Medical Cannabis: Review of Literature and Treatment for Pain Management

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OBJECTIVES

1. Current Law
2. Review the history of Cannabis
3. Describe the ECS and physiology
4. Literature Review
5. Impact on Healthcare
6. Opioid Epidemic
7. Qualifying Conditions
8. Physician's role

Florida Law- Qualifying Conditions

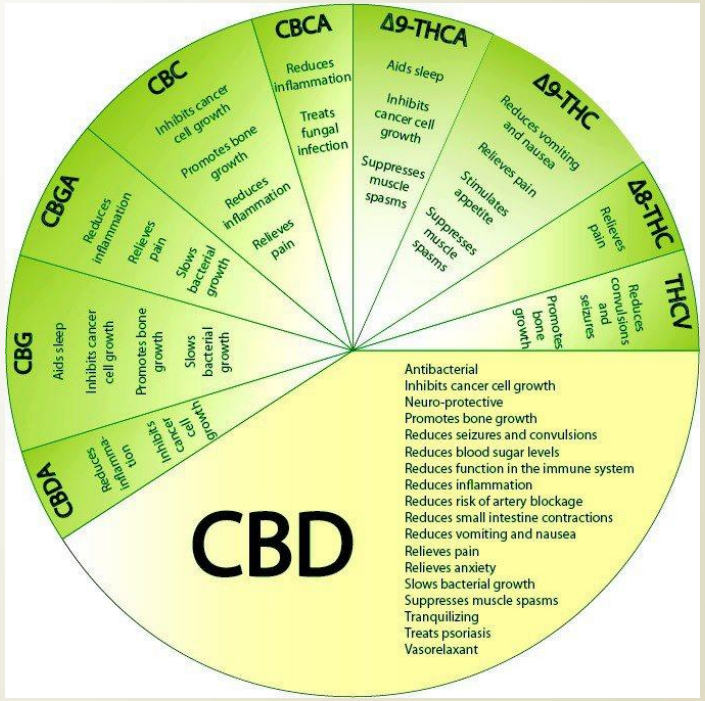
- 2014- Low THC- Cancer, Chronic disorders causing epilepsy, spasms
- June 2016- **Right To Try Act-** terminal condition (Florida Statue 499.0295)
  - progressive disease causes functional impairment not reversible with FDA options, will result in death within one year if runs normal course
- Nov 2016- **Amendment 2**
  - Cancer, Epilepsy, Glaucoma, HIV, AIDS, PTSD, ALS, MS, Crohn's, Parkinson's, other debilitating medication conditions of same kind or class in which med cannabis use outweigh health risks under
- Jan 3 2017 **Amendment 2-** 6 months to implement rules
  - Bax/OCU- Disgression of Physician

Current Florida Law

- Diagnosed with 1/10 qualifying condition
  - HIV, AIDS, Parkinson, MS, ALS, Crohn's, Glaucoma, Epilepsy, Cancer, PTSD
  - Medical conditions of same kind or class
  - Chronic nonmalignant pain caused by a qualifying med condition
- Florida Resident
- Under 18, second physician agree
- Tried other treatments without success; Risks vs benefit
- Registered with Compassionate Use by ordering Physician, 2 hr CME course $500
- 70 day supply, 2 refills (210 days vs 45/90); 30 week fu
- Caregiver- one hour course
- 10 new licenses, 100,000 pts registered 4 more licenses, 25 cap
- Medical Director of Dispensing Organization- unrestricted license, 2 hour CE

Low THC vs Medical Cannabis

- Low THC
  - Plant of genus Cannabis, 0.8% or less THC and >10% of Cannabidiol (CBD) weight
- Medical Cannabis
- CBD Hemp Oil
- Whole Flower
- Cannabinoids
  - CBGA, CBDA, THCA- decarboxylation- THC, CBD, CBC



History of Cannabis for Medical Use

- Middle East, Egypt, India for >5,000 years
  - Anxiety, seizures
- 1892 Sir William Osler wrote in the Principles and Practice of Medicine
  - "Cannabis is the most satisfactory remedy for migraines"
- Marijuana Tax Act (1937)
  - Made Marijuana illegal, Decrease in education
- Controlled Substances Act (1970)
  - Marijuana is a Schedule I drug:
    - *"No currently accepted medical use"*
    - *High potential abuse*
    - *Lack of evidence about safety*

Discovery of Endocannabinoid System (ECS)

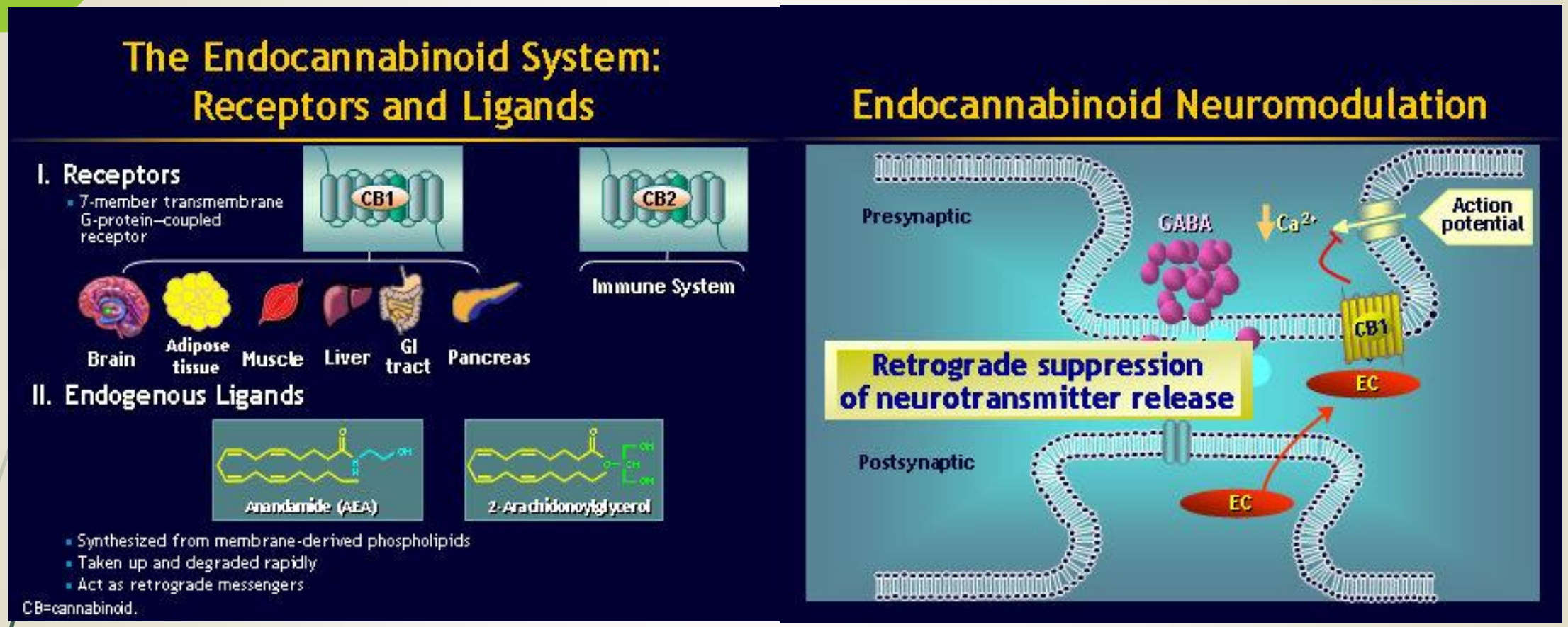
- Endocrine system
  - Homeostasis
  - Deficiencies

TABLE 2.1 Landmark Discoveries Since the 1982 IOM Report

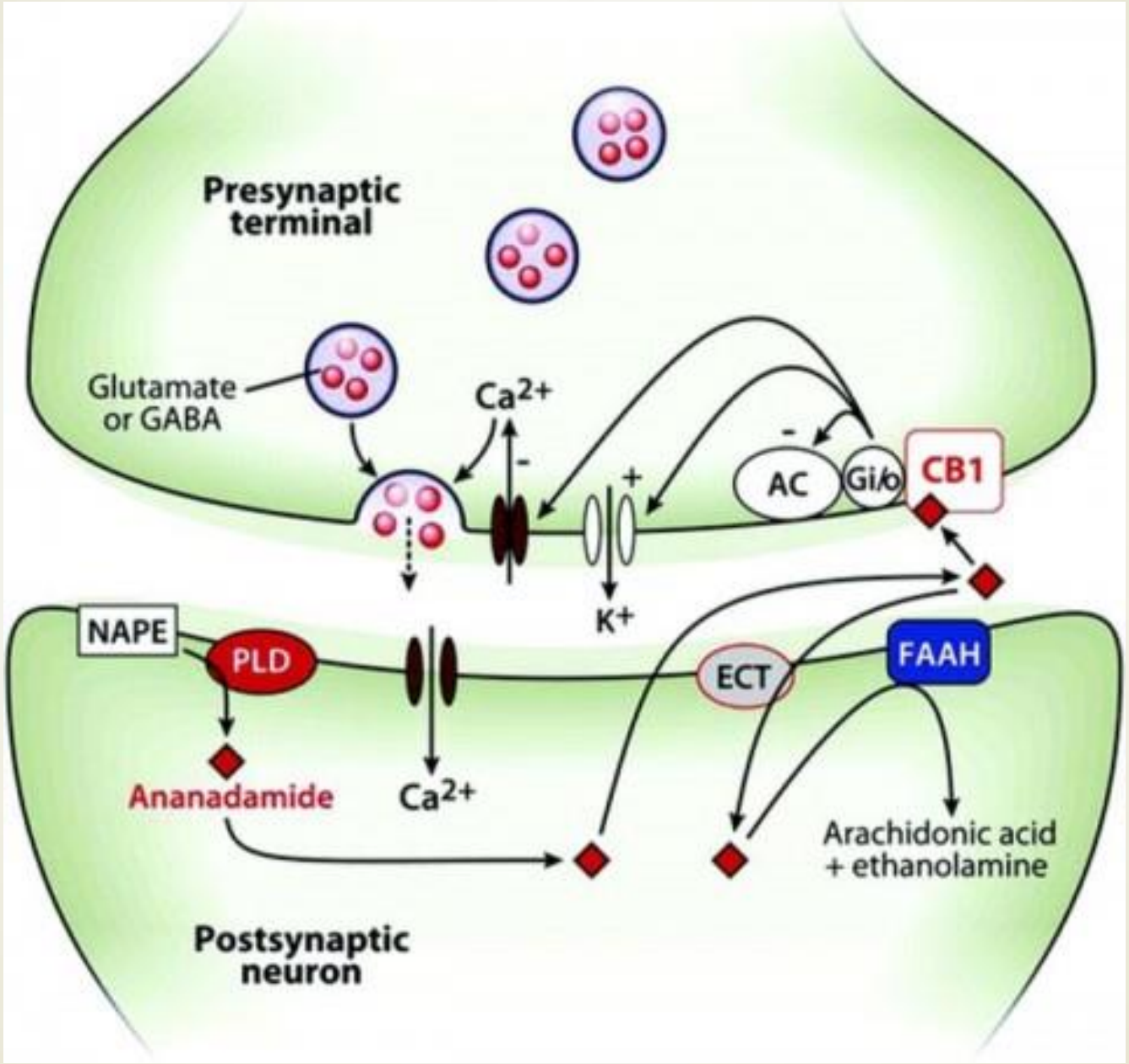
Year	Discovery	Primary Investigators
1986	Potent cannabinoid agonists are developed; they are the key to discovering the receptor.	M. R. Johnson and L. S. Melvin[75]
1988	First conclusive evidence of specific cannabinoid receptors.	A. Howlett and W. Devane[36]
1990	The cannabinoid brain receptor (CB_1) is cloned, its DNA sequence is identified, and its location in the brain is determined.	L. Matsuda[107] and M. Herkenham et al.[60]
1992	Anandamide is discovered—a naturally occurring substance in the brain that acts on cannabinoid receptors.	R. Mechoulam and W. Devane[37]
1993	A cannabinoid receptor is discovered outside the brain; this receptor (CB_2) is related to the brain receptor but is distinct.	S. Munro[112]
1994	The first specific cannabinoid antagonist, SR 141716A, is developed.	M. Rinaldi-Carmona[132]
1998	The first cannabinoid antagonist, SR144528, that can distinguish between CB_1 and CB_2 receptors discovered.	M. Rinaldi-Carmona[133]

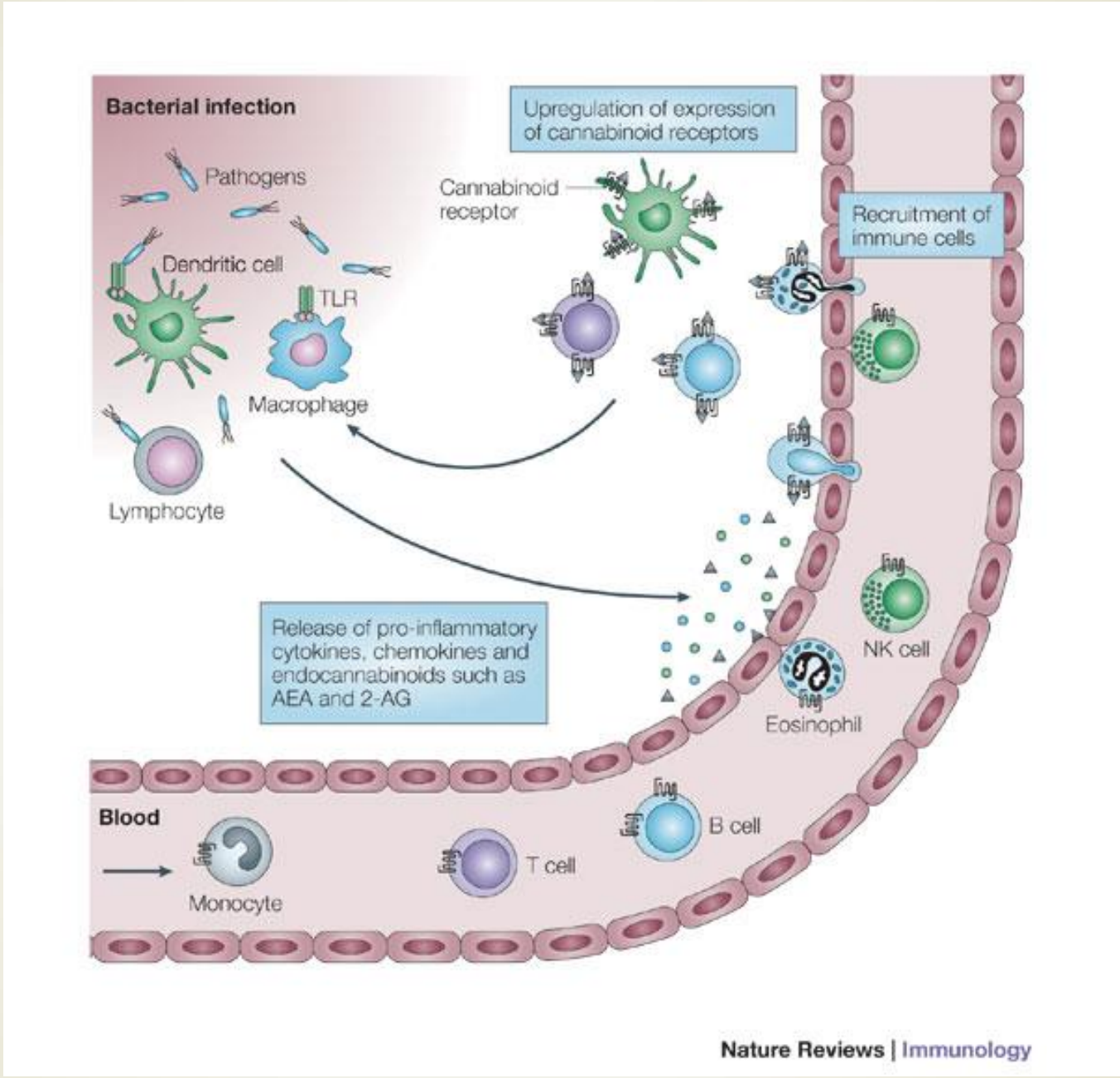
ENDOCANNABINOID SYSTEM (ECS)

- Cannabinoid receptors - early 1990s, G protein coupled receptors
  - **CB1**- Expressed on presynaptic peripheral and **central** nerve terminals
    - Some exposure on peripheral organs- CV GI
    - Pain, memory, mood, appetite
    - Decrease in diseased state
  - **CB2**- Concentrated in **peripheral** tissues and immune cells
    - Increased in diseased state- inflammatory response
- Ligands- 1992; made from phospholipids
  - Anandamide: binds to CB1 receptors
  - 2-arachidonylglycerol (AG)
    - Change with age
- Eat, sleep, relax, forget and protect



- Endocannabinoids – made on demand, travel retrograde to inhibit Neurotransmitter release, Complex signaling pathway
- Regulated by CB1, CB2, TRPV1, GP55, Prostaglandin and cytokine pathways


Presynaptic terminal
Glutamate or GABA
Ca2+
-
+
AC
Gi/o
CB1
K+
NAPE
PLD
ECT
FAAH
Ananadamide
Ca2+
Arachidonic acid + ethanolamine
Postsynaptic neuron


Bacterial infection
Upregulation of expression of cannabinoid receptors
Pathogens
Cannabinoid receptor
Recruitment of immune cells
Dendritic cell
TLR
Macrophage
Lymphocyte
Release of pro-inflammatory cytokines, chemokines and endocannabinoids such as AEA and 2-AG
NK cell
Eosinophil
Blood
B cell
T cell
Monocyte
Nature Reviews | Immunology

THC vs Cannabidiol

Cannabidiol (CBD)

- Isolated in 1963
- Does not bind to either CB1 or CB2
- **Inhibits FAAH (breaks down Anandamide)**
- Inhibits cyclooxygenase, lipoxygenase – anti-inflammatory, analgesic
- Inverse agonist; decreases the psychotropic activity of THC
  - Dec tachycardia, sedation, anxiety
- Enhance the activity of anandamide
- Anti-anxiety effect

THC

Isolated in 1964

Partial agonist at CB1 and CB2 receptors

Mimics Anandamide and 2AG

Antineoplastic

Antispasmodic

- Analgesic
- Anti-nausea
- Appetite stimulant
- Sleep aide

Literature Review

- National Academy of Sciences, Engineering and Medicine : 396 pg report
  - 10,000 research studies on marijuana
    - therapeutic benefits and risk factors
  - 100 different conclusions
- "conclusive or substantial evidence" that marijuana is effective for
  - Treatment of chronic pain
  - Nausea and vomiting in cancer patients undergoing chemo
  - Treatment of spasticity in multiple sclerosis

LITERATURE REVIEW

- Smoking marijuana is not associated with lung, head, neck cancers
- "Moderate to limited evidence" that marijuana is therapeutic
  - insomnia relating to painful syndromes
  - increasing appetite in people with HIV/AIDS
  - decreasing severe anxiety
  - combating the effects of PTSD

RISKS BASED ON LITERATURE REVIEW

- Substantial evidence – regular marijuana smokers are more likely to experience chronic bronchitis
  - Improve when stop smoking
- Substantial evidence suggests a link between prenatal cannabis exposure and lower birth weight
- Substantial evidence shows an increased risk for developing schizophrenia
  - NOT clear if use contributed to the psychoses or people developing psychoses were turning to marijuana as a form of self-medication.
    - Link/correlation vs causation

Assessment of the current state of Cannabis research

More than half of states in the country allow some form of medical marijuana.

Eight states and the District of Columbia allow recreational use.

- RESEARCH is needed
- Schedule I status

Cannabis and Health Care

- Americans over-65 only account for 14 percent of the nation's population, but they use more than 30 percent of all prescription drugs
- Medicare saved more than $165 million in 2013 on prescription drugs in D.C. and 17 states that allowed cannabis to be used as medicine.
- If every state in the nation legalized medical marijuana, the study forecast that the federal program would save more than $468 million a year on pharmaceuticals for disabled Americans and those 65 and older.
- Prevalence of past-year cannabis has risen approximately 60 % age 50 to 64, and increased 250% over 65 years of age.

Pain Epidemic

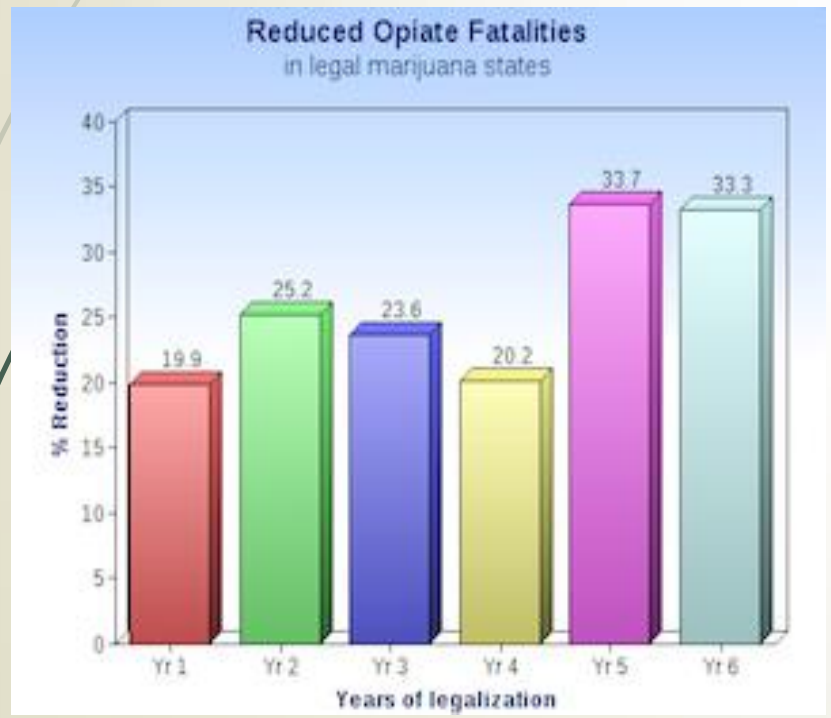
- Two million Americans either abused or were dependent on prescription opioids in 2014, according to CDC
- Overdose deaths involving prescription opioids have quadrupled since 1999 (200% increase)
  - US 5% world's population- 80% worlds opioids
  - 2.5 million people in U.S. have opioid use disorder
  - More than 130 people die every day from opioid overuse
  - 200 million opioid painkiller prescriptions written every year in US
  - 7000 treated in ER for misuse
- $72 billion in medical costs each year in US for Opioid abuse

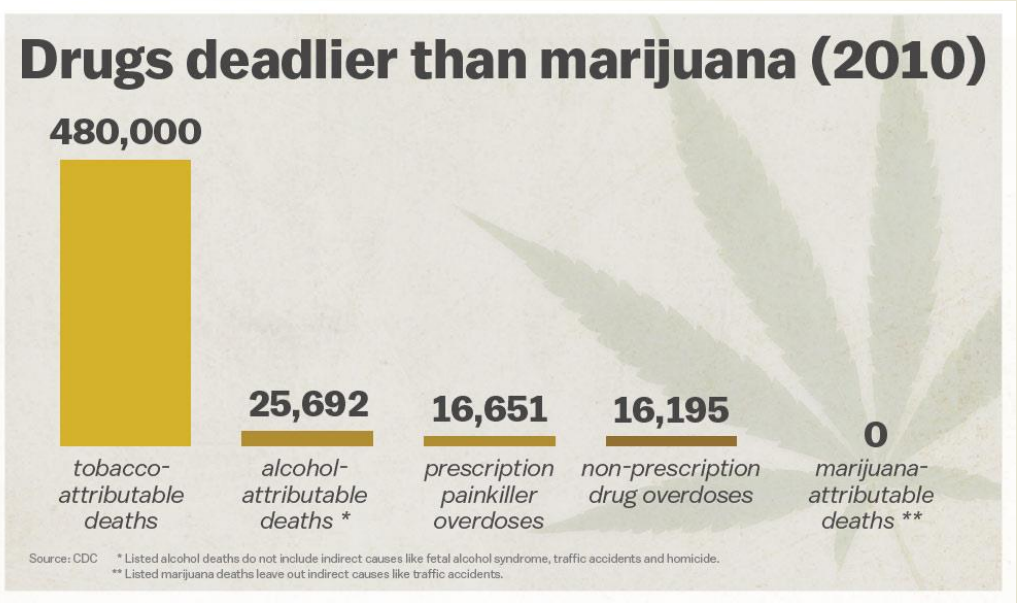
IMPACT ON OPIOID USE

No increase in adolescent Cannabis use after legal medical cannabis

Not one death from Cannabis- No CB receptors in Brainstem

Preventable Deaths: Falls- 26,852; Guns- 31,672; MVA- 33,687





Pain

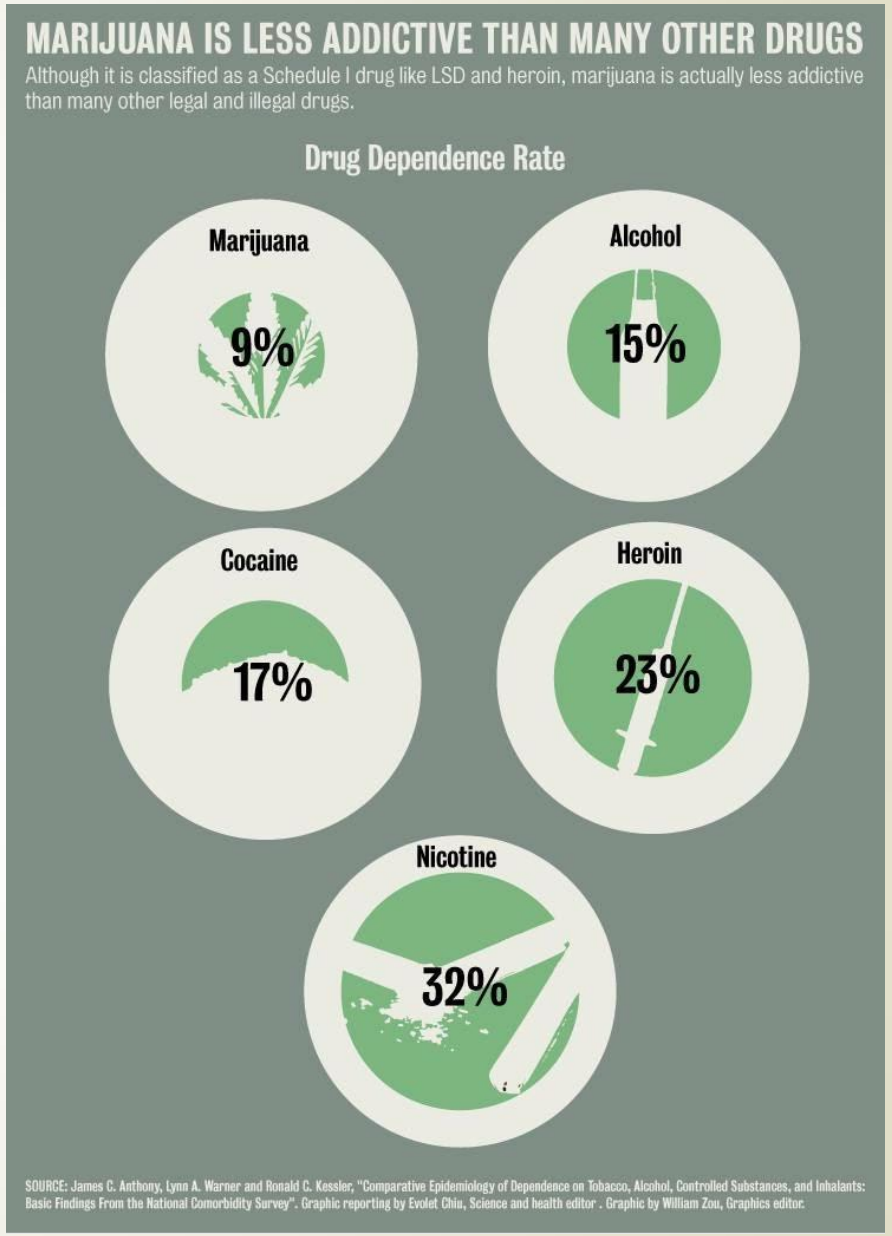
- 25 million Americans, 11% have daily pain
  - 40 million adults- severe (17.6%)
  - 126 million adults (55.7%) some type of pain is last 3 months
- The Hebrew University, 2016 - cannabis effective treating chronic pain
- 176 participants, unresponsive to conventional medicines and treatments, inhaled a monthly amount of 20 grams of cannabis for six-month
  - 66% 'experienced improvement in their pain symptom scores after cannabis therapy, and most reported "robust" improvements in quality of life.'
  - reduced consumption of opioid by 44 percent!
- U of Michigan, studied 185 chronic pain patients, 64% reduction in opioid use after increasing their cannabis consumption.
  - 45% improvement in quality of life using cannabis

Pain

- Peripheral- paracrine function from glia, histiocytes, macrophages (Immune)
- Central- CB1 receptor tightly coupled with Mu receptor, activation of endorphins
- Interrupts pain signals at DRG and neurons
- THC induces analgesia by inhibiting neurons activated by pain by binding to presynaptic CB1 receptors
- CBD binds TRPV1 to mediate desensitization inhibit inactivation of Anandamide
- CB2- anti-inflammatory
- Psychotropic euphoric effect, short term memory reduction mitigates stress
- FM, IBS, Migraines- defic ECS?

ADDICTION

- 9% (Less than chocolate)
  - Medicinal?
  - Number is overinflated
  - Increase dopamine (desire)
- Substitution effect
  - 16% decrease in benzo
  - 12% decrease in antidepressants
  - 12% replaces cigarettes with cannabis
- Potential treatment for opioid withdrawal
- Tolerance- desensitize, holiday, ratio



Drug Interactions

- THC and CBD and Cytochrome P450 enzyme
  - Clarithromycin, ketoconazole, verapamil, cimetidine, fluoxetine increase bioavailability of THC
  - Rifampin, carbamazepine, phenobarbital decrease bioavail of THC
- CYP3A4- carbamazepine, phenytoin could decrease CBD
- Interactions with sympathomimetic activity (tachy, hypertension), CNS depressants and anticholinergics (tachy, drowsy)
- Acute psychosis
- Alcohol, Anticoagulants, Anticholinergics, CNS depressants, benzo, SSRI

Cannabis Based Medicine

- ENDOGENOUS CANNABINOIDS- Anandamide and 2-AG
- Botanical cannabis (plant- PHYTO): “Medical Cannabis”

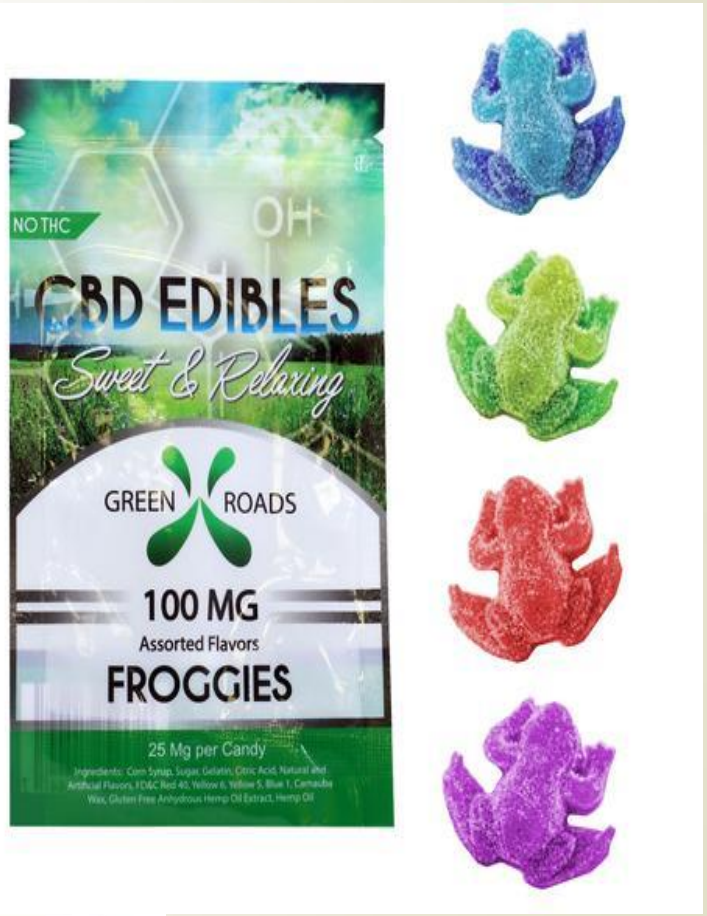
- Synthetic delta 9 THC medications (schedule III)
  - Dronabinol (Marinol®) (FDA approved for anorexia AIDS, CINV)
  - Syndros- (CINV, anorexia AIDS) Insys

- Nabilone, synthetic chemical structure similar to THC
  - (Cesamet®) (FDA approved for CINV)
  - Epidiolex- phase 3 trials, Dravet and Lennox-Gastaut

- Other medications not available in U.S.:
  - Nabiximols (Sativex®) THC/cannabidiol mouth spray for pain relief, muscle spasms; currently being investigated by FDA
  - Rimonabant (Accomplia®, Zimulti®) for treatment of obesity and nicotine dependence (selective cannabinoid receptor-1 blocker)

- Current research
  - CBD- uveitis, macular degen (Nemus Bioscience)
  - CBD-refractory epilepsy, OA knee, Fragile X syndrome

CBD Hemp vs Medical Cannabis oil



Routes of Administration

- Smoking- rapid onset, short duration, lungs
- Vaporizing- not cheap, easy to titrate, subcombustible (200C, 390F)
- Eating- long onset, long duration, calories, hard to titrate, after meal
  - Bioavailability- 1st pass, delta9→11hydroxyTHC in liver (long)
- Tincture- SL, rapid and short, variable (oil, glycerin, alcohol)
- Topicals, patches (lipophilic)- vehicle (emulsified, liposomal), depth
- Rectal/vaginal- avoid 11 hydroxy, pelvic/CA
- Capsules- less potent than edibles
- Concentrates
  - Long vs short acting

Cannabis Dosing

- Herbal medicine takes time, not immediate
- Lab tested
- Sweet spot- if increase → diminishing results, side effects, more not better
  - Low (anxiolytic) vs High (anxiogenic)
- Full plant extract enhanced compared to partial extracts
- Strains, routes, sativa vs indica
- Antitumoral- high THC
- Antipsychotic- high CBD
- Consider terpenes

Entourage Effect

- TERPENES
- Aromatic compounds
- GW Pharm, Ethan Russo
- Acne, anxiety, sleep, MRSA
- Destroyed by direct heat therefore vaping maintains

- Flavonoids, amides, sterols

WHAT YOU SMELL = HOW YOU'LL FEEL

IDENTIFYING COMMON CANNABIS TERPENES

TERPENE:	ALPHA-PINENE BETA-PINENE	MYRCENE	LIMONENE	ACARYOPHY-LLENE	LINALOOL
					
	PINE	MUSKY, EARTHY, CITRUS HINTS	CITRUS	SPICY, WOODY, PEPPERY, CLOVE	FLORAL, CANDY, CITRUS
	FOUND IN: Pine, Dill, Parsley, Basil, Rosemary	FOUND IN: Mango, Thyme, Lemongrass, Hops	FOUND IN: Juniper, Rosemary, Fruit Rinds, Peppermint,	FOUND IN: Black Pepper, Clove, Cotton	FOUND IN: Lavender
	Alertness, Euphoria, Creativity, Memory Retention	"Couchlock", Sedation, Relaxation, Body High	Elevated Mood, Stress Relief	No noted effects	Anxiety Releif, Sedation
	Asthma, Antiseptic	Antioxidant, Pain, Muscle Tension, Sleeplessness, Anti-Carcinogenic	Gallstones, Gastroprotective, Heartburn, Anti-fungal, Depression	Gastroprotective, Anti-inflammitory, Arthritis, Ulcers	Anti-anxiety, Anti-convulsant, Anti-depressant, Anti-acne
	Jack Herer, Trainwreck, Bubba Kush, Chem Dawg, Super Silver Haze	Pure Kush, El Nino, Himalayan Gold, Skunk #1, White Widow	OG Kush, Super Lemon Haze, Jack the Ripper, Lemon Skunk	Big Bang, Damn Sour, Great White Shark, Ice Dream	G-13, Lavender, Amnesia Haze, LA Confidential

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PHYSICIAN'S ROLE

- OBJECTIVE, GOALS
- EDUCATE; PATIENT ADVOCATE
- TAILOR/INDIVIDUALIZE
  - Strain, dose, delivery system (not smoked)
  - previous history, mood
- MONITOR

CANNABINOID	BENEFIT
THC ■ Tetrahydrocannabinol THCA	Psychotropic, painkiller, anti-inflammatory, anti-microbial
CBD ■ Cannabidiol CBDA	Relieve anxiety, convulsions, depression, inflammation and nausea sedative, sleep aid and muscle relaxant
CBC ■ Cannabichomene CBCA	Anti-inflammatory, painkiller, treats acid reflux, anti-anxiety,antidepressant
CBG ■ Cannabigerol CBGA	Painkiller, muscle relaxant, anti-erythemic analgesic, digestive aid, stomachic (stomach function)
CBN ■ Cannabichromene CBNA	Mild psychotropic, may stimulate bone growth, anesthetic, anti-convulsive, analgesic, anti-anxiety
THCV ■ Tetrahydracannabivarin THCVA	Anti-obesity, aids memory, calming aid, antibacterial, antiviral, immune system
CBDV ■ Cannabidivarin CBDVA	Anti-inflammatory, analgesic, protects cells lining digestive tract

Redefining Paradigm/Challenges

- Do not relinquish, list of 10, standardization
- Educate- Dr. > budtender, med school
- Stigma, Time, Cost
- Visit dispensaries
- HIPAA- name
- "Recommend"
- CI: Pregnant, Active psychosis

5 U.S. Cannabis Patents

U.S. Patent #20160074357

This U.S. patent relates to the use of tetrahydrocannabivarin (THCV) in the treatment of nausea and vomiting.

U.S. Patent #6630507

This U.S. patent relates to the use of cannabinoids as antioxidants and neuroprotectants .

U.S. Patent #6,448,288

This U.S. patent relates to the use of cannabinoid compounds for inhibiting, inducing apoptosis, antitumoral actions.

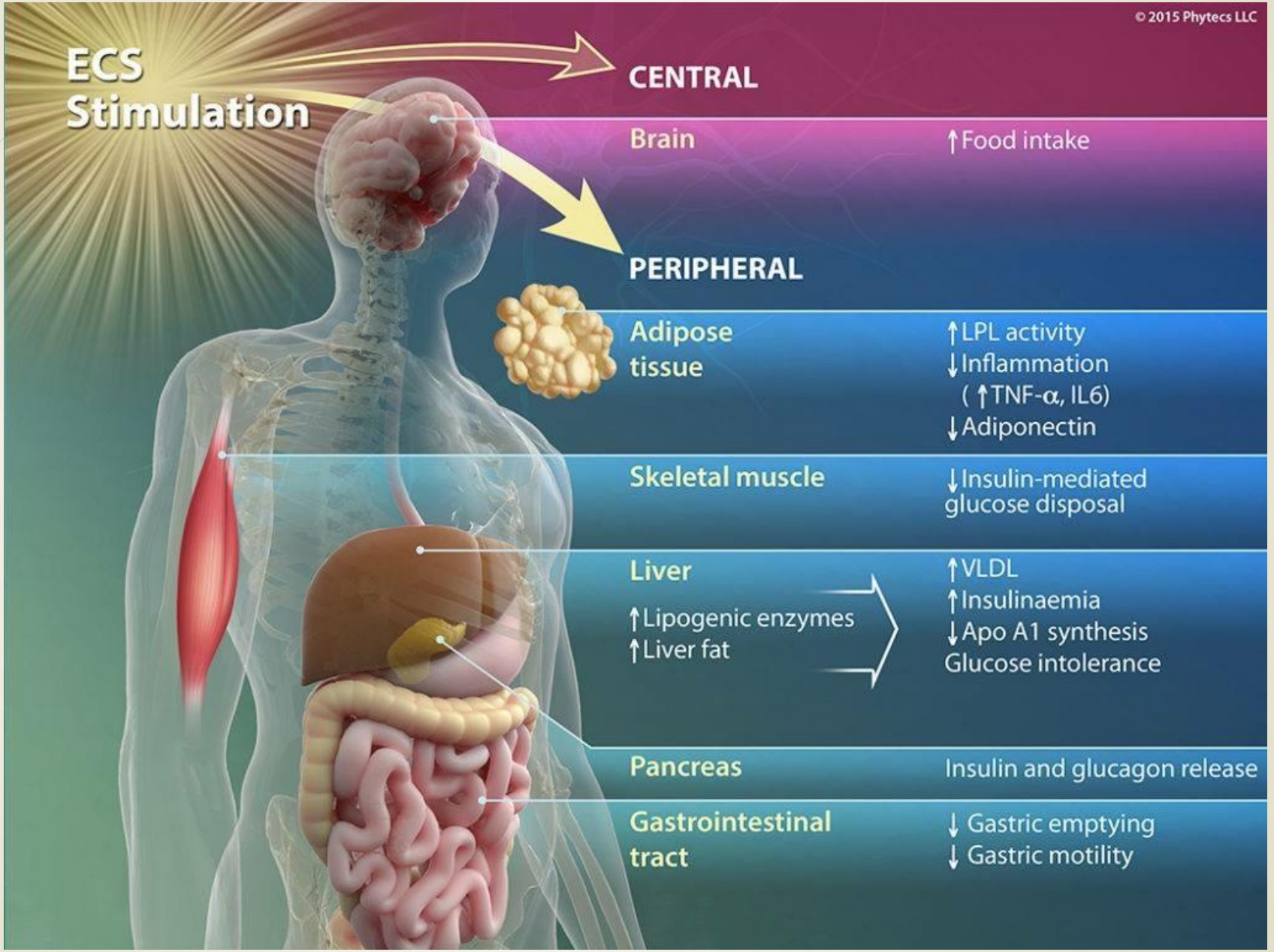
U.S. Patent #4,876,276

This patent relates to special use of cannabinoid compounds in cases of acute, and chronic pain.

U.S. Patent #7,179,800

Relates to the usefulness of cannabinoids for therapy, especially in the treatment of pain, inflammation and autoimmune disease.

www.scannabis.webs.com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ECS Stimulation
CENTRAL
Brain
↑Food intake
PERIPHERAL
Adipose tissue
↑LPL activity
↓Inflammation
(↑TNF-α, IL6)
↓Adiponectin
Skeletal muscle
↓Insulin-mediated glucose disposal
Liver
↑Lipogenic enzymes
↑Liver fat
↑VLDL
↑Insulinaemia
↓Apo A1 synthesis
Glucose intolerance
Pancreas
Insulin and glucagon release
Gastrointestinal tract
↓ Gastric emptying
↓ Gastric motility

Neurogenesis

- CBD promote brain growth in hippocampus (mice), The International Journal of Neuropsychopharmacology
- CBD neuroprotectant- protects NS from
  - oxidative stress
  - potassium and ATP loss associated with stroke
  - neurotoxin damage associated with Parkinson's
- Floods the ECS, body response is to make more CB receptors
  - Neurodegenerative disease and TBI, athletes
- THC inhibits enzyme responsible for aggregation of amyloid plaque, Neuroprotective
- Nature Medicine, U of Bonn and Hebrew University- rejuvenate cognitive function in older brains (maze)
  - Alzheimer's

PTSD

- Loneliness→ chronic stress reduces the production of endocannabinoids, which affect our cognition, emotion and behavior, and have been linked to feelings of pain and anxiety, increases in appetite and overall feelings of well-being.
- PTSD- normal CB-1 receptor signaling deactivates traumatic memories and allows us to forget
  - Memory, Acetylcholine
- Low levels of anandamide or skewed CB1 signaling Results in impaired fear extinction, aversive memory consolidation, and chronic anxiety, hallmarks of PTSD
- Depression- THC blocks GABA, increase in dopamine; CBD increases serotonin
- Benefit- Heightened Imagination, Increased Creativity

Other Neurodegenerative Disease

- Oxidative stress is another pathogenesis of AD. Cannabidiol (CBD) reduces
  - nitric oxide synthase, suppressing inflammation
  - lipid peroxidation and affects tau phosphorylation involved in progression of AD
- CBD may be the preference when treating neurodegenerative diseases
- Normalizing calcium homeostasis as well as inhibiting glutamate with cannabinoids also inhibit excitotoxicity can act as a neuroprotectant in AD.
- "Delusions, agitation, aggression, irritability, apathy, sleep and caregiver distress, were decreased with THC was added in an attempt to relieve symptoms of dementia in a recent 2016 Israeli study.

Parkinson's Disease (PD)

- *Clinical Neuropharmacology*, using smoked medical cannabis had significant
  - improvements in motor disability and impairment
  - decreases in tremor (repetitive shaking), rigidity (stiffness or inflexibility), and dyskinesia (difficulty in performing voluntary movements),
  - improvements in pain and sleep disturbance
- *Journal of Psychopharmacology* in Sept 2014 found treatment with 300 mg/day of CBD in PD, without dementia or comorbid psychiatric conditions, increased well-being and quality of life
- *Journal of Neurology, Neurosurgery and Psychiatry* in 2013, TH

  useful in the treatment of PD by
  - assisting in the prevention of damage caused by free radicals
    - antioxidant, neuroprotectant