Into the Weeds: Clinical Updates in Medical Cannabis

Francine Arneson, MD, FAAHPM
Palliative Care Medical Director

Disclosures

- I am a consultant for Medtronic
- Clinical recommendations are evidence based and free of commercial bias

Objectives

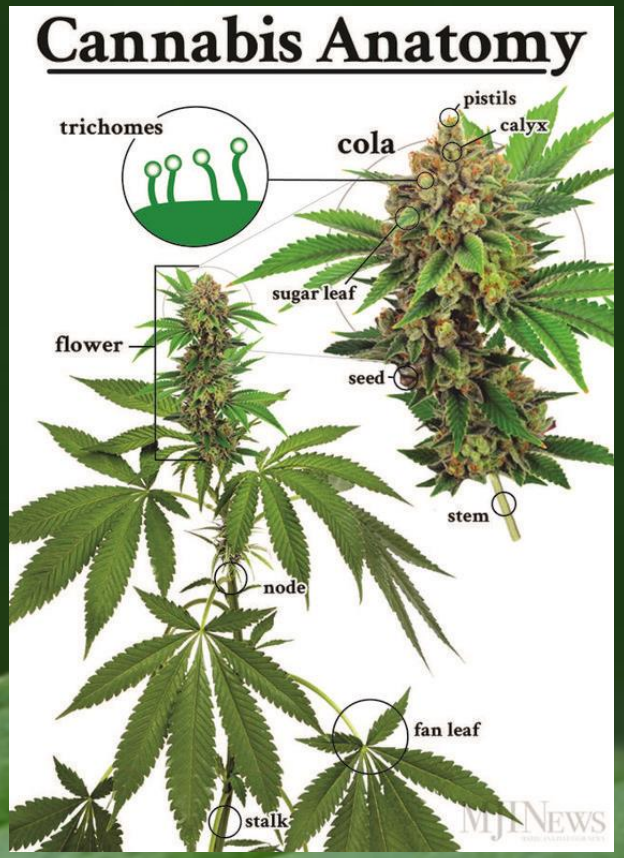
- Gain a better understanding of the endocannabinoid system
- Understand symptoms that may be treated with cannabis

History of Cannabis

- Dates back to at least the third millennium BC
- Valued for its use for:
  - Fiber and rope
  - Food and medicine
  - Psychoactive properties for religious and recreational use

Cannabis

- A type of flowering plant in the *Cannabaceae* family, generic term for plants belonging to genus *Cannabis*
- Derived from the plant *Cannabis sativa, Cannabis indica, and Cannabis ruderalis*
- Hardy plant, can be grown indoors or out
- Psychoactive components
- Hemp versus marijuana
- Cannabinoids and terpenes are the main active compounds in the plant



MARIJUANA VERSUS HEMP

Marijuana	Hemp
Characteristics: - Cannabis plant with > 0.3% THC (usually 5-35%) - Schedule I restricted substance - Psychoactive	Characteristics: - Cannabis plant with 0.3% or less THC - Completely legal - Non-psychoactive
Uses: - Recreational ▪ Psychoactive/euphoria ▪ Mellow - Disease modification ▪ Crohn's Disease ▪ Glaucoma ▪ Epilepsy ▪ Tourette's Syndrome ▪ Anti-cancer properties ▪ PTSD - Symptom management ▪ Pain ▪ Nausea ▪ Spasticity ▪ Muscle spasm ▪ Appetite ▪ Anxiety ▪ Bronchodilation ▪ Anti-inflammatory	Uses: - Textiles - Nutritional supplements - Paper - Rope - Insulation - Biofuels and bioplastics - Clothing and shoes

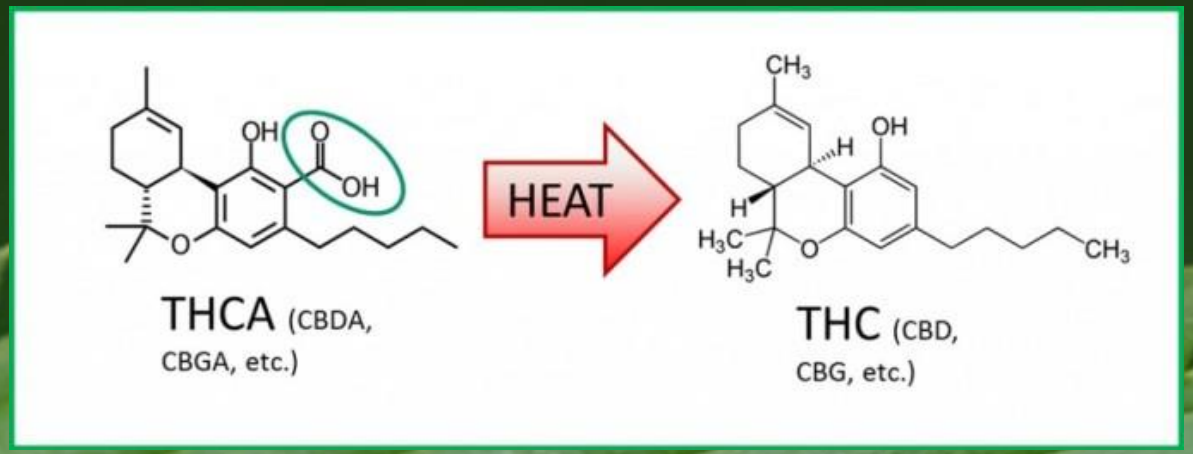
Phytocannabinoids

- Cannabinoids that occur naturally in the cannabis plant

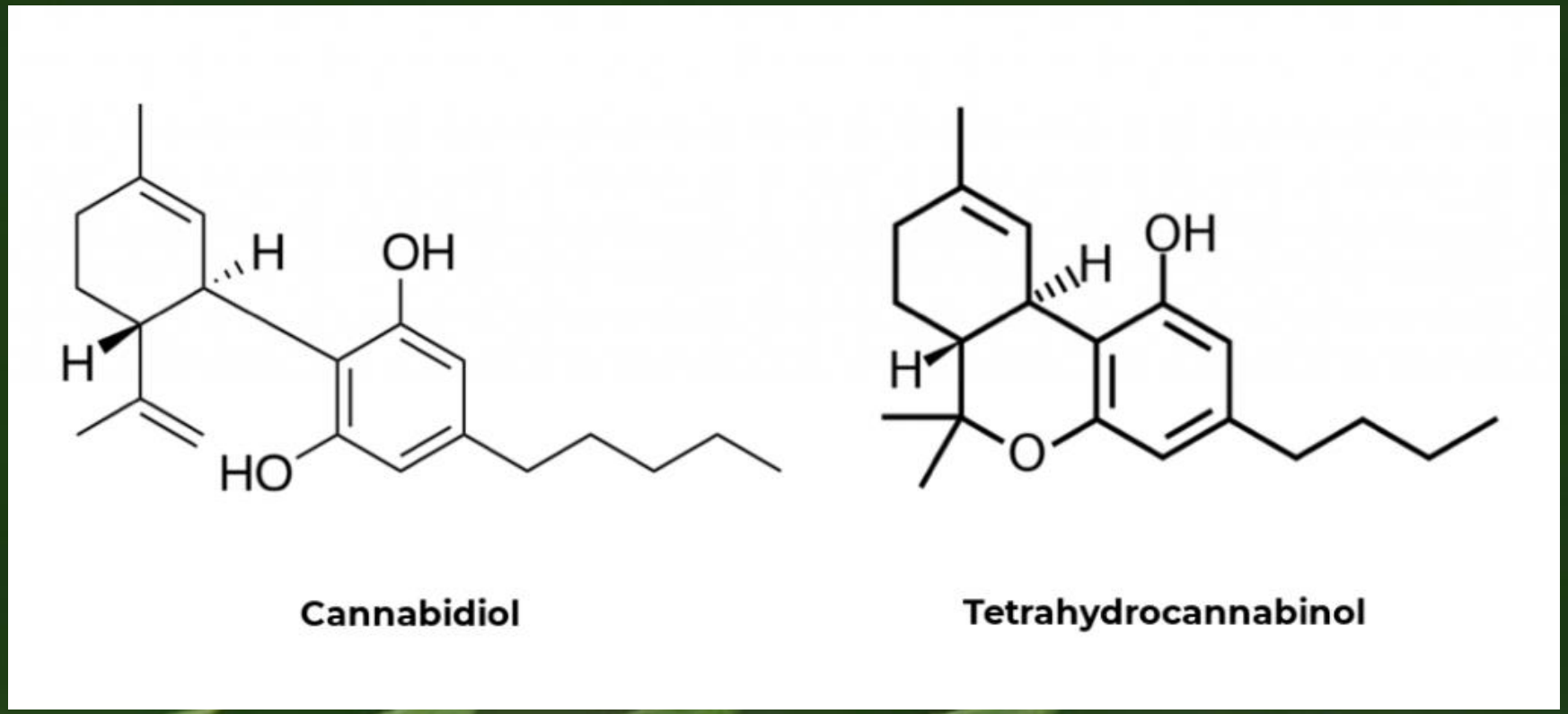
Phytocannabinoids

- 8 major cannabinoid acids produced by cannabis
- Each cannabinoid acid can be decarboxylated (usually by heat) to yield the compounds of the corresponding cannabinoid

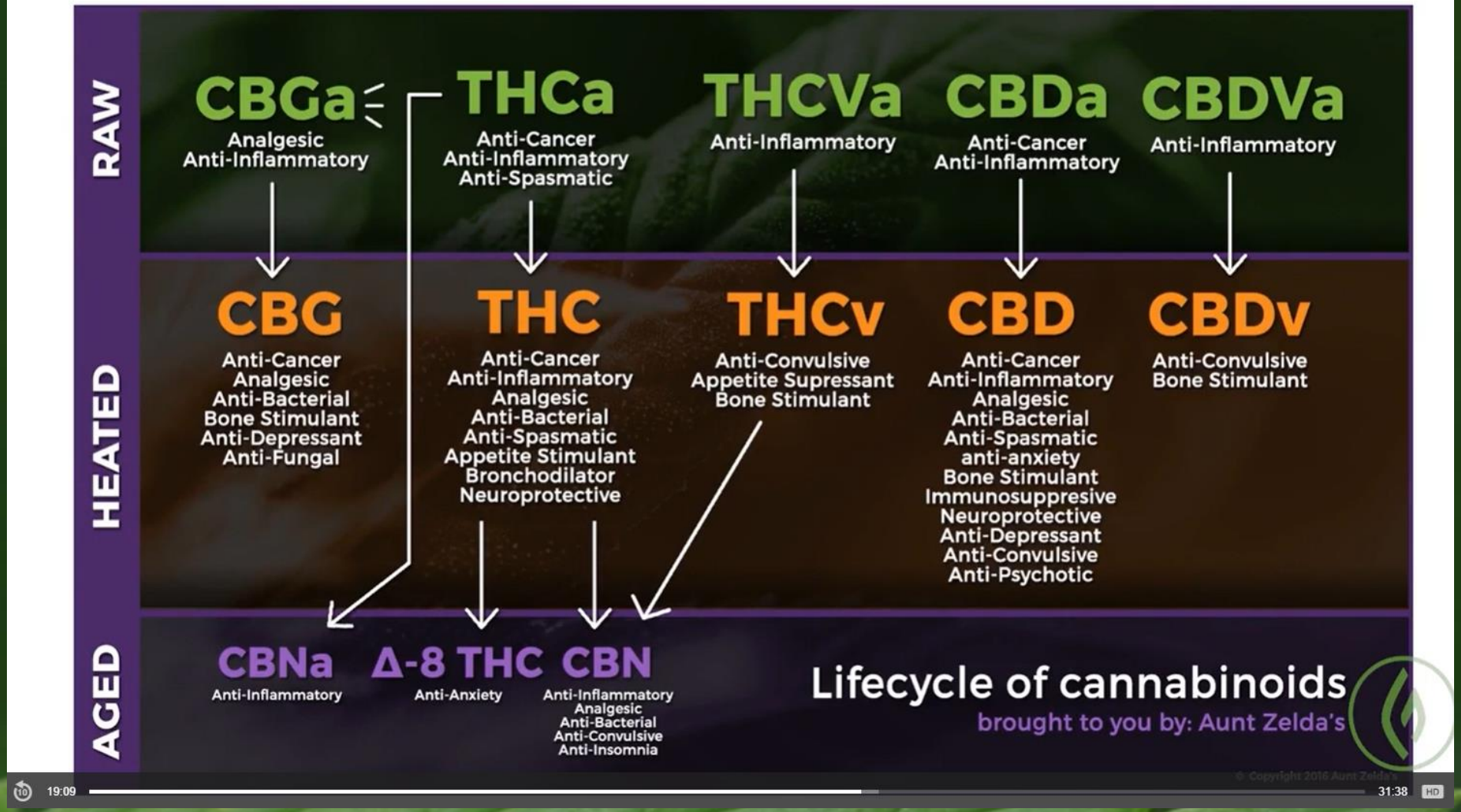
THCA (Δ^9-tetrahydrocannabinolic acid)	THC
CBDA (Cannabidiolic acid)	CBD
CBGA (Cannabigerolic acid)	CBG
CBCA (Cannabichromenenic acid)	CBC
CBGVA (Cannabigerovarinic acid)	CBGV
THCVA (Tetrahydrocanabivarinic acid)	THCV
CBDVA (Cannabidivarinic acid)	CBDV
CBCVA (Cannabichromevarinic acid)	CBCV



CBD versus THC



Which Cannabinoid to Choose?



Terpenes

- Scent component, complex aromas
- Hundreds, but eight main below

Myrcene

Caryophyllene

Limonene

Pinene

Linalool

Terpinolene

Humulene

Ocimene

Terpenes

	Fuel	Earth	Fruit	Floral
Descriptors	-Racy -Euphoric -Aggressive -Powerful high	-Relaxing/calming -Sedating -Mellowing	-Uplifting -Energetic	-Variable -Contemplative -Introspective
Examples and ECS interaction	-Og Kush -Pinene (no affinity towards CBRS described, interacts with GABAa receptors)	-Babba Kush -Humulene	-Tangie -Limonene (does not react at CB1R or CB2R)	-Lemon haze -Linalool (modulated GABAergic synaptic transmission) -Caryophyllene (full CB2 agonist)
Disease state	-Inflammatory conditions	-Inflammatory conditions	-Fungal/bacterial infections -Depression	-Depression -Anxiety/psychosis -Inflammatory conditions -Inflammatory bowel
Symptom targeted	-Decrease short term memory loss from THC -Promote alertness	-Can suppress appetite	-Elevates mood -Stress reliever	-Stress relieving -Boosts immune system -Decrease lung inflammation
Aroma	-Pine -Chemically	-Fresh dirt -Coffee -Chocolate -Wood	-Any fruit -Sweet	-Flowery -Spicy -Complex

Strains (Chemovars)

- Three most common species of Cannabis genus grown:
  - *C. indica:* Known for being more relaxing and sedating
  - *C. Sativa:* Known for being a “head-high”, more energizing
  - Hybrids also prominent
- Physiological effect depends on receptors they bind to

Indica Dominant	Sativa Dominant	Hybrid
Death Star	Lemon Brulee	Red Dragon
High Crew	Lemon OG Haze	Grape Diamonds
Salmon River OG	Stardawg	Apex
Snowball #1	MTF	NF1
Scout Breath	Agent Orange	Grease Monkey
Blue Dream	Sour Diesel	Original Glue
Girl Scout Cookies	Purple Haze	Wedding Cake

Routes of Administration

	Inhaled	Oral	Topical
Mode of delivery	-Smoked (joint, blunt, pipe) -Vaped (flower, oil, extraction) -Dabbing (flash vaporization)	-Tincture -Infused into food/drinks -Oils -Pills, capsules -Sprays	-Creams -Oils -Transdermal patches
Titration	Quick	Lengthier	Lengthier
Average Bioavailability	10-25%	6-20%	5-10%
First onset of effect	3-10 minutes	60-90 minutes	15-45 minutes
Peak psychoactive effects	15 minutes	3 hours	N/A
Duration of effects	2-4 hours	8-12 hours	Up to 2 hours
Dosing frequency	5-6/day	1-3/day	As needed

Pharmacokinetics		
Route of administration	**Inhaled**	**Oral**
Peak effect	~15 minutes	~ 1-4 hours Variable
Bioavailability	~ 30%	~ 6%, with fat intake
Excreted	Feces/urine	Feces/urine
Metabolized	Liver	Liver

Withdrawal Symptoms
Irritability
Sleeplessness
Decreased appetite
Anxiety
Cravings

Side Effects		
Short-term	Long-term	Other effects
Altered senses and time	Can affect brain development	Breathing problems
Relaxation	Impair thinking and memory	Increased heart rate
Euphoria		Nausea and vomiting
Impaired movement		Sedation
Difficulty thinking		Dry mouth
Impaired memory		Increased blood pressure
Hallucinations		Anxiety
Delusions		
Psychosis		

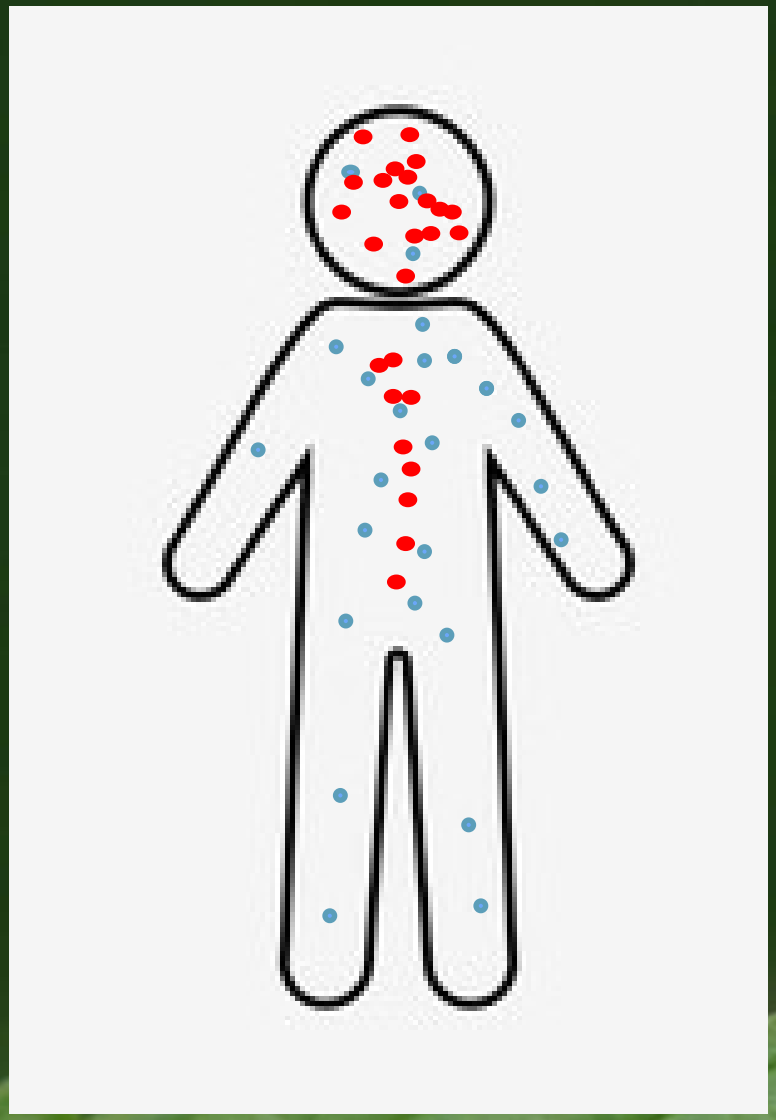
Endocannabinoid System -Complex Cell Signaling System

3 Core Components:

1. Endocannabinoids: Agonists of endocannabinoid receptors
    1. Anandamide (AEA)
    2. 2-Arachidonylglyerol (2-AG)

2. Endocannabinoid Receptors
    1. CBR1-Most prominent in central nervous system
    2. CBR2-Most prominent in peripheral nervous system, immune cells

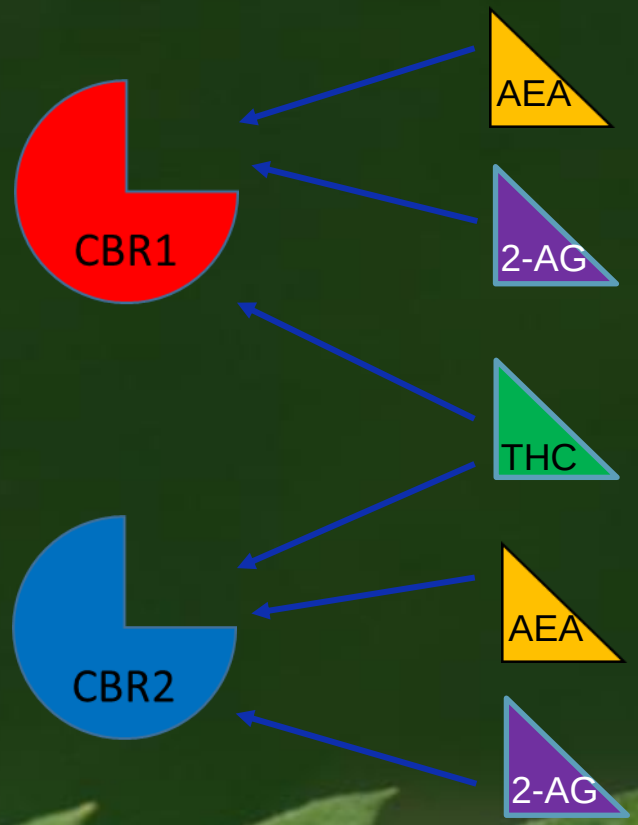
3. Enzymes that break down endocannabinoids
    1. Fatty acid amide hydrolase breaks down → AEA
    2. Monoacylglycerol acid breaks down → 2-AG



CBR1-Brain (cortex, cerebellum, amygdyla, hippocampus, basal ganglia), less but more widespread in the periphery

CBR2- More prominent on immune cells and in the periphery (adipose, cardiovascular, liver, bone, GI)

Receptors and Ligands



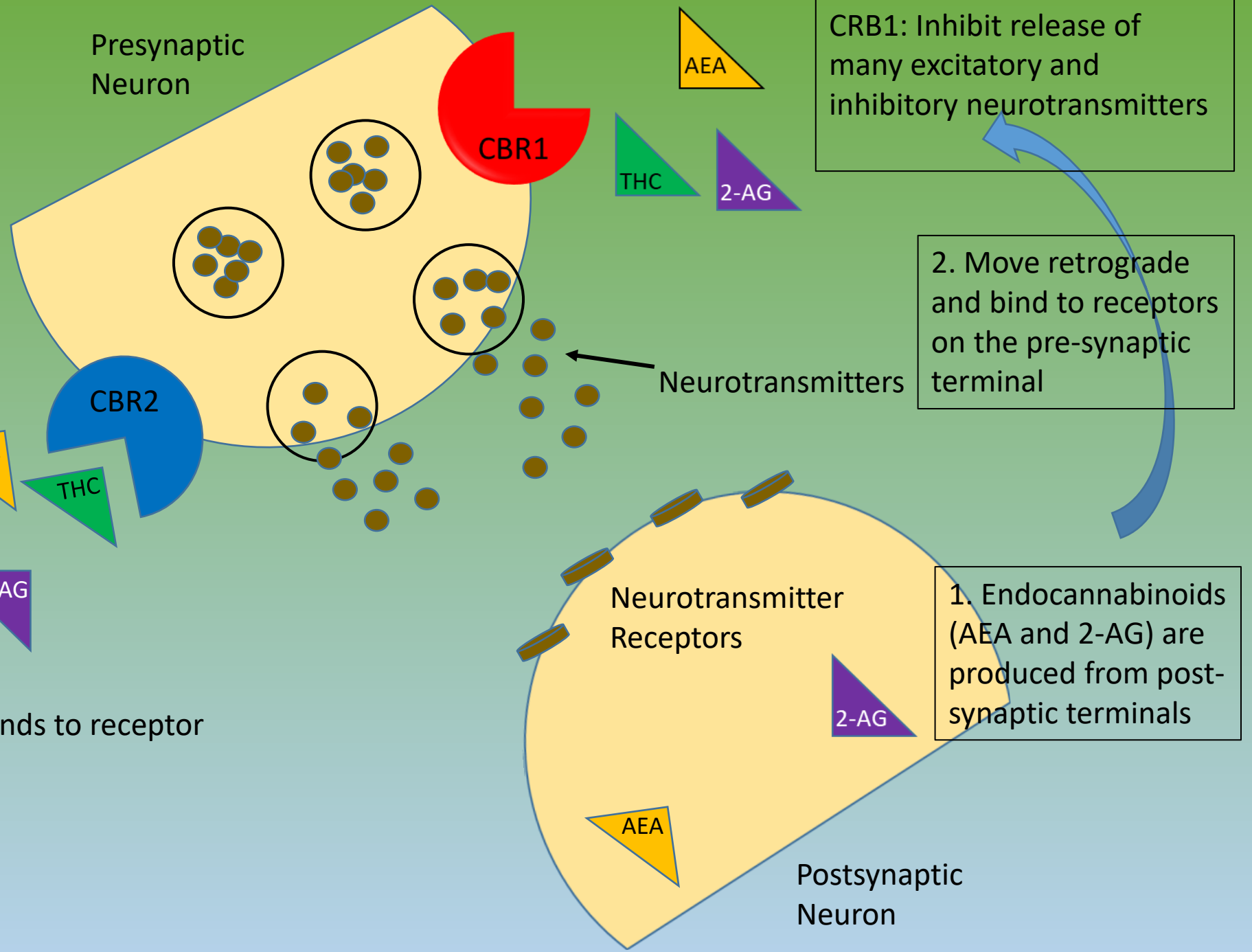
- Both endocannabinoids (AEA and 2-AG) and phytocannabinoids (THC) can bind to the receptors on the pre-synaptic neuron

AEA: High affinity, partial agonist
At CBR1, almost inactive at CBR2

2-AG: Low-moderate affinity and full agonist at both CBRs

THC: Partial agonist at both receptors

CRB2: Alter release of Chemical messengers
Ie, cytokines from immune cells



CRB1: Inhibit release of many excitatory and inhibitory neurotransmitters

2. Move retrograde and bind to receptors on the pre-synaptic terminal

1. Endocannabinoids (AEA and 2-AG) are produced from post-synaptic terminals

Ligand (AEA, 2-AG, THC) binds to receptor

Endocannabinoid System (ECS)

- Plays a role in regulating a range of functions and has many pharmacologic properties:
  - Sleep
  - Mood
  - Appetite
  - Memory
  - Inflammation
  - Anti-nociceptive
  - Alagesic
  - Anti-tumor
  - Antioxidant
  - Anti-puritic
  - Anti-convusant

YOU CANNABIS LIVE BETTER

CLINICAL BENEFITS OF CANNABIS IN CHRONIC AND SERIOUS ILLNESS

DISEASE STATES

SYMPTOMS

SAFETY AND USE

HISTORICAL USES TO TREAT AILMENTS

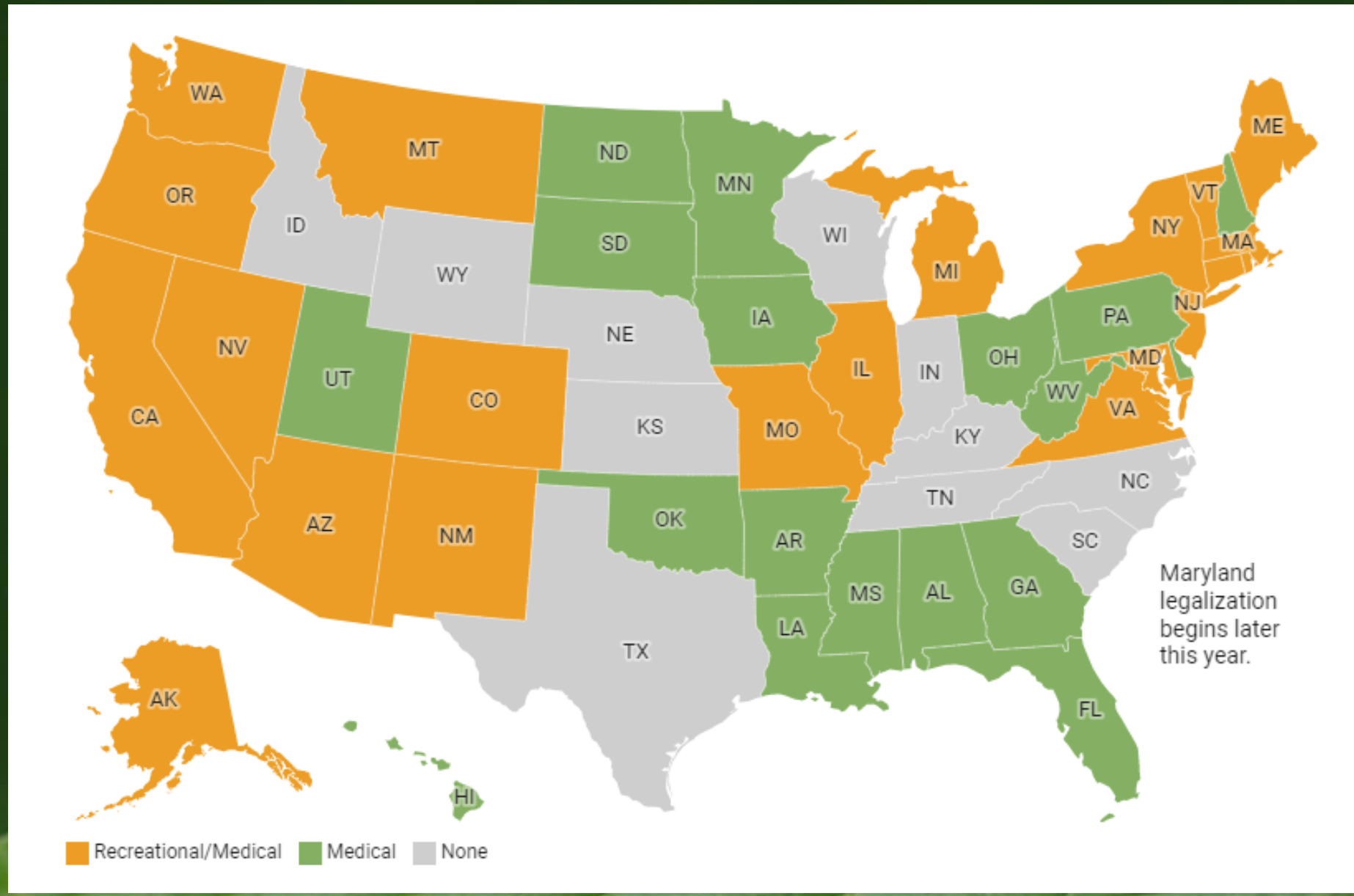
- ANCIENT USE: DESCRIBED USE AS EARLY AS 2700 B.C.E. FOR FIBERS, FOOD SOURCE, AND PSYCHOACTIVE PROPERTIES
  - ASSYRIA: OINTMENTS FOR INFLAMMATION, FUMES FOR ARTHRITIS, BATHS/DRINKS FOR DEPRESSION AND IMPOTENCE, KIDNEY STONES AND "HAND OF GHOST" IE SEIZURES
  - EGYPT: WASHING OF EYES FOR GLAUCOMA, VAGINAL SUPPOSITORY FOR CHILDBIRTH, PAIN RELIEF
  - INDIA: TREATMENT OF DIARRHEA, PHLEGM, ANXIETY, APHRODISIAC, APPETITE, DIGESTION, HAPPINESS, PAIN RELIEF
  - CHINA: RHEUMATISM, GOUT, MALARIA, MOVEMENT DISORDERS, BERIBERI, ANALGESIC, SLEEP, SEED LAXATIVE
- LATE 18TH CENTURY, WESTERN EUROPE :
  - RECREATIONAL USE BY SOLDIERS
- 1839: RE-INTRODUCED TO WESTERN MEDICINE BY WILLIAM BROOKE O'SHAUGHNESSY
  - EXPERIMENTS PROVING SAFETY, ADMINISTERED RESINS TO DOGS, FIRST CLINICAL TRIALS FOR CANNABIS USE
  - RELIEVE PAIN OF RHEUMATISM, ANTI-SEIZURE, DECREASED MUSCLE SPASM 2/2 RABIES AND TETANUS, DECREASED SPASTICITY, NAUSEA, DELIRIUM TREMENS
- 1850: ADDED TO US PHARMACOPEIA

HISTORICAL USES TO TREAT AILMENTS

- 1800'S, UNITED STATES:
  - DONOVAN CONDUCTED ADDITIONAL HUMAN TRIALS, RECOMMENDED FOR PAIN AND ANOREXIA, PHARMACEUTICAL COMPANIES PATENTED TINCTURES MARKETED FOR INSOMNIA, PAIN, ARTHRITIS, GONORRHEA, EPILEPSY, BRONCHITIS
  - 1892: SIR WILLIAM OSLER RECOMMENDED IT AS TREATMENT FOR MIGRAINE
- 1937: MARIJUANA TAX ACT PASSED PLACING A TAX ON THE SALE OF CANNABIS
- 1942: REMOVED FROM THE US PHARMACOPEIA
- 1947: SYNTHETIC THC DEVELOPED FOR TREATMENT OF EPILEPSY IN CHILDREN, STUDY DONE BY RAMSES AND DAVIS, PUBLISHED IN 1949
- 1950S: MULTIPLE FEDERAL LAWS PROHIBIT CANNABIS POSSESSION/USE
- 1964: THC FIRST IDENTIFIED AND SYNTHESIZED
- 1960'S: DRAMATIC INCREASE USE IN THE US, PARTICULARLY IN YOUNG AND COLLEGE STUDENTS
- 1970: CONTROLLED SUBSTANCE ACT PROHIBITING CANNABIS FEDERALLY, REPLACING 1937 ACT, CLASSIFYING AS A SCHEDULE I DRUG, "NO ACCEPTED MEDICAL USE"

HISTORICAL USES TO TREAT AILMENTS

- 1947: SYNTHETIC THC DEVELOPED FOR TREATMENT OF EPILEPSY IN CHILDREN, STUDY DONE BY RAMSES AND DAVIS, PUBLISHED IN 1949
- MARINOL APPROVED IN 1985 FOR ANOREXIA IN AIDS PATIENTS AND NAUSEA IN CANCER PATIENTS
- 1978: MEDICAL USE FOR TREATMENT OF GLAUCOMA
  - PATIENT WITH GLAUCOMA TRANSFORMED LANDSCAPE WITH A LAWSUIT, COMPASSIONATE USE MANDATED WITH A COMPELLING PHYSICIAN TESTIMONY, PROGRAM SHUT DOWN IN 1992
- 1990: CANNABINOID RECEPTORS IDENTIFIED IN THE HUMAN BRAIN
- 1996: CALIFORNIA IS THE FIRST STATE TO LEGALIZE MEDICAL USE
- 2020: LEGALIZED IN SOUTH DAKOTA FOR MEDICAL USE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Maryland legalization begins later this year.
Recreational/Medical
Medical
None

Target and data for symptom management

- Generally patients with terminal illness experience significant symptom burden, most common:
  - Fatigue
  - Pain
  - Nausea
  - Anorexia
  - Cachexia
  - Dyspnea
  - Anxiety
  - Depression

JAMA
The Journal of the American Medical Association

Cannabinoids for Medical Use: A Systematic Review and Meta-analysis

Penny F. Whiting, PhD[1,2,3]; Robert F. Wolff, MD[3]; Sohan Deshpande, MSc[3]; et alMarcello Di Nisio, PhD[4,5]; Steven Duffy, PqD[3]; Adrian V. Hernandez, MD, PhD[6,7]; J. Christiaan Keurentjes, MD, PhD[8]; Shona Lang, PhD[3]; Kate Misso, MSc[3]; Steve Ryder, MSc[3]; Simone Schmidlkofer, MSc[9]; Marie Westwood, PhD[3]; Jos Kleijnen, MD, PhD[3,10]

JAMA. 2015;313(24):2456-2473. doi:10.1001/jama.2015.6358

- 79 trials included, 6462 participants
- Moderate quality evidence to support use in pain and spasticity
- Low quality evidence suggesting improvement in nausea and vomiting due to chemotherapy, weight gain in HIV, sleep disorders or Tourette syndrome
- Associated with increased risk of short term adverse effects:
  - Dizziness
  - Dry mouth
  - Nausea
  - Fatigue
  - Somnolence
  - Euphoria
  - Vomiting
  - Disorientation
  - Drowsiness
  - Confusion
  - Loss of balance
  - Hallucination

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- Nausea and Vomiting:
  - All studies suggested benefit, but not statistically significant
- Appetite Stimulation:
  - Some studies suggested benefit, not statistically significant
- Chronic Pain:
  - Conditions including neuropathic, cancer related, fibromyalgia, and others
  - Some mixed results, but overall moderate quality evidence to suggest may be beneficial for chronic neuropathic and cancer pain
- Spasticity Due to MS or Paraplegia:
  - Generally suggest improvement in spasticity, moderate quality evidence to support use

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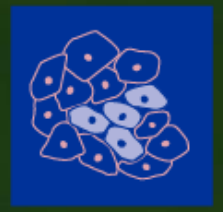
- Depression:
  - No difference compared with placebo
- Anxiety:
  - Mixed results
- Psychosis:
  - No difference in mental health outcomes seen
- Movement Disorder Due to Tourette Syndrome:
  - Suggested association with a significant improvement in tics



cancers

Cannabis Consumption Used by Cancer Patients during Immunotherapy Correlates with Poor Clinical Outcome

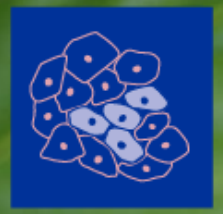
Cancers (Basel). 2020 Sep; 12(9): 2447.

- 102 patients, stage IV disease (>50% NSCLC), initiating checkpoint inhibition treatment, prospective observatory study
- 34 used cannabis, 68 did not use. Of users 71% used lowest recommended dose per month (20 grams), started 9 months to 2 weeks prior to immunotherapy
- Users had significant decrease in time to tumor progression and decreased overall survival, reduced therapy related immune adverse effects
- Decreased clinical benefit (CR + PR + SD) 39% vs 59%
- Time to progression (primary outcome) 3.4 months vs 13.1 months
- Overall survival (secondary outcome) 6.4 months vs 28.5 months

JOURNAL OF CLINICAL ONCOLOGY

The effect of concomitant cannabinoids during immune checkpoint inhibitor treatment of advanced stage malignancy.
Journal of Clinical Oncology ,Volume 38, Issue 15_ suppl

- 104 patient with advanced cancer, 70 received Nivolumab and 27 received Pembrolizumab, mean duration 10.2 months of therapy
- 28 with concomitant use of cannabis during treatment
- Non-cannabis users had significantly longer overall survival (40 months versus 16 months)
- Thought to be 2/2 anti-inflammatory properties of cannabis



cancers

Anti-Cancer Potential of Cannabinoids, Terpenes, and Flavonoids Present in Cannabis

Cancers (Basel). 2020 Jul; 12(7): 1985.

Andrea M. Tomko,[1,†] Erin G. Whynot,[1,†] Lee D. Ellis,[2] and Denis J. Dupré[1,*]

- Cannabinoids have been suggested to have an anti-tumor impact
  - Suppress proliferation, migration, and/or invasion of cancer cells
  - Suppress tumor angiogenesis
  - Other compounds in cannabis, terpenes and flavonoids also have suggested anti-tumor actions
- Need more research and data

Is Medical Cannabis Right for You?

Do you have a medical condition that qualifies for medical cannabis?

- Debilitating Medical Condition or its treatment that causes one or more of the following:
- -Cachexia/wasting Syndrome
- -Severe pain
- -Severe nausea
- -Seizures
- -Severe muscle spasms

Do you have health concerns that put you at higher risk of cannabis use?

- Pregnant or breastfeeding
- Severe Heart Disease
- Severe lung disease
- History of stroke or stroke risk factors
- Tachycardia or hypotension
- History of Psychosis or bipolar disorder
- Age < 25 yo

Are you on any medications or supplements that have potential interactions with cannabis?

- Blood Thinners
- Anti-arrhythmic medications
- Immunosuppressant medications
- Anti-depressants
- Anti-anxiolytics
- Immunotherapy for cancer treatment
- Regular alcohol use

Safety and Monitoring

Considerations	Precautions	Relative Contraindication	Contraindication
Immunocompromised	Mood or anxiety disorder	Under 25 years of age	Unstable CVD
CKD	Risk for CVD	Cannabis use disorder	Respiratory disease (if smoking)
Elderly	Tobacco use	Substance use disorder	Personal or family history of psychosis
Multiple medical problems	Severe liver dysfunction		Pregnancy or breastfeeding
Polypharmacy	Sedating medications		
Potential drug interactions	Driving or safety sensitive occupations		

How Safe is it?

- ~30% of those who use may have some degree of marijuana use disorder

- Those who begin use before age 18 are 4-7x more likely to develop a marijuana use disorder

- In 2015 ~4 million people in the US met diagnostic criteria for marijuana use disorder

- Potency of confiscated samples has increased over the past few decades, THC content in 1990’s less than 4%, in 2018 15%

How Safe is it?

- No good evidence to support the idea of a “gateway drug” to “harder” substances
- Can have an impact on attention, memory, and learning, higher concern <25 yo
- Adolescents that use regularly significantly less likely to complete high school or obtain a degree
- Fatal marijuana overdose is unlikely

Practical Approach

- Preparations high in CBD, low in THC
  - Getting “high” is undesirable for most patients
- Start low, go slow
- Avoiding smoked cannabis – alternate routes as effective without health hazards of smoking
  - Vaporizing: rapid onset, easy to titrate to effect
  - Oral: longer acting
  - Topical: short acting, local effects
- Work to discern clinical appropriateness from substance misuse

Practical Stuff

What does this mean for us?

- Schedule I Controlled Substance, illegal at the federal level
- Medical Marijuana is NOT prescribed
- Clinicians can provide certification or attestation that the patient has a qualifying condition

Criteria:

- Must have a "debilitating medical condition," which is defined as "a chronic or debilitating disease or medical condition or its treatment that produces one or more of the following: cachexia or wasting syndrome; severe, debilitating pain; severe nausea; seizures; or severe and persistent muscle spasms, including those characteristic of multiple sclerosis".

- Physicians and APP’s can certify patients if they are licensed to prescribe drugs to humans in the state of patient’s residence

- 2 flowering and 2 non-flowering plants, can have a caregiver

Practical Stuff

- In person evaluation, discussing risks/benefits, therapeutic or palliative benefit, available for further consultation, number of designated caregivers

- Application Fees:
  - Low income: $20
  - All others: $75

Practical Stuff

Type of cannabis	Amount equivalent to one ounce of cannabis
Concentrated cannabis in smokable form	8 grams (net weight)
Vaporizer pens or cartridges	8 grams (net weight)
Oils in oral dosage syringe or capsule form	5 grams (net weight)
Edibles (excluding oils)	800 milligrams THC
Topical (ointment, cream, or lotion)	12 fluid ounces
Topical (dried plant material or powder)	1 ounce
Transdermal patches	800 milligrams THC

Re-HASH

Symptom/Condition	Evidence of Benefit
Nausea/vomiting	Low
Appetite stimulation	Low/Moderate
Glaucoma	Low
Epilepsy	Whole plant – Low/Moderate CBD - High
Pain management	High
PTSD	Short term, PRN use – Moderate/High Daily/chronic use – Low (may cause harm)
Crohn's Disease	Moderate
Multiple Sclerosis	Pain and spasticity – High Other symptoms - Low

Re-HASH

- Nice to have additional options for symptom management
- Safe option in most patient populations
- Learning curve to make sure we are doing the best by our patients
- Data that exists is promising, more is needed

Disclaimer

- I do not consider myself to be an expert in symptom management with cannabis
- I *may* have tried it once, but I did not inhale

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