The Endocannabinoid System & Cannabis

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Conflict of Interest Disclosure

- *I have no relevant conflict of interest*
- *I have a financial interest / affiliation with these commercial entities:*

Vertex Pharmaceuticals, Inc – Employed
McKesson Life Sciences – Consultant
NEMA Research – Consultant

ROME REGIONAL OSTEOPATHIC MEDICAL EDUCATION 2019 NEW ENGLAND Providence, RI, August 8 - 11 RISOPS COMS

My Background

- ABMS Certified in Pain Management, Addiction Medicine and Anesthesiology
- Practicing for over 18 years in Academic and Private Practice settings
- Currently developing non-opioid pharmaceuticals for pain management
- Immediate Past President of the Connecticut Pain Society
- Former Chairman of the Ct. State Medical Society's Taskforce on Opioids
- Ct. State Police Surgeon

Cannabis and its derivatives

Image of a live marijuana plant

Image of Marijuana bud

Image of Hashish

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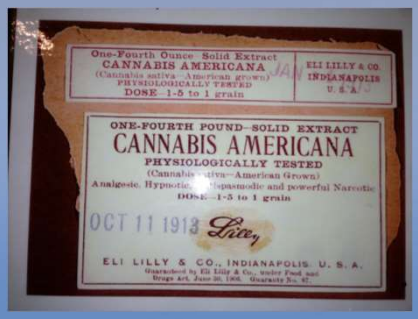
Cannabis: not a new medicine



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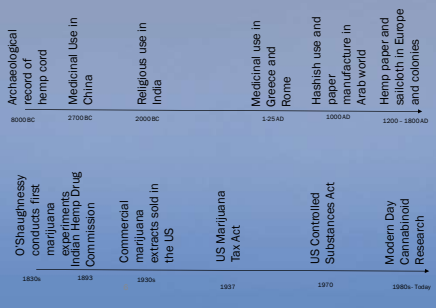
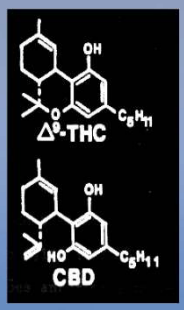
Marijuana Timelines



Phytocannabinoids



Y. Gaoni, Raphael Mechoulam. J. Am. Chem. Soc. 86, 1964: 1646

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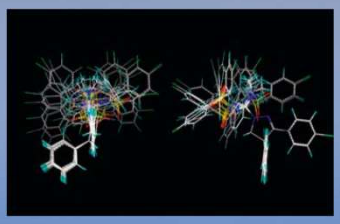
Isolation of the CBD receptor



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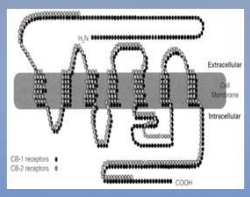
Cannabinoid Receptor 1&2 : A Closer Look



- G-protein-coupled receptor
- Cannabinoid receptor ligands bind reversibly and stereo selectively
- The CB-1 receptor is larger than Cb-2 receptor
- CB-2 receptor is has 44% homology to the CB-1 receptor.

Cannabinoids and Animal Physiology." Institute of Medicine. 1999. *Marijuana and Medicine: Assessing the Science Base.* Washington, DC: The National Academies Press.

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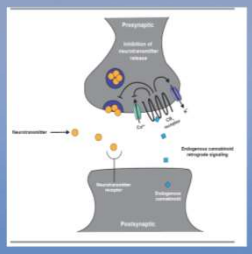
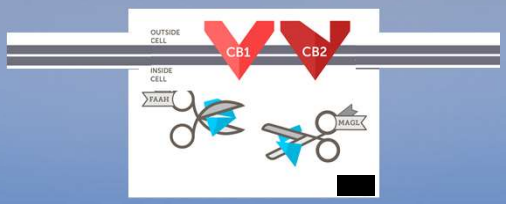
Mechanism of Action



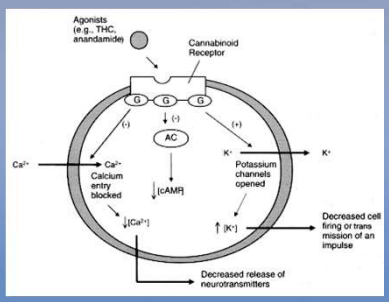
- Cannabinoid receptors are G protein–coupled receptors are mostly inhibitory to downstream signaling cascades.
- Stimulation of the CB1 receptors leads to inhibition of neurotransmitter release and direct effects on ion channels, resulting in closing of calcium channels and opening of potassium channels.
- These intracellular signaling cascades ultimately lead to inhibition of neurotransmitter release. Ca, calcium; CB1, cannabinoid receptor type.

FAAH and MAGL are the key enzymes of the endocannabinoid system



https://www.leafly.com/news/science-tech/what-is-the-endocannabinoid-system

Cannabinoid Agonists trigger a series of intracellular reactions

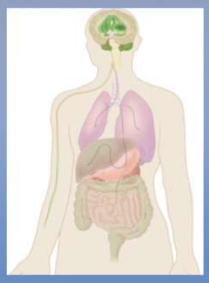


Distribution of CB1 Receptors

Green shading indicates distribution of cannabinoid receptors in the body

- CNS
- Intestine
- Liver

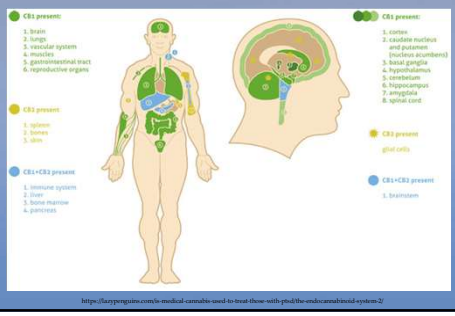
From www.cmcr.ucsd.edu



Distribution of CB1 Receptors in the CNS

From www.cmcr.ucsd.edu

CB2 : The less known receptor



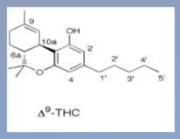
https://lazypenguins.com/is-medical-cannabis-used-to-treat-those-with-ptsd/the-endocannabinoid-system-2/

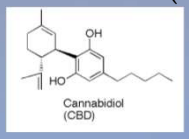
Other Endocannabinoid receptors

- TRYPY1[1]
  - CBD a non-psychotomimetic compound which induces anxiolytic- and antipsychotic-like effects in rodents. These effects could be mediated by facilitation of the endocannabinoid system or by the activation of 5-HT1A receptors
- GPR55[2]
  - Found in the brain, vascular endothelium, vascular smooth muscle and immune system
  - Is thought to be involved with vascular tone

1 Resstel, et al. British Journal of Pharmacology (2009), 156, 181–188
2 Ryberg. British Journal of Pharmacology (2007) 152, 1092–1101

Structure of THC and Cannabidiol (CBD)

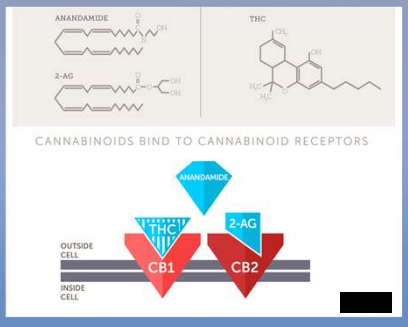




- Partial agonist and binds equally well to CB1 and CB2.
- Psychoactive, anti-nausea and appetite-stimulating effects are mediated through CB1.
- Polymorphisms of the CB1 gene have been found in schizophrenia, drug addiction and eating disorders.

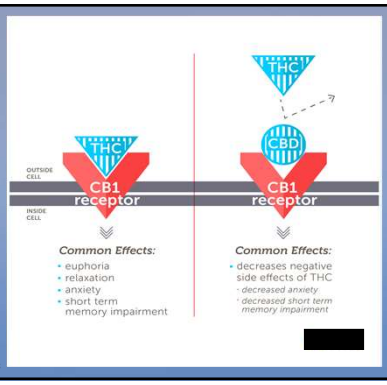
- Natural component of Cannabis plant
- Constitutes up to 40% of marijuana extracts
- Devoid of psychotropic effects of THC
- Potential antagonism of d9-THC when both molecules administered concomitantly

How THC plays alone



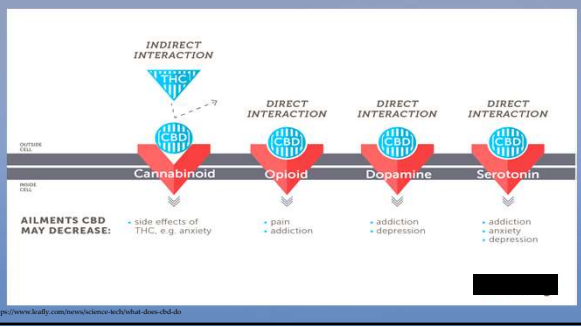
https://www.leafly.com/news/science-tech/what-is-the-endocannabinoid-system

How THC and CBD play in the same sandbox:



https://www.leafly.com/news/science-tech/cbd-vs-thc-cbd-not-intoxicating

The Potential Benefits of CBD



https://www.leafly.com/news/science-tech/what-does-cbd-do

{ What is Medical Cannabis

Marijuana – Cannabis Sativa

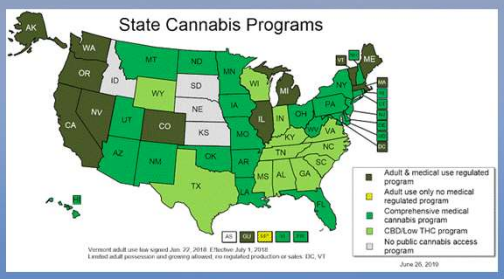
- Made up of numerous compounds:
  - Approximately 500
  - Most Abundant cannabinoids
    - CBD
    - THC
  - Also include other active compounds
    - Flavonoids
    - Terpenes

Atakan Z. *Ther Adv Psychopharm.* 2012;2:241-254

What Is Medical Cannabis?

- Who determines if it is medical?
- California became the first state to legalize MM in1996
- Individual states' medical cannabis laws are vary widely in terms of
  - Process of obtaining
  - Acceptable medical conditions
  - Amounts
  - Regulating dispensaries

State Medical Marijuana Laws



http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx

Federal Law

- CSA (1970) made cannabis a Schedule I drug
  - Drugs with no currently accepted medical use
  - High potential for abuse
- Remains illegal at the federal level
- Must obtain a Sch 1 License to conduct clinical trials
- Physician's are unable to 'prescribe'
  - They 'certify' medical conditions

US Drug Enforcement Administration. Drug Scheduling. Available at: http://www.justice.gov/dea/ds/ds1.htm#sch1

What is available at Dispensaries?

- Non-FDA Approved
- Lack standardized doses
- Limited safety and efficacy data to support
- Concentrations of CBD and THC can vary
- Use of pesticides on product
  - Unknown Composition

Dose and Label Accuracy

75 Products (47 different brands) from 3 dispensaries in 3 different cities.

Accuracy of THC labeling

	Accurately Labeled	Under-labeled	Over-labeled
n (%)	13 (17)	17 (23)	45 (60)

- Non-THC content was low
- 44 (59%) had detectable levels of CBD
  - 13 had CBD content labeled
    - 4 under-labeled
    - 9 over-labeled
- Median THC:CBD ratio
  - 36:1
- 7 had less than 10:1 ratio
- Only 1 had a 1:1 ratio

Vandrey R, Raber JC, Raber ME, Douglass B, Miller C, Bonn-Miller MO. Cannabinoid Dose and Label Accuracy in Edible Medical Cannabis Products. *JAMA*. 2015;313(24):2491–2493. doi:10.1001/jama.2015.6613

Is It a Drug(s)?

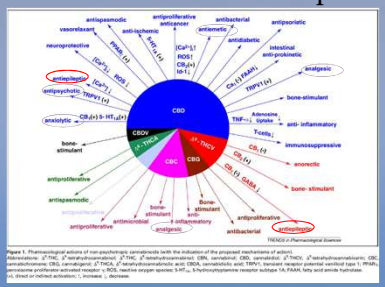
- Made up of numerous compounds:
  - Approximately 500
- FDA Definition of a drug
  - Is intended for the use in the diagnosis, cure, mitigation, treatment, or prevention of disease
  - Is intended to affect the structure or any function of the body.
- Pharmaceutical and clinical research is done with precise doses of active compounds. The absence of well-established identification and dosages severely limited medical advances in cannabis

FDA website

What is Medical Cannabis

- Is it legal or illegal?
- Should it be legal?
- Is it safe?
- Is there an evidence basis for efficacy?
- If it's sold in a dispensary, should it therefore be considered "medical"?
- If it's "medical", can it be abused like recreational?
  - Is the goal to maximize THC?

Proposed Mechanisms of Action per Indication



Source: Izzo AA et al., 2009

Currently Available Cannabinoid Based Therapies with FDA-Approved Indication

- Dronabinol
  - DEA CII and CIII
  - Approved to treat
    - AIDS related anorexia
    - CINV
- CBD
  - DEA CV
  - Approved to treat
    - Dravet syndrome
    - Lennox-Gastaut syndrome (LGS)

Practical considerations in medical cannabis administration and dosing

Conclusive or substantial evidence of efficacy

- Adult chronic pain treatment
- Multiple sclerosis spasticity symptoms
- Chemotherapy-induced nausea and vomiting
- Treatment of intractable seizures in Dravet and Lennox-Gastaut syndromes (CBD

Moderate evidence of efficacy

- Improving outcomes in individuals with sleep disturbances associated with chronic pain
- Multiple sclerosis
- Fibromyalgia
- Obstructive sleep apnea syndrome
- Decreasing intraocular pressure in glaucoma

MacCallum C, et al. European Journal of Internal Medicine 49 (2018) 12–19

Practical considerations in medical cannabis administration and dosing

Limited evidence of efficacy

- Symptoms of dementia
- Symptoms of Parkinson disease
- Positive and negative symptoms of schizophrenia
- Symptoms of posttraumatic stress disorder
- Appetite and decreasing weight loss associated with HIV/AIDS

Limited evidence of efficacy cont.

- Multiple sclerosis spasticity (clinician-measured)
- Traumatic brain injury/intracranial hemorrhage associated disability, mortality, and other outcomes
- Symptoms of anxiety in social anxiety disorders(CBD)
- Symptoms of Tourette syndrome

MacCallum C, et al. European Journal of Internal Medicine 49 (2018) 12–19

Practical considerations in medical cannabis administration and dosing

Limited evidence of inefficacy

- Depressive symptoms in chronic pain or multiple sclerosis patients

Insufficient evidence of efficacy or inefficacy

- Addiction abstinence
- Symptoms of irritable bowel syndrome
- Cancers, including glioma
- Cancer-associated anorexia, cachexia syndrome and anorexia nervosa
- Symptoms of amyotrophic lateral sclerosis
- Chorea and some neuropsychiatric symptoms associated with Huntington disease
- Dystonia

MacCallum C, et al. European Journal of Internal Medicine 49 (2018) 12–19

Effect of cannabis use in people with chronic non-cancer pain prescribed opioids: findings from a 4-year prospective cohort study – Lancet Study published 7/2018

- This is one of the longest, in-depth, prospective studies of a community cohort of people with chronic non-cancer pain, examining the effects of cannabis use on pain and prescribed opioid use.

- Chronic non-cancer pain for a median of 10 years (IQR 4·5–20·0) and had been
- Prescribed a strong opioid for a median of 4 years (1·5–10·0).
- The median oral morphine equivalent taken was 75 mg/day (36–150).
- The most common types of pain reported at baseline were
  - Back or neck pain (1159 [77%] participants)
  - Arthritis (933 [62%] participants)
  - Comorbid pain was common, with participants reporting a median of two (IQR 2–3) chronic pain conditions at baseline in the preceding 12 months.
  - 937 (62%) participants reported neuropathic pain at baseline.

- The Results:
  - 1514 participants completed the baseline interview and were included in the study
  - 295 (24%) participants had used cannabis for pain.
  - Interest in using cannabis for pain increased from 364 (33%) participants (at baseline) to 723 (60%) participants (at 4 years)

VOLUME 2, ISSUE 7 , PE341-E350, JULY 01, 2018

Participants who used cannabis reported that the mean effectiveness of cannabis on pain was 7 out of a possible score of 10, in unadjusted cross-sectional and longitudinal analyses

However the clinical results showed:

- Greater pain severity score
- Greater pain interference score
- Lower pain self-efficacy scores
- Greater generalized anxiety disorder severity scores
- No evidence of a temporal relationship between cannabis use and pain severity or pain interference,
- No evidence that cannabis use reduced prescribed opioid use or increased rates of opioid discontinuation.

Interpretation

- Cannabis use was common in people with chronic non-cancer pain who had been prescribed opioids,
- Found no evidence that cannabis use improved patient outcomes.
- People who used cannabis had greater pain
- Lower self-efficacy in managing pain
- No evidence that cannabis use reduced pain severity or interference or exerted an opioid-sparing effect.

{ Negative effects of cannabis

Adverse Effects associated with Cannabis

All effects are at least additive with other CNS depressants

Most Common

- Drowsiness/ fatigue
- Dizziness
- Dry mouth
- Cough, phlegm, bronchitis (smoking only)
- Anxiety
- Nausea
- Cognitive effects

Common

- Euphoria
- Blurred vision
- Headache

Rare

- Orthostatic Hypotension
- Toxic psychosis/ paranoia
- Depression
- Ataxia/ dyscoordination
- Tachycardia (after titration)
- Cannabis hyperemesis
- Diarrhea

MacCallum C, et al. European Journal of Internal Medicine 49 (2018) 12–19

'Cannabis Psychoses'

- Marijuana-smoking patients with these symptoms frequently have a family history of psychiatric illness as well (depression, bipolar disorder, anxiety disorders, or schizophrenia)
- These anomalous effects of marijuana may go on to develop psychotic disorders from not stopping their marijuana use in time.
- Symptoms contrary to the usual effects of marijuana may signal that continued use of marijuana may possibly and seriously jeopardize their future mental health

Role of endocannabinoid system in schizophrenia

- Schizophrenics have heightened levels of anandamide(endogenous cannabinoid neurotransmitter) in their CSF than control
- Schizophrenics (that have never taken cannabis) have increased CB_1 receptors in their forebrain compared to matched controls.

Cannabinoid Hyperemesis Syndrome

- Characterized by a syndrome of cyclic vomiting, abdominal pain, and compulsive showering in some habitual users
- Symptoms improve with cessation utilization
- The prevalence of cannabinoid hyperemesis syndrome seen in EDs has doubled since the liberalization of marijuana laws in Colorado[1]
- Can masquerade as an eating disorder[2]

1. Kim HS, et al. Acad Emerg Med. 2015;22:694-699.
2. Brewerton TD, Anderson O. Int J Eat Disord. 2016

Withdrawal syndrome

- Has been identified, but it is mild and short-lived but depends on chronicity and dose
- The syndrome includes
  - restlessness
  - irritability
  - mild agitation
  - insomnia
  - sleep EEG disturbance
  - nausea
  - cramping.

Dependency/ Overdose

- Dependence potential of THC and cannabinoid drugs, the
  - IOM concluded that "Although few marijuana [cannabinoid botanicals] users develop dependence, some do.
  - Risk factors are similar to those for other forms of substance abuse.
- Risk of Dependency as well as overdose are part of FDA labels for approved cannabinoid products

Institute of Medicine (IOM), 1999

Pharmacology

{ Cannabis is not one drug, it's a mixture of drugs
–Primarily interested in CBD and THC

Routes of Administration

Smoking

- Most common route of administration
- Onset (min)
  - 5-10
- Duration (hr.)
  - 2-4
- Combustion at 600–900 °C producing toxic biproducts
  - Tar
  - CO
  - Ammonia
  - PAH (polycyclic aromatic hydrocarbons)

Vaporization

- Heats cannabis at 160–230 °C.
- Reduced CO, but not complete elimination of PAH
- Onset (min)
  - 5-10
- Duration (hr.)
  - 2-4

- Pros:
  - Rapid onset – acute episodic symptoms (nausea/pain)
- Cons:
  - Expense

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Routes of Administration

Oral

- Increasingly popular due to convenience and accuracy of dosing
- Edibles (brownies/cookies) may be more difficult to dose.
- Onset (min).
  - 60-180
  - Oromucosal: 15-45
- Duration (hr.)
  - 6-8
- Pros:
  - Advantage for chronic symptoms
- Cons:
  - Titration challenge due to delayed onset

Topical

- Onset (min)
  - Variable
- Duration (hr.)
  - Variable
- Pros:
  - Less systemic effect
  - Good for local symptoms
- Con:
  - Only local effect

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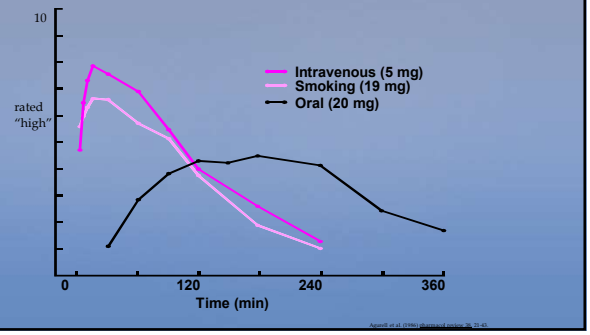
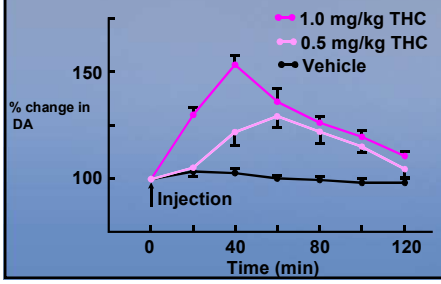
Pharmacokinetics



Effects of THC on Dopamine



- Cannabis Abuse/Dependence : assoc. w/ chronically lower dopamine levels and is a possible marker for Addiction

Entourage Effect Background

- Described by researcher Mechoulam and Ben-Shabat in the late 1990s
- A concept that believes in whole plant medicine that suggests:
  1. Combination of **cannabinoids** have the ability to improve efficacy and attenuate negative symptoms to improve safety profile
  2. Cannabinoids and **terpenes** used together can synergistically optimize therapeutic efficacy

Benefits of Combination Therapy

- CBD has demonstrated ability to antagonize undesirable effects of THC (i.e., intoxication, sedation, tachycardia) while contributing analgesic, anti-emetic, and anti-carcinogenic properties and has allowed use of higher THC doses
- Therapeutic potential reported for spasticity, central pain, lower urinary tract symptoms in multiple sclerosis, sleep disturbances, peripheral neuropathic pain, brachial plexus avulsion symptoms, rheumatoid arthritis, intractable cancer pain, etc.

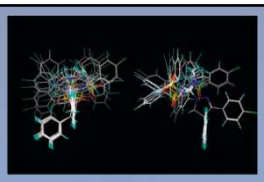
Russo et al., 2006

Cannabinoids and their Therapeutic Effects

More evidence based medicine is needed to support findings of Entourage Effect given that conflicting data has been observed in human trials

Next steps

- Entourage Effect lead Dr. Vandrey at Johns Hopkins University
- Focus future strategies on disease areas where individual and combination cannabinoids with terpenoids will be effective



{ Thank You

Questions??