Medical Cannabis
Cannabidiol and Hemp Oils

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Many Medications originate in plants

- Digitalis purpurea – fox glove – CHF etc
- Papaver somniferum – opium poppy
- Atropa belladonna – nightshade –IBS etc
- Ephedra sinica – ephedrine - hypotension
- Salix alba – willow tree - ASA
- Taxis brevifolia – Pacific Yew tree – breast cancer

Marijuana vs Hemp

- Two strains of the same plant:
  - Cannabis Sativa
- Marijuana cultivated for years for THC content
- Hemp cultivated for many other uses:
  - Paper
  - Clothing
  - Food

History

- 6000 BC – Cannabis seeds used as food in China
- 4000 BC – Textiles made of hemp in China
- 2727 BC – first recorded medicinal use in Chinese Pharmacopoeia
- 1400 BC to AD – trade moves product through India, Mediterranean countries, Europe – numerous medicinal uses reported

History

- 1378 – Emir of the Ottoman Empire makes the first edict against eating hashish or smoking cannabis – 1st "War on Drugs"
- 1798 – Napoleon declared total prohibition on marijuana after realizing much of the Egyptian lower class were habitual smokers
- 1868 – Egypt – 1st modern country to outlaw cannabis ingestion
- 1890 – Hashish made illegal in Turkey

History

- Introduced to North America in 1600s by Puritans – Hemp for ropes, sails, clothing; cannabis a common ingredient in medicines, sold openly in pharmacies
- 1937 – Marijuana Tax Act – transfer of cannabis illegal throughout US except for medicinal and industrial use, expensive excise tax and detailed logs required
- 1969 – found to be unconstitutional since it violated 5th Amendment privilege against self-recrimination

History

- 1970 – Controlled Substance Act – classified cannabis as having:
  - High abuse potential
  - No medical use
  - Not safe to use under medical supervision
- 1975 – FDA establishes Compassionate Use Program for Medical Marijuana – Glaucoma, Multiple Sclerosis, Cancer
- 1986 – Dronabinol placed into Schedule II by DEA
- 1996 – CA first state to legalize
- 2003 – Canada – 1st country in world to offer medical marijuana to patients

Medical Cannabis

Two classifications of cannabis:

1) Recreational

2) Medical

Rapid evolution of laws and availability in recent years

Patients may ask to be “certified” for medical cannabis

What is the current state of knowledge?

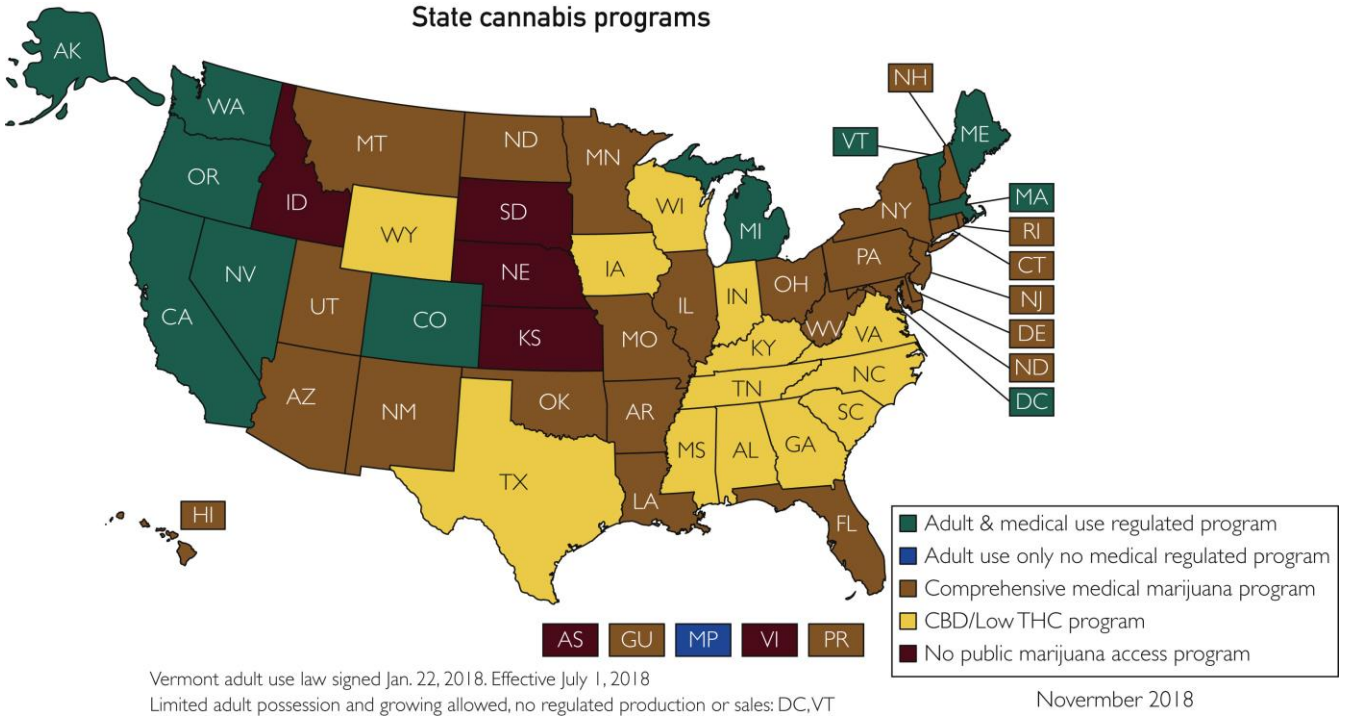
Medical Cannabis

- Group of pharmacological agents
- Subspecies of flowering plant Genus Cannabis
- Intention of use: alleviating symptom or condition
- Inhaled, buccal, swallowed, or topical applications
- Public opinion and policies changing (despite limited evidence)

Legal Status

- US Comprehensive Drug Abuse Prevention and Control Act of 1970:
  - Schedule 1
- US states became 1st governmental bodies in world to legalize
- Now ~30 states and DC have medical cannabis programs
- States restrict indications for specific conditions

Figure 3



Terms and Conditions

Legal Status and Clinicians

- Medical Cannabis remains illegal federally
- Clinicians cannot prescribe
- Pharmacies cannot dispense
- Clinicians thus only certify a patient has a specified condition
  - Limit liability to clinician,
  - Certify qualifying medical condition under state law
- Product supplied by: State Certified Dispensaries

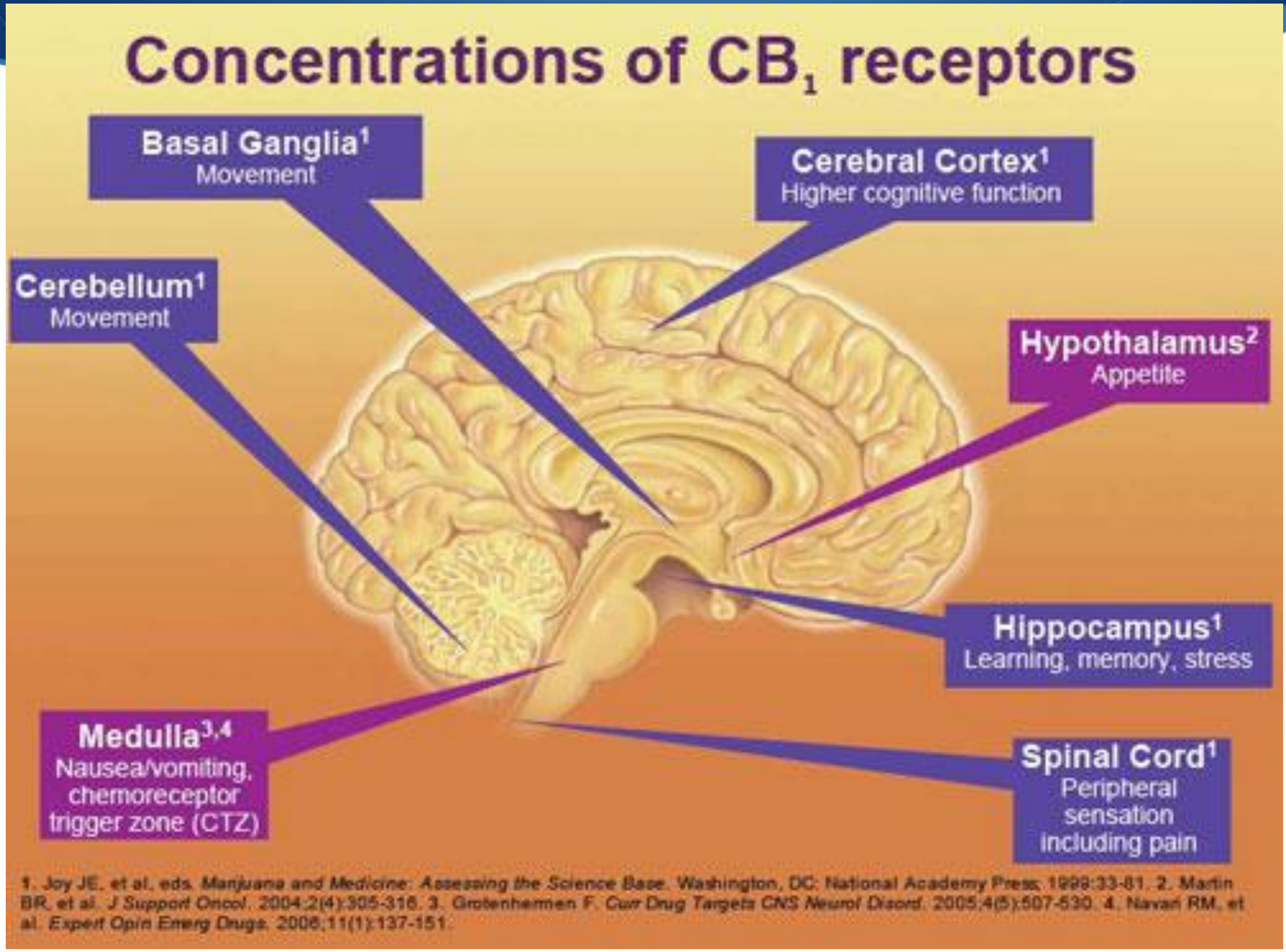
Dispensaries

- Predominantly for profit
- No “good manufacturing” practices exist
- Product and routes of ingestion vary by state
- Must pay a fee to participate in program and enter dispensary
- Not covered by insurance

Endocannabinoid System

- Receptors, signaling molecules and enzymes
- Type 1 Cannabinoid Receptor: CB1 (throughout CNS)
  - Hippocampus
  - Cortex
  - Olfactory areas
  - Basal ganglia
  - Cerebellum
  - Spinal cord
- Type 2 Cannabinoid Receptor: CB2 (immune system)

Concentrations of CB_1 receptors



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Endocannabinoid signaling molecules

- *N*-arachidonoylethanolamine (AEA or anandamide)
- 2-arachidonoylglycerol
- Both are agonists at CB1 and CB2
- Important in regulatory, homeostatic, inflammation

Phytocannabinoids

- Naturally occurring molecules
- Affinity for mammalian cannabinoid receptors
- Over 100 isolated from cannabis
- Strain and horticultural techniques yield a great variety
- THC, CBD, terpenoids such as beta-caryophylline and limonene

Delta 9-tetrahydrocannabidiol (THC)

- Primary psychoactive constituent
- Agonist at CB1 and CB2
- Activates presynaptic CB1 receptors
  - Impaired learning, memory, spatial recognition, attention
  - Tachycardia, orthostasis, xerostomia, xerophthalmia
  - NO respiratory effects (no receptors in medulla)
  - Analgesic and anti-inflammatory

Cannabidiol (CBD)

- Lacks THC intoxicating properties
- Weak affinity at CB1 and CB2
- Few pharmacologic targets identified
  - Inhibition of endocannabinoid reuptake
  - G-Protein Receptor activation
  - Increasing 5-HT1A receptor activity
- Anticonvulsant, anxiolytic, anti-inflammatory, neuroprotective
- May modulate THC psychosis effects

CBD / Hemp Oils

CBD Oils

- 1970 Controlled substances act outlawed Hemp and MJN
- 2014 Agricultural Act
  - Distinguished Hemp from MJN
  - Hemp: Cannabis Sativa L. plant or any part of plant
    - Less than 0.3% delta-9-THC on dry weight basis
  - Allowed industrial hemp for "research purposes"
  - CBD oils do not require clinician certification because of low THC content
- Most states allow CBD oils except Idaho, S Dakota and Nebraska
- Legal or not? Confusion between government agencies:
  - Department of agriculture: ok
  - DEA: ok or maybe not
  - FDA: not ok especially if ANY health claims made; cannot be used in ANY health or food product
- Federal government and DEA still consider CBD and Hemp oils considered Schedule I although Epidiolex allowed to be Schedule IV

CBD / Hemp Oils

- Varied legislation and tremendous increase in products
  - Unclear what is in different types of CBD and hemp oils
- Flowers and leaves: phytocannabinoids
- Seeds: Omega 3's & 6's, ALA
- Cannabis Oils or MJN Oils: high THC content
- "Full Spectrum" formulations
  - May contain CBD + terpenoids
  - May also contain added ashwagandha and other products and may have limited CBD

CBD / Hemp Oils

- Yet a paucity of research (most on CB1 and THC)
- Main good research = Epidiolex (2.5-5mg/kg bid CBD dosing)
- Touted for mood, anxiety, pain, migraines and inflammatory conditions via pre-clinical trials.
- Chronic pain and addiction
- Safety and adverse effects
  - CBD doses up to 300mg/day up to 6mos w/o adverse effects
  - Somnolence, decreased appetite, diarrhea (when as AED)
  - Elevated LFT's
- At this time it is not recommended for any psychiatric disorder
- Keep in mind drug interactions: CYT P450 3A system

CBD / Hemp Oils

- Finding quality product:
  - Consider product from Europe re: more rigorous
  - Use organic product verified by third party labs
  - Full spectrum vs “pure” CBD oil
  - Care with the many legal issues

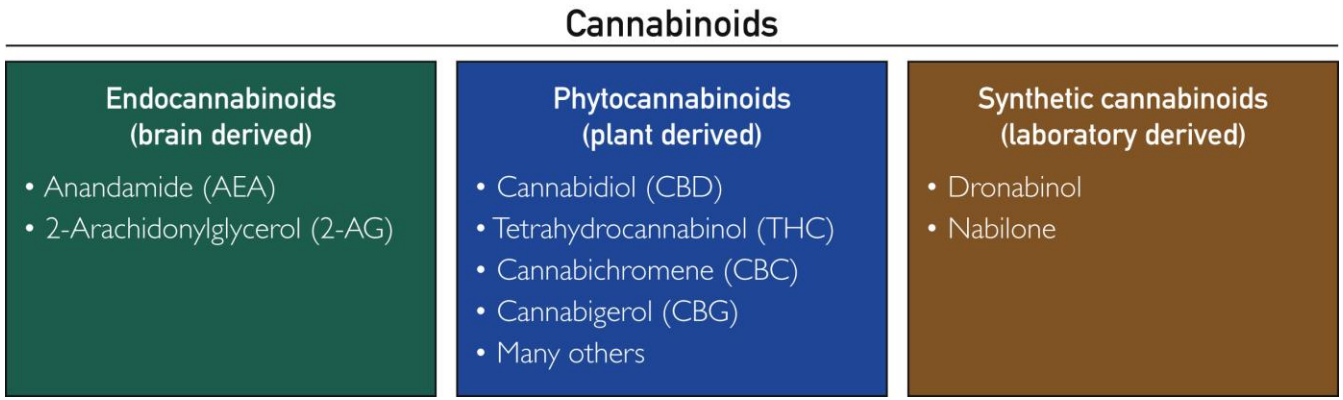
Minor Phytocannabinoids

- Cannabigerol: antibacterial activity
- Cannabinol: sedative
- Tetrahydrocannabivarin: antiepileptic

Synthetics

- Dronabinol: biochemically identical THC
  - (1986 DEA: Schedule II)
  - Nausea, vomiting, appetite, pain, spasticity
- Nabilone: THC analog
- Illegally synthesized agonists with unpredictable pharmacologic properties:
  - “Incense” “Spice” “Crazy Clown” “Black Mamba”

Figure 2



Terms and Conditions

Efficacy

- The National Academies of Sciences, Engineering, and Medicine (NASEM): comprehensive literature review:
  - Treatment of chronic pain in adults
  - Antiemetic in treatment of chemo induced n/v
  - Improving muscle spasticity in MS

Chronic pain

- Use may be associated with increased nonmedical opiate use
- States with medical cannabis: lower opiate OD rates
- Smoked flower
- Little known about efficacy, routes, doses
- Blended THC –CBD seem better than CBD alone

Nausea, Vomiting and Muscle Spasms

- 3 decades of dronabinol and nabilone
- No good evidence for CBD exclusive for this
- Muscle spasticity in MS (but not in spinal cord injury)
  - Two Systematic reviews
  - Modest efficacy
  - Cannabis extract, Nabiximols (1:1 THC-CBD, oral THC

Seizures

- Began with anecdotal reports
- June 25, 2018 FDA approved CBD Oil
  - Lennox-Gastaut syndrome
  - Dravet Syndrome

Keep in mind…

- Trials evaluated:
  - Smoked or vaporized plant flower
  - Plant derived oral THC
  - THC-CBD combos
  - Synthetic THC
- Limited clinical evidence for other conditions
- Many of state approved medical conditions not supported by high level evidence of efficacy

Health Risks

- Smoking = respiratory disease
- MVA's
- Lower birth weight offspring
- Schizophrenia and other psychoses
- Abuse Liability

Counseling Patients

- Invite patients into discussion when patients inquire or when progress is difficult to achieve
- Disclose gaps in knowledge and where good evidence of efficacy along with risks
- Caution in using in patients under 25 years old
- We cannot prescribe and discuss logistics of obtaining Medical Cannabis vs CBD)
- Discuss D/C or when experiencing adverse effects
- Importance of other therapies
- Discuss how to monitor progress with cannabis use
- Tapering off other agents (such as opiates)