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Psychiatry and Addictions Case Conference

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UPDATE ON MEDICINAL CANNABIS

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Integrated Care Training Program
UW Psychiatry & Behavioral Sciences

project ECHO

UPDATE ON MEDICINAL CANNABIS

- UW Psychiatry and Addictions Case Conference (PACC).
- Thursday May 03, 2018
- 12.00pm to 1.30pm

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DISCLOSURES

- The University of Washington School of Medicine also gratefully acknowledges receipt of educational grant support for this activity from the Washington State Legislature through the Safety-Net Hospital Assessment, working to expand access to psychiatric services throughout Washington State.

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SPEAKER DISCLOSURES

- The speaker has no disclosures or conflicts of interest

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LEARNING OBJECTIVES: *AT THE COMPLETION OF THIS LECTURE THE ATTENDEE SHOULD*

- 1. be able to identify the key components of the endocannabinoid system
- 2. characterize the key active components in cannabis
- 3. describe appropriate medical uses of cannabis and be able to distinguish that from recreational use

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"HEMP IS OF FIRST NECESSITY TO THE WEALTH & PROTECTION OF THE COUNTRY."- THOMAS JEFFERSON

- Many cannabis based medications were produced by Eli-Lilly, Parke Davis, and Sharp Dohme (now Merck Sharp Dohme).
- Tinctures; Pills; Liniments
- Widely prescribed by physicians 1890-1937

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CANNABIS FOR NEURALGIA 1925

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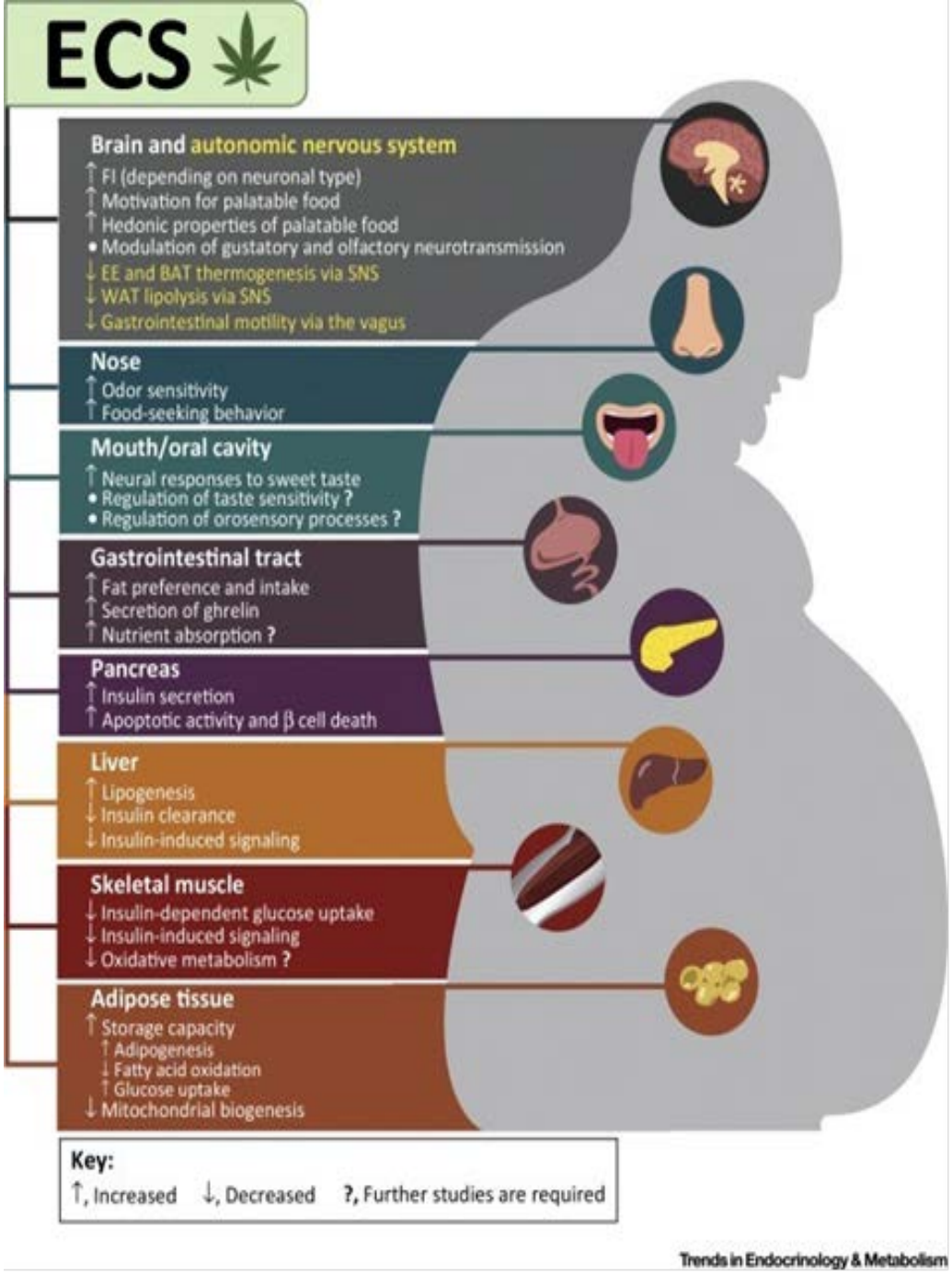
THE ENDOCANNABINOID SYSTEM

- is intricately involved in normal human physiology, specifically in the control of movement, pain, memory, mood, motor tone, and appetite, among others.
- Cannabinoid receptors are found in the brain and peripheral tissues.
- Dense receptor concentration in the cerebellum, basal ganglia, and hippocampus
- Few cannabinoid receptors in the respiratory areas in brainstem
- The cannabinoid receptors CB1 and CB2, two G protein-coupled receptors that are located in the central and peripheral nervous systems.

THE ENDOCANNABINOID SYSTEM

- endocannabinoids are both neuromodulators and immunomodulators
- Controls pain, appetite, mood, sleep,
- gut motility, muscle coordination, short term memory
- Inflammatory levels – cannabinoids suppress inflammation
- activation of cannabinoid receptors leads to activation of GTPases in macrophages, neutrophils, and B/T cells.
- CB2 receptors regulate migration of B cells and maintain healthy IgM levels.



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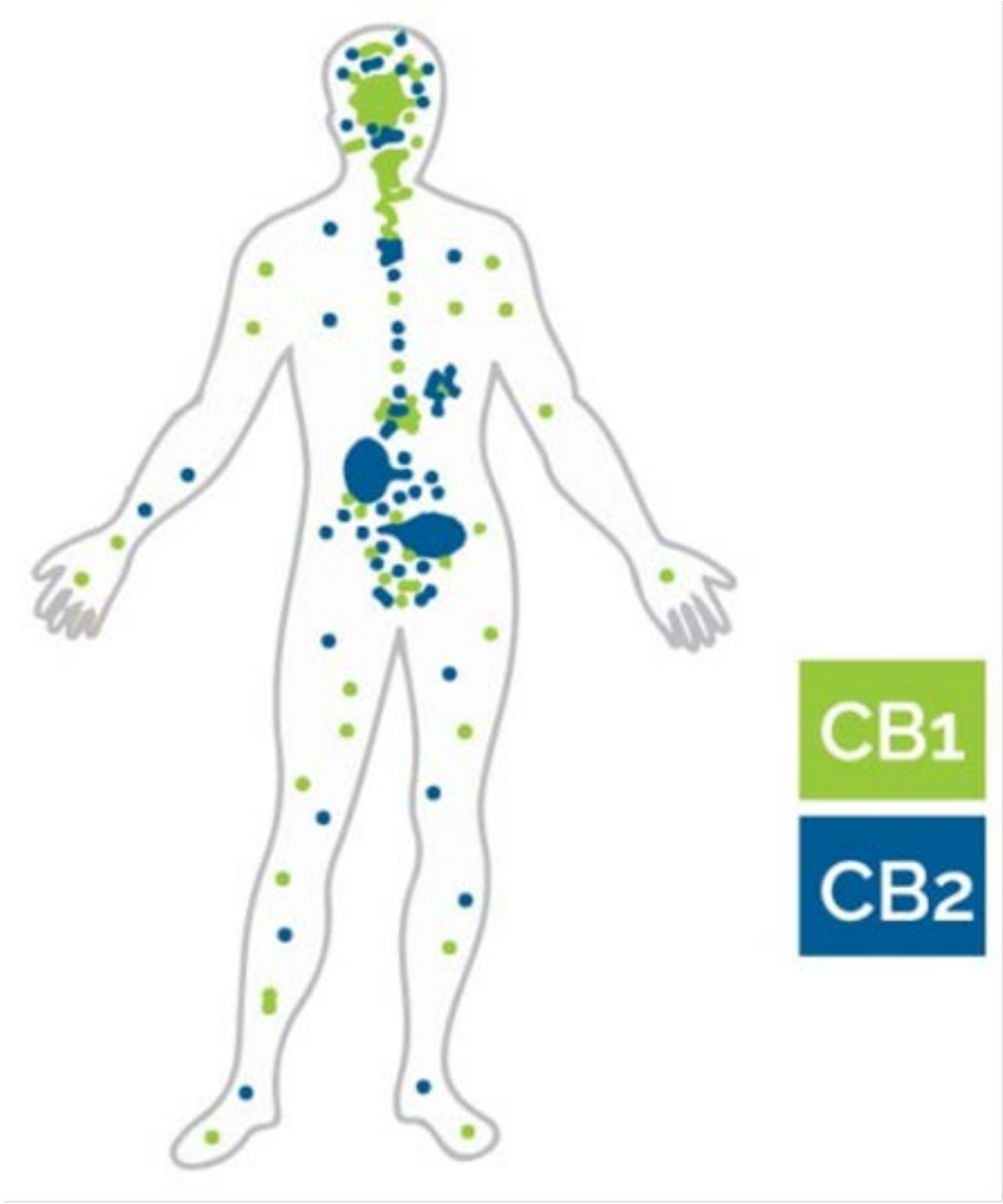

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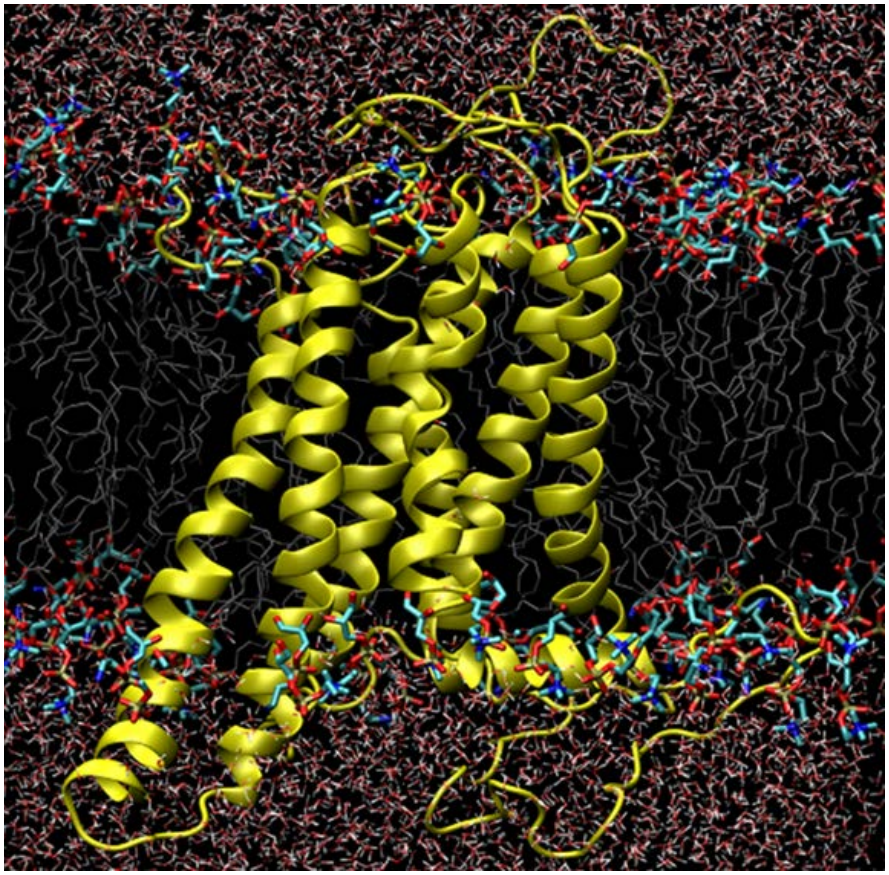
THE CB_1 RECEPTOR



The CB1 receptor consists of 7 transmembrane helices.

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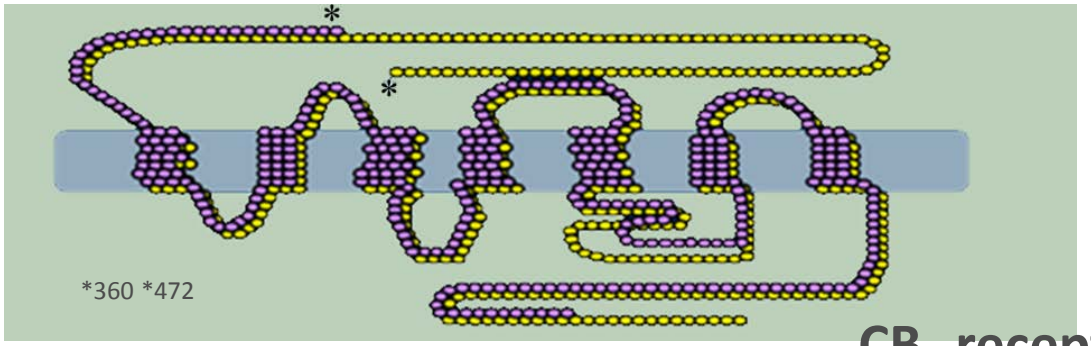
KEY ECS ELEMENTS

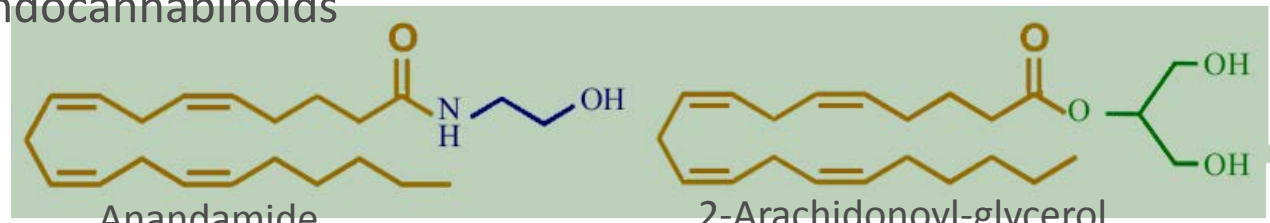
Cannabinoid receptors are G-protein-coupled receptors



CB_1 receptor

- Central nervous system
  - Hippocampus
  - Basal ganglia
  - Cortex
  - Cerebellum
  - Hypothalamus
  - Limbic structures
  - Brainstem
- GI tract (myenteric neurons and epithelial cells)
- Liver (hepatocytes)
- Adipose tissue
- Muscle
- Pancreas (α-cells)

Endocannabinoids



Anandamide

2-Arachidonoyl-glycerol

Endogenous, phospholipid-derived metabolites that bind to and activate cannabinoid receptors.

CB_2 receptor

- Immune cells and tissues
  - T cells, B cells
  - Macrophages
  - Dendritic cells
  - Spleen, tonsils
  - Adipose tissue

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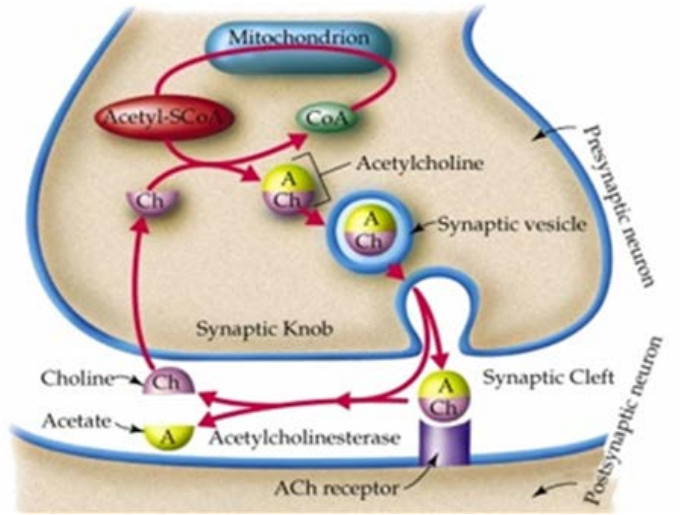
DIFFERENCE BETWEEN CLASSICAL & RETROGRADE NEUROTRANSMISSION

Classical neurotransmitter

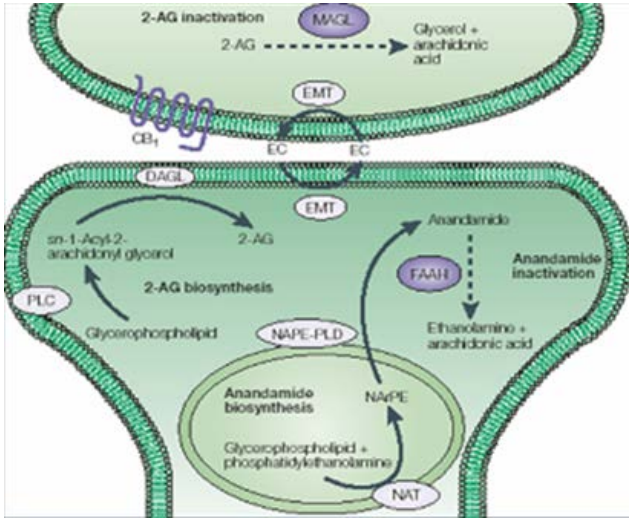
Presynaptic



Postsynaptic

Retrograde neurotransmitter

Presynaptic



Postsynaptic

PHYSIOLOGICAL EFFECTS OF ENDOCANNABINOIDS

- Endocannabinoids are often produced as an adaptive response to cellular stress, aimed at reestablishing cell homeostasis. “Runner’s high”
- Neuromodulation – putting the brakes on the system

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ENDOCANNABINOIDS AFFECT A LARGE NUMBER OF PHYSIOLOGICAL PROCESSES INCLUDING:

- Feeding behavior
- Energy balance, metabolism, GI function
- Pain perception
- Motor control and posture
- Learning, memory emotions
- Immune and inflammatory responses
- Cardiovascular function
- Reproduction
- Bone formation

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BOTANICAL CANNABIS

- 3 species of cannabis: sativa, indica, and ruderalis
- sativa grows 5-18 feet, few branches.
- indica grows 2-4 feet tall, compactly branched.
- > 700 strains of cannabis: Some are strains of 1 of the 3 subspecies. Many are crossbred hybrids.

NATURAL VS COMPOUNDED

- Natural cannabis contains over 100 cannabinoids, most of the non-psychoactive yet therapeutic
- NATURAL CANNABIS IS 15% THC AT BEST – recreational uses like/want THC
- CANNABIS GROWN ON FEDERAL FARMS IN MISSISSIPPI FOR DRUG TRIALS IS 3% THC
- Delta-9-tetrahydrocannabinol (THC): in PURE FORM is a schedule 3 drug (MARINOL)
- –NATURAL CANNABIS, at 3 - 15% THC is schedule I, dangerous, no medical use –

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CANNABINOIDS

- ***Cannabidiol (CBD): analgesia; moderates effects of THC – important in pain management***
- Cannabinol (CBN): anticonvulsant
- Tetrahydrocannabivarin (THCV): anti-inflammatory
- Cannabichromene (CBC): mixed effects
- Cannabicyclol (CBL)
- Plus 80-100 other cannabinoids –
- THESE CANNABINOIDS ARE NOT INTOXICATING
- new strain in Israel with no THC but potential medical use

3 TYPES OF THC:CBD RATIOS IN A CANNABIS PLANT:

- Type 1: High THC, Low or No CBD*
- Type 2: Equal amounts of THC and CBD**
- Type 3: Low THC, High CBD/CBN**

- **generally preferred for recreational use*
- ***generally preferred for medical use*

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CANNABIS INDICA

- Indicas are short dense plants, darker green. After flowering starts they will be mature in 6 to 8 weeks. The buds will be thick and dense, both narrow and wide leaf
- Narrow leaf are Type 1 cannabinoid producers: high amount of THC and little to no CBD.
- Wide leaf are Type 2 and Type 3 cannabinoid producers: produce high amounts of CBD or equal amounts to the THC produced.

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CANNABIS SATIVA

- Sativa are tall, thin plants, light green in color. Grow quickly and reach heights of 20 feet in a single season. Once flowering has begun, they can take anywhere from 10 to 16 weeks to fully mature.
- Hemp is a subspecies of Sativa plants
- Sativa plants also have a typically overall lower cannabinoid content that Indica plants.

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INDICA VS SATIVA

- Moderate to high-CBD producing plants can be found among both the Indica and Sativa species
- Overall, there is greater amount of genetic variety in Sativa species – may require a greater degree of crossbreeding to produce plants with higher CBD
- Most cannabis plants today are from hybrids - crosses of Sativa and Indica varieties, selected for various desired characteristics of growth, appearance and effect. The genetics and hence the effects of one lineage will usually be dominant

JIKOMES N, ZOOROB M. THE CANNABINOID CONTENT OF LEGAL CANNABIS IN WASHINGTON STATE VARIES SYSTEMATICALLY ACROSS TESTING FACILITIES AND POPULAR CONSUMER PRODUCTS. SCI REP. 2018 14;8(1)

- Analysis of publicly available seed-to-sale traceability dataset from Washington state containing measurements of the cannabinoid content of legal cannabis products from state-certified laboratories.
- commercial Cannabis strains fall into three broad chemotypes defined by the THC:CBD ratio.
- systematic differences in the cannabinoid content reported by different laboratories noted
- relative stability in cannabinoid levels of commercial flower and concentrates over time (intralab)
- However interlab differences in cannabinoid reporting noted
- need for standardized laboratory methodologies in the legal cannabis industry

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CLINICAL PHARMACOLOGY OF CANNABIS & CANNABINOIDS

- *95-99% plasma protein bound -hydroxylation, oxidation, and conjugation for rapidly clearance from plasma*
- *First-pass metabolism (after PO admin) to 11-OH-THC*
- *Elimination is slow: days to weeks 20-35% found in urine; 65-80% found in feces; stored in adipose;*
- *Pregnancy Category C: in breast milk*

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CLINICAL PEARL – KNOW THIS

- SAFE, NO OVERDOSE, WELL TOLERATED –
- NO CONSTIPATION or RESPIRATORY SUPPRESSION
- RELIEVES PAIN, IMPROVES SLEEP
- IMPROVES APPETITE
- DECREASES NEED FOR OPIOIDS
- WORKS SYNERGISTICALLY WITH OPIOIDS
- Higher CBD/lower THC strains best

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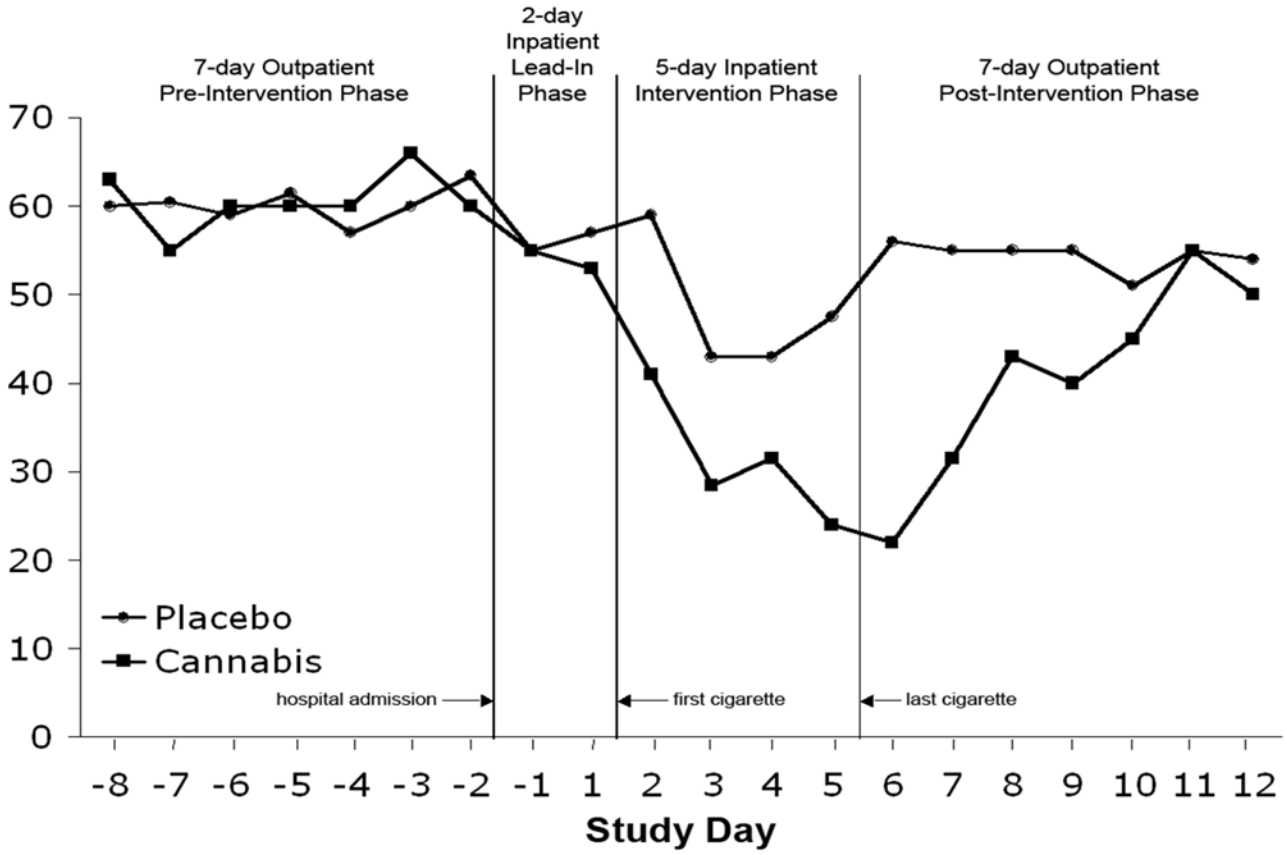
HISTORY OF HUMAN RESEARCH

- Studies have tended to be small, imperfectly controlled, using smoked cannabis-limited by regulations
- Feds require using Mississippi cannabis of poor composition and irregular bioavailability. Delivered as “joints”
- evaluation of medicinal cannabis in humans is still evolving – don’t have pharma funding though
- the discovery of the endocannabinoid system has stirred research

ABRAMS DI, ROWBOTHAM MC, PETERSEN KL, ET AL. CANNABIS IN PAINFUL HIV-ASSOCIATED SENSORY NEUROPATHY: A RANDOMIZED PLACEBO-CONTROLLED TRIAL.

NEUROLOGY 2007; 68(7):515-21.



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BRADFORD AC, BRADFORD WD. MEDICAL MARIJUANA LAWS REDUCE PRESCRIPTION MEDICATION USE IN MEDICARE PART D. HEALTH AFF (MILLWOOD). 2016 1;35(7):1230-6.

- Data from all prescriptions filled by Medicare Part D enrollees from 2010 to 2013 showed use of prescription drugs for which marijuana could serve as a clinical alternative fell significantly, once a medical marijuana law was implemented.
- overall reductions in Medicare spending when states implemented medical marijuana laws were estimated to be $165.2 million per year in 2013.

BRADFORD AC, BRADFORD WD, ABRAHAM A, ADAMS GB. ASSOCIATION BETWEEN US STATE MEDICAL CANNABIS LAWS AND OPIOID PRESCRIBING IN THE MEDICARE PART D POPULATION. JAMA INTERN MED. PUBLISHED ONLINE APRIL 2, 2018.

- Longitudinal analysis of the daily doses of opioids filled
- Hydrocodone use decreased by 2.320 million daily doses
- Morphine use decreased by 0.361 million daily doses
- CONCLUSIONS AND RELEVANCE Medical cannabis laws are associated with significant reductions in opioid prescribing in the Medicare Part D population. This finding was particularly strong in states that permit dispensaries, and for reductions in hydrocodone and morphine prescriptions.

COHEN NL, HEINZ AJ, ILGEN M, BONN-MILLER MO. PAIN, CANNABIS SPECIES, AND CANNABIS USE DISORDERS. J STUD ALCOHOL DRUGS. 2016 77(3):515-20.

- 163 medical cannabis users completed assessments of medical cannabis use motives, history, preferences (species type), and problems, as well as current pain level.
- Individuals who used cannabis to manage chronic pain experienced fewer cannabis use problems than those who did not use it for pain; among those who used it for pain, the average pain level in the past week was not associated with cannabis use problems.
- individuals who used cannabis for chronic pain were more likely to use indica over sativa. Preference for indica was associated with fewer cannabis use problems than preference for hybrid species.

LYNCH ME, CAMPBELL F. CANNABINOIDS FOR TREATMENT OF CHRONIC NON-CANCER PAIN; A SYSTEMATIC REVIEW OF RANDOMIZED TRIALS. BR J CLIN PHARMACOL 2011 2(5):735-44 PMID: 21426373

- systematic review of RCTs for cannabis treating chronic non-cancer pain: neuropathic pain, fibromyalgia, rheumatoid arthritis, and mixed chronic pain.
- quality of trials = excellent;
- 15 of the 18 trials showed significant analgesic effect of cannabis
- No serious adverse effects; only a few withdrawals from the studies
- Overall evidence indicates that cannabinoids are safe and effective

LYNCH ME, WARE MA. CANNABINOIDS FOR THE TREATMENT OF CHRONIC NON-CANCER PAIN: AN UPDATED SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS. J NEUROIMMUNE PHARMACOL. 2015; 10(2):293-301.

- Eleven new trials
- Quality of trials excellent.
- Seven trials showed significant analgesic effect.
- Several trials also showed improvement in sleep, muscle stiffness and spasticity
- Adverse effects most frequently reported such as fatigue and dizziness were mild to moderate in severity and generally well tolerated.
- This review adds further support that currently available cannabinoids are safe, moderately effective analgesics that provide a reasonable therapeutic option in the management of chronic non-cancer pain.

HILL KP. MEDICAL MARIJUANA FOR TREATMENT OF CHRONIC PAIN AND OTHER MEDICAL AND PSYCHIATRIC PROBLEMS: A CLINICAL REVIEW. JAMA 2015; 23-30;313(24):2474-83.

- Use of marijuana for chronic pain, neuropathic pain, and spasticity due to multiple sclerosis is supported by high-quality evidence.
- Six trials that included 325 patients examined chronic pain
- 6 trials that included 396 patients investigated neuropathic pain
- 12 trials that included 1600 patients focused on multiple sclerosis
- “Several of these trials had positive results, suggesting that marijuana or cannabinoids may be efficacious for these indications”

WHITING PF, WOLFF RF, DESHPANDE S, DI NISIO M, DUFFY S, HERNANDEZ AV, ET AL. CANNABINOIDS FOR MEDICAL USE: A SYSTEMATIC REVIEW AND META-ANALYSIS. JAMA 2015; 23-30;313(24):2456-73.

- 79 trials (6462 participants) were included
- Most trials showed improvement in symptoms associated with cannabinoids nausea and vomiting
- reduction in pain
- reduction in spasticity
- Common AEs included dizziness, dry mouth, nausea, fatigue, somnolence, euphoria, vomiting, disorientation, drowsiness, confusion, loss of balance, and hallucination.

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MOHITE PN, ZERIOUH M, SÁEZ DG, POPOV AF, SABASHNIKOV A, ZYCH B ET AL. INFLUENCE OF HISTORY OF CANNABIS SMOKING IN SELECTED DONORS ON THE OUTCOMES OF LUNG TRANSPLANTATION. EUR J CARDIOTHORAC SURG. 2017;51(1):142-147.

- METHODS: We retrospectively analysed lung 'organ offers' and LTx at our centre between January 2007 and November 2013.
- RESULTS: A total of 302 LTxs were performed during this period and were grouped depending on the history of cannabis smoking in donors-'cannabis' (n = 19) and control group (n = 283). All the donors in 'cannabis' group were tobacco smokers compared with 43% in the control group. Preoperative characteristics in recipients in both groups were comparable. Intraoperative and post-LTx variables including 1- and 3-year survivals were comparable in both groups.
- CONCLUSIONS: The history of donor cannabis smoking does not appear to affect early and mid-term outcomes after LTx and potentially improve the donor pool. As it does not seem to negatively affect the outcomes after LTx, it should not be per se considered a contraindication for lung donation.

SO HOW DOES THIS ALL WORK IN REAL LIFE CLINICAL MEDICINE?

- Methods of Use
- Dosing paradigms
- Patient instructions
- What clinicians should know

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USE IN CLINICAL SETTING

- ***DO NOT SMOKE*** – USE VAPORIZER FOR FAST EFFECT; INGESTION FOR LONGER EFFECT; TOPICAL FOR LOCAL EFFECT
- USE LOW DOSES OF CANNABIS THAT HAS HIGH CBD/CBN AND LOW THC
- DO NOT NEED TO BE HIGH TO GET PAIN RELIEF

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VAPORIZATION OF CANNABIS – SAFE ALTERNATIVE TO SMOKING

- examples

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HOW DO VAPORIZERS WORK?

- When cannabinoids are heated to between 285 °F (140 °C) and 392 °F (200 °C) they literally boil and vaporize.
- Studies show that vaporization is most effective at around 338 °F (170 °C)
- A vaporization temperature over 392 °F (200 °C) will burn the cannabis, creating unwanted smoke.

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DOSING

- START LOW; GO SLOW
- 2-3 inhalations, stop, wait ten minutes
- Do not need to be high to get pain relief
- Ingestion takes about an hour to get effects so harder to dose but lasts longer
- Transdermal works well as a linament
- No current injectable forms

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SIDE EFFECTS

- Disinhibition, relaxation, drowsiness
- Feeling of well being, exhiliration, euphoria
- Sensory - perceptual changes
- Recent memory impairment
- Balance/stability impaired
- Decreased muscle strength, small tremor
- Poor on complex motor tasks (e.g., driving)

SIDE EFFECTS

- can get impaired judgement
- Slowed reaction time
- Motor impairment
- disorganized thoughts, confusion
- May get paranoia, agitation

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ADVISING THE PATIENT

- Adverse effects: mainly seen in new users
- Start low, go slow and easy
- These are reversible, short lived effects (3-4 hours max)
- Serious adverse effects NOT seen in chronic users

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CLINICAL PEARLS

- FOR CHRONIC PAIN? ***Screen patient*** – do the risk screening tools –
- if the patient is legit, try the standard non-opioid drugs first
- If the standard first line meds do not work then consider cannabis
- ***Starting patient on opioids may pose considerably higher risk for dependency and dose escalation and morbidity/mortality***

WHY CANNABIS?

- It works, Not many drug-drug interactions
- Side effects mild; low toxicity, NO LD50
- Cannabis has other potential benefits: reduce inflammation, neuroprotective, anti-tumor properties
- You still need to monitor the patient!
- They may still ask you for opioids…but not all will, and you have leverage

IS CANNABIS FOR EVERYONE? NO!

- some people cannot tolerate it or it does not work for them
- There is a risk for psychological addiction
- Minimal physical dependence (withdrawal is mainly irritability, depression)
- Tolerance may develop in heavy, long term users - may need higher doses
- Patient/family will have to purchase it

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CLINICAL PEARL IF YOU CHOOSE TO RECOMMEND *MEDICINAL CANNABIS…*

- FOLLOW THE LAW – and be aware that things may change under a Trump/Sessions administration
- Properly counsel the patient and family
- Patient should use high quality cannabis to improve efficacy: high CBD, CBN, lower THC – do not need to be high to get pain relief and use a delivery route that maximizes benefits and minimizes side effects

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CME EDUCATION ON-LINE

- http://adai.uw.edu/mcacp/
- Medicinal cannabis and chronic pain project
- UW ADAI – PI: Beatriz Carlini, Ph.D., M.P.H.; Research Scientist, Alcohol & Drug Abuse Institute, UW
- Co-investigators
- Gregory Carter, M.D.
- Roger Roffman, Ph.D.
- Reinaldo Naoto Takahashi, Ph.D.
-

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THANK YOU

- Any questions
- E-mail: gtcarter@uw.edu

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