HIV/AIDS (cannabis and oral)
2. Improving clinician-measured MS spasticity symptoms (oral)

Randomized Clinical Trials

Limitations

Overall, there is a lack of "***Gold Standard***" clinical trials that have rigorously evaluated the efficacy of cannabis for treating chronic pain

RCTs using any route of administration

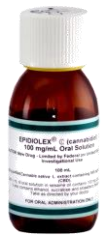
1. Short duration
2. Small sample sizes
3. Lack of control groups

RCTs using inhaled/vaporized vannabis

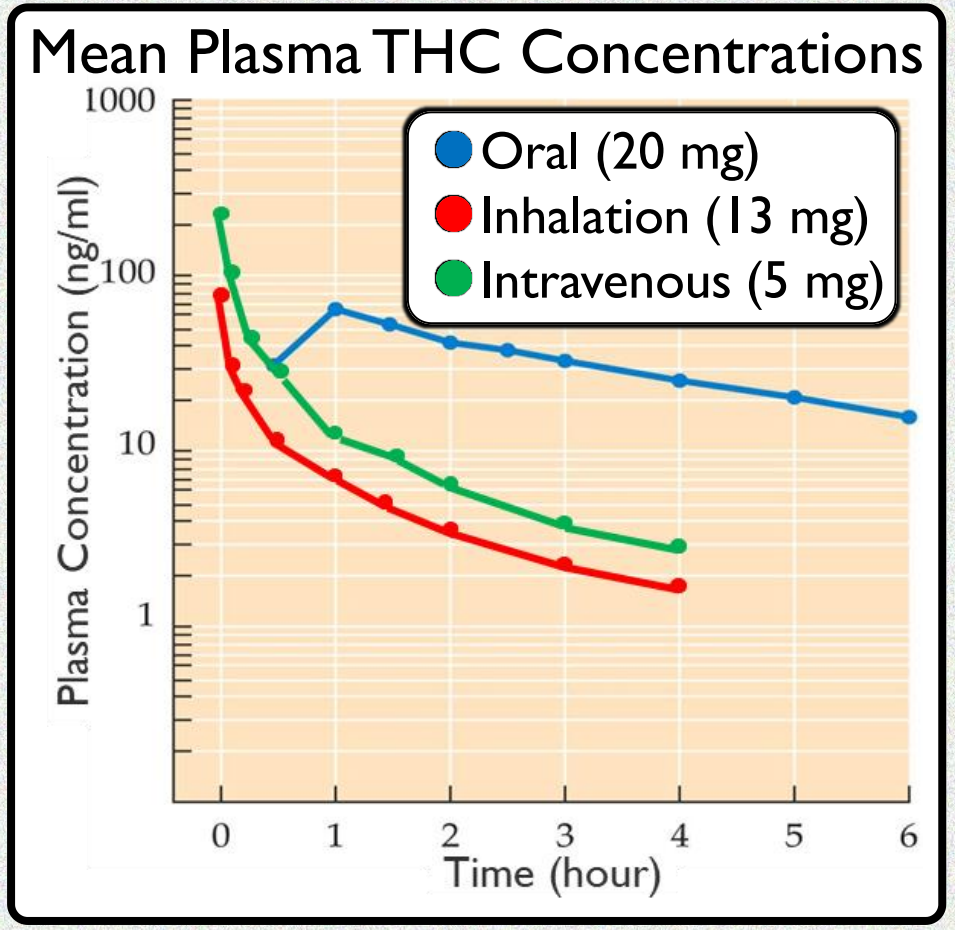
1. Conducted in cannabis-experienced patients only
2. Standardization of the cannabis not employed
3. Quantification of delivered doses not determined
4. Blinding is difficult if not impossible

Cannabinoid Pharmacokinetics

FDA-Approved Medications



Medical Marijuana

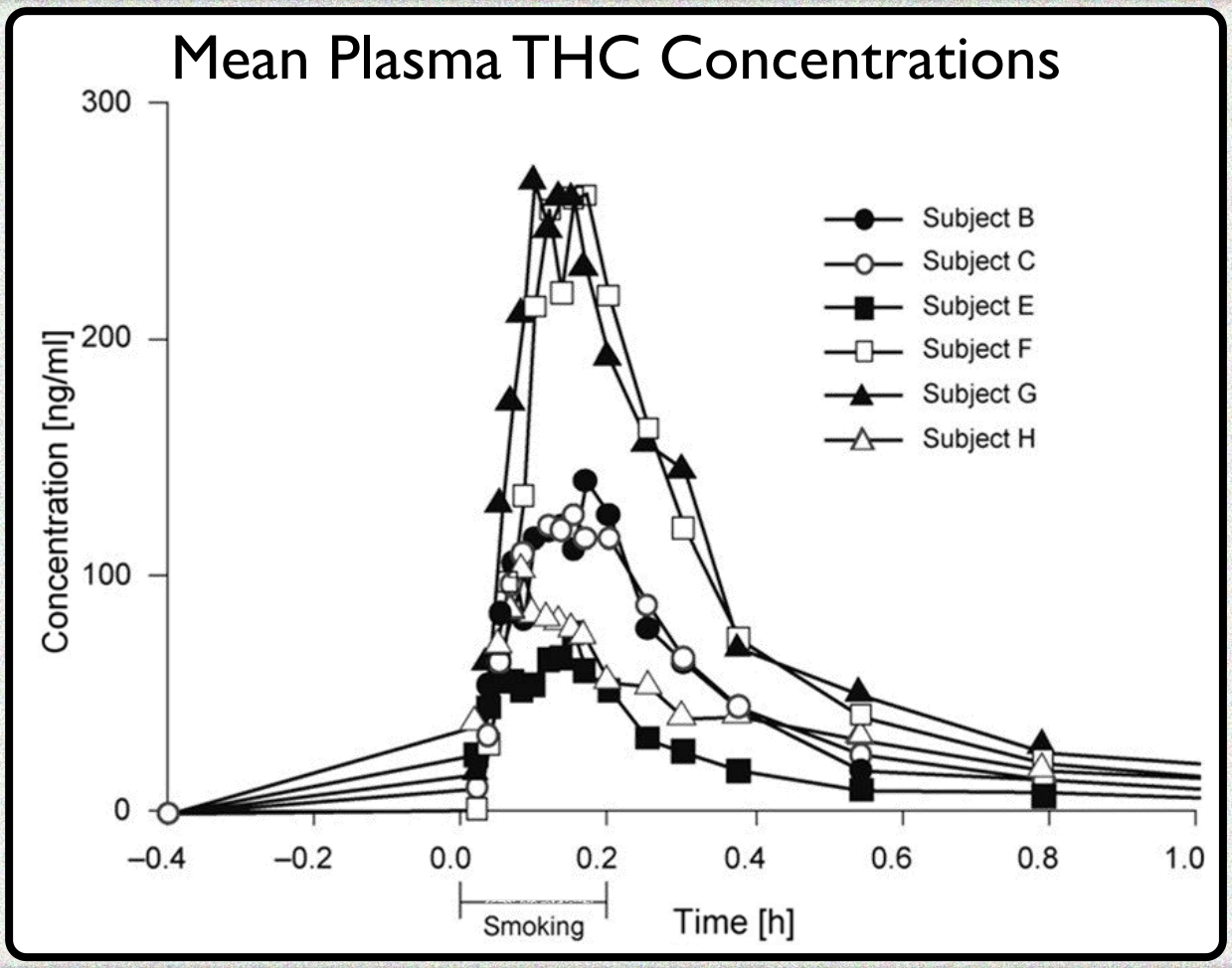


Cannabinoid Pharmacokinetics

Smokers only

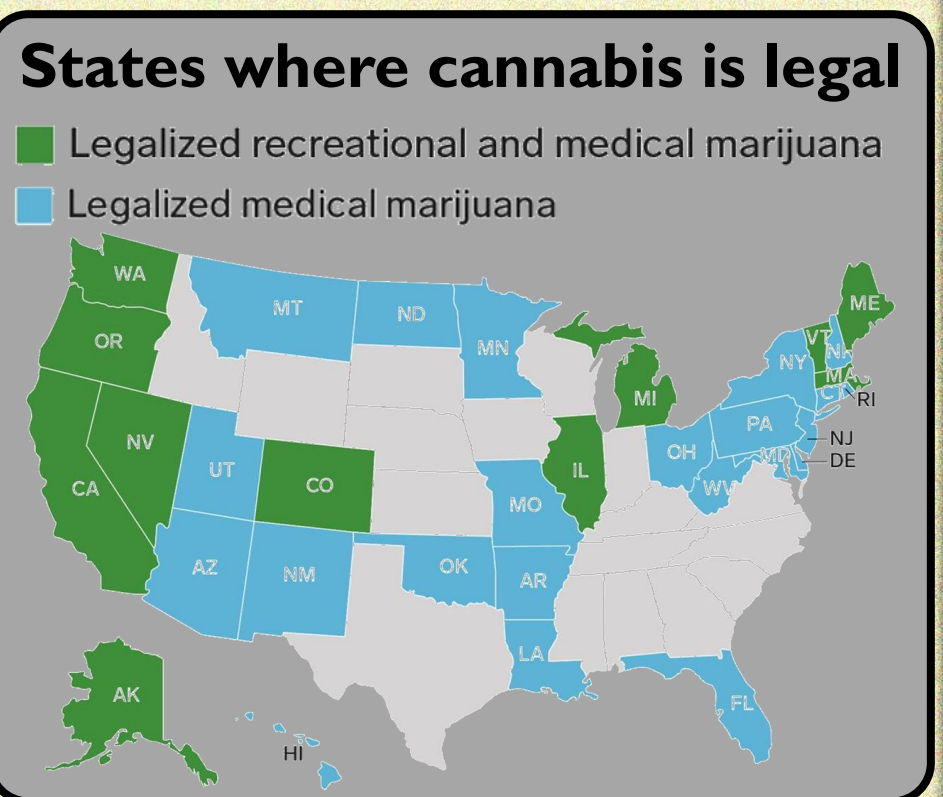
Subject Variability

1. Experience
2. Volume inhaled
3. Number of puffs
4. Hold time in lungs



Clinical Concerns

States where cannabis is legal



Use of the Whole Plant

- Quality standards
- Uncertainty regarding titration/dosing
- Lack of control over product composition

Hemp	THC = 0.3%
Marijuana	THC = 1-5%
Sinsemilla	THC = 4-8%
Hashish	THC = 8-14%
Hash Oil	THC = 15-60%

Clinical Advantages

Risk of Overdose

- It is virtually impossible to overdose from cannabinoids

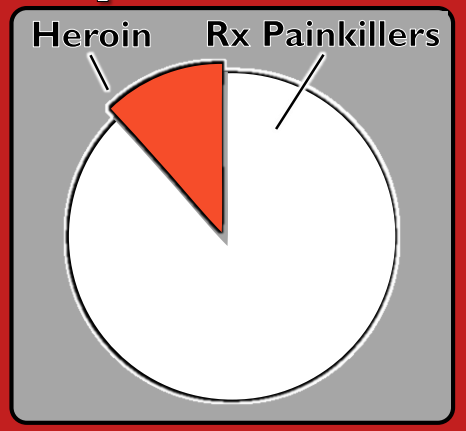
Risk of Abuse

Overdose Deaths per Year

Cannabis = 0

Rx Painkillers = 16,790

Heroin = 2,000



- The abuse potential of **oral THC** is very low
- The abuse liability cannabidiol is exceedingly low

Therapeutic Potential

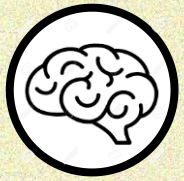
The potential for cannabinoids to reduce opioid use and improve analgesia should not be understated.

As an adjuvant to opioid treatment, cannabis or cannabinoids have the potential to:

- Decrease use of opiates, NSAIDS, antidepressants
- Synergize with opioids and thereby lower the effective dose needed to achieve pain relief
- Increase pain relief in those who
  1. Are unable to achieve effective relief with opioids
  2. Have developed tolerance to opioids
- Decrease adverse outcomes because cannabinoids have lower abuse potential (especially among adults) & lower risk of overdose

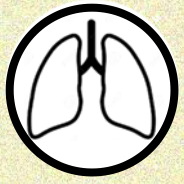
Relative Contraindications

Psychiatric



Substance use

Cardio-pulmonary



Liver or renal

Pregnant

Onset or Aggravation of Psychiatric Disorders

Schizophrenia, psychosis, anxiety, depression, bipolar.

Use cautiously in patients with personal or family history.

Particular attention: Adolescents under stress who may be at increased risk of developing psychosis.

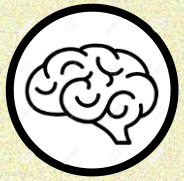
Substance Use Disorder

An estimated 9% of people who smoke cannabis will become dependent.

A history of drug dependence may be a contraindication or require additional monitoring.

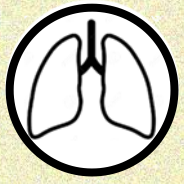
Relative Contraindications

Psychiatric



Substance use

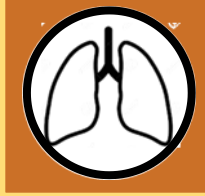
Cardio-pulmonary



Liver or renal

Pregnant

Cardio-pulmonary Disease or Respiratory Insufficiency



Smoking may exacerbate bronchitis and respiratory infections.

Hypertension, syncope, and tachycardia are potential AEs.

Severe Liver or Renal Disease

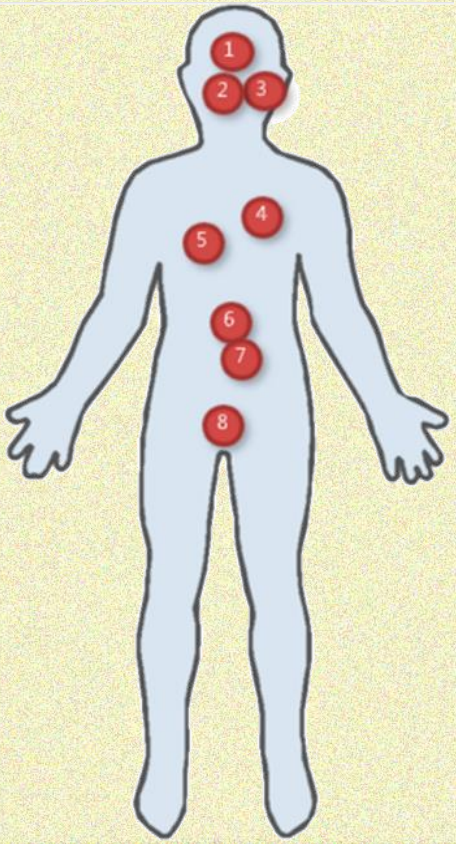
May be at greater risk of steatosis if cannabis is used daily

Ingested cannabis is metabolized in liver by common drug enzymes

Pregnancy or Breastfeeding

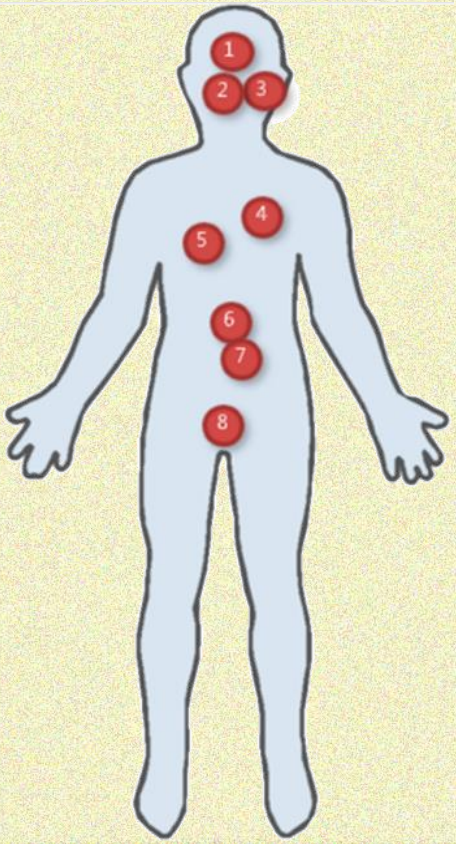
Pregnant and nursing mothers should not be considered candidates for this treatment

Side Effects



1. Unwanted psychoactive effects
2. Short-term memory loss
3. Impaired psychomotor function
4. Tachycardia
5. Bronchitis & lung irritation
6. Increased appetite
7. Cannabinoid Hyperemesis Syndrome
8. Decreased sperm count

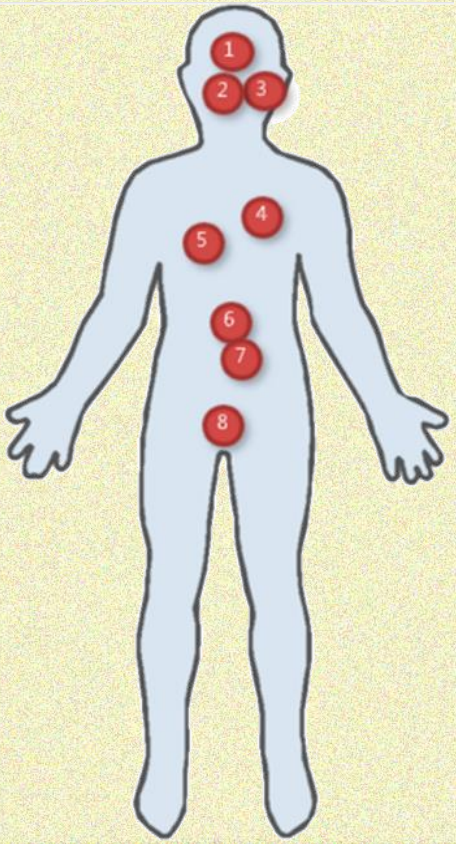
Side Effects



Unwanted psychoactive effects

- Typically dose-dependent
- Decline with tolerance
- Apprehensive patients and the elderly more prone
- *Counsel Patients*. Look for high CBD, low THC.
- Psychoactive effects may occur but will be short-lived. Call if severe.

Side Effects



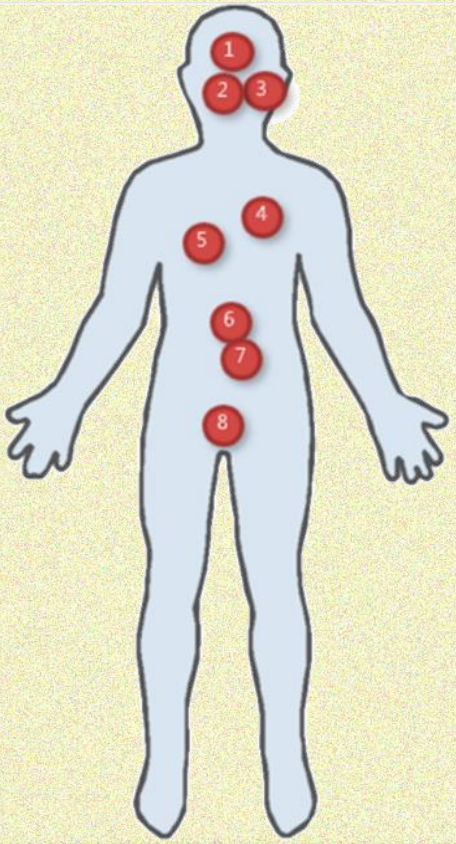
Short-term memory loss

- THC temporarily weakens neural connections
- *Counsel Patients*. Look for higher CBD levels to prevent this effect.

Impaired psychomotor function

- Patients may be more susceptible to falls
- Reaction times may decrease
- *Counsel Patients*. Do not drive or operate heavy machinery.

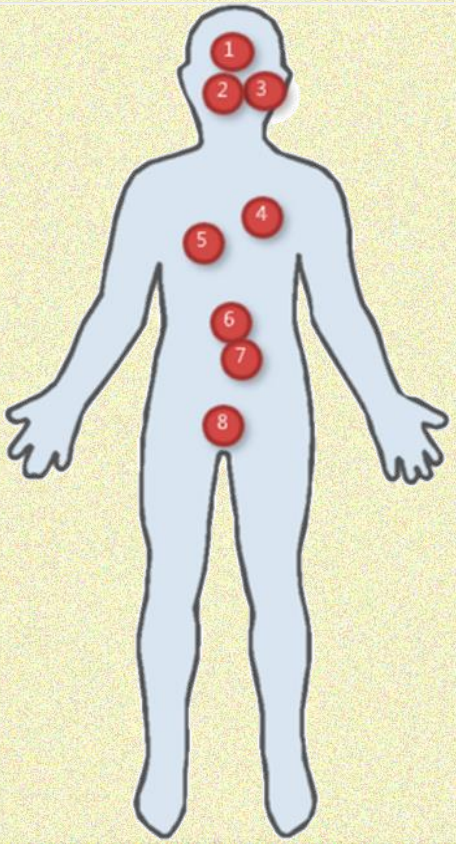
Side Effects



Tachycardia

- Dose-related
- Not a concern for relatively healthy young users
- May be consideration when recommending to older patients with cardiac disorders or angina
- Increased tolerance diminishes degree of tachycardia

Side Effects



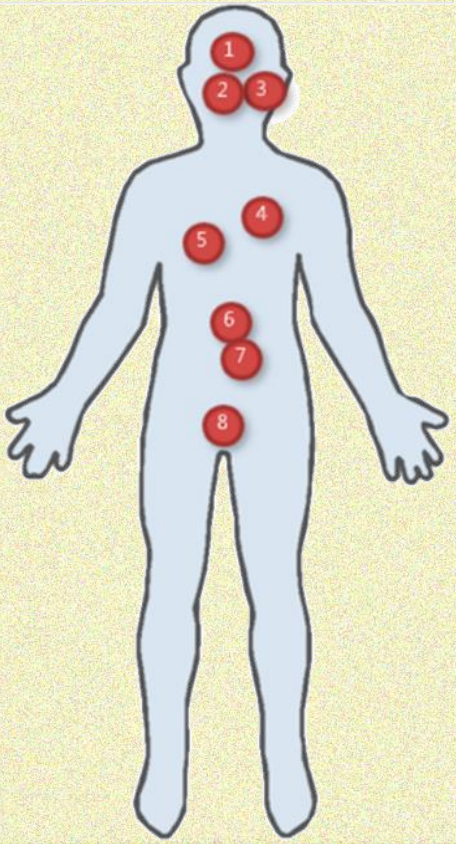
Bronchitis & lung irritation

- Associated with smoking cannabis
- Other routes of administration bypass these effects
- No consistent evidence regarding a relationship between smoking cannabis and lung cancer

Increased appetite

- Cannabis associated with increased appetite

Side Effects



Cannabinoid Hyperemesis Syndrome

- Rare
- Nausea and vomiting, sometimes paired with compulsive bathing
- *Counsel Patients*. Discontinue use immediately

Decreased sperm count

- Cannabis may decrease sperm count or cause sperm abnormalities
- *Counsel Patients*. May take up to 3 months for normal sperm count to return

Final Thoughts

Finding an alternative pain treatment would have major health, economic and societal benefits given:

1. The increasing prevalence and enormous costs of pain
2. The current opioid epidemic

American adults suffer from **Chronic Pain**

ONE IN FIVE

That's nearly

50 Million

Americans

Total costs for treating pain in the US are estimated to be as high as $635 billion annually

130 Americans die every day from opioid overdoses

46 people die every day from overdoses involving Rx opioids

Questions?