Clinical Evidence of Marijuana Use

Jeremy Daniel, PharmD, BCPS, BCPP
Associate Professor, SDSU College of Pharmacy and Allied Health Professions
Adjunct Clinical Associate Professor, USD Sanford School of Medicine
Clinical Pharmacist, Avera Behavioral Health Center
President, South Dakota Society of Health-System Pharmacists
May 26, 2021

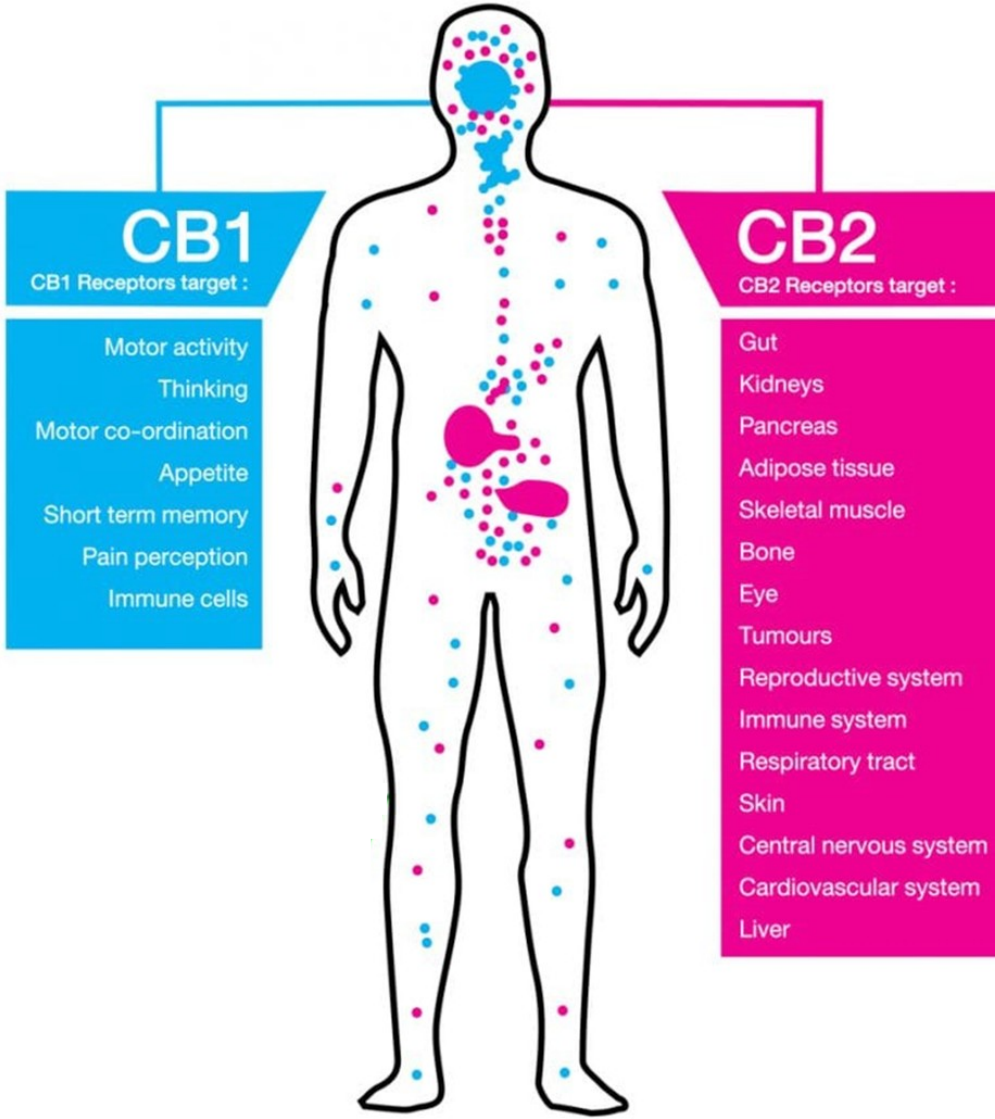
Disclosure

- This speaker has no conflicts of interest or commercial financial relationships with the information presented today

- Here as private citizen. The information presented is not a reflection of the views of
  - SDSU
  - USD
  - The State of South Dakota Board of Regents
  - Avera Health
  - SDSHP
  - SDPhA

Endocannabinoid System

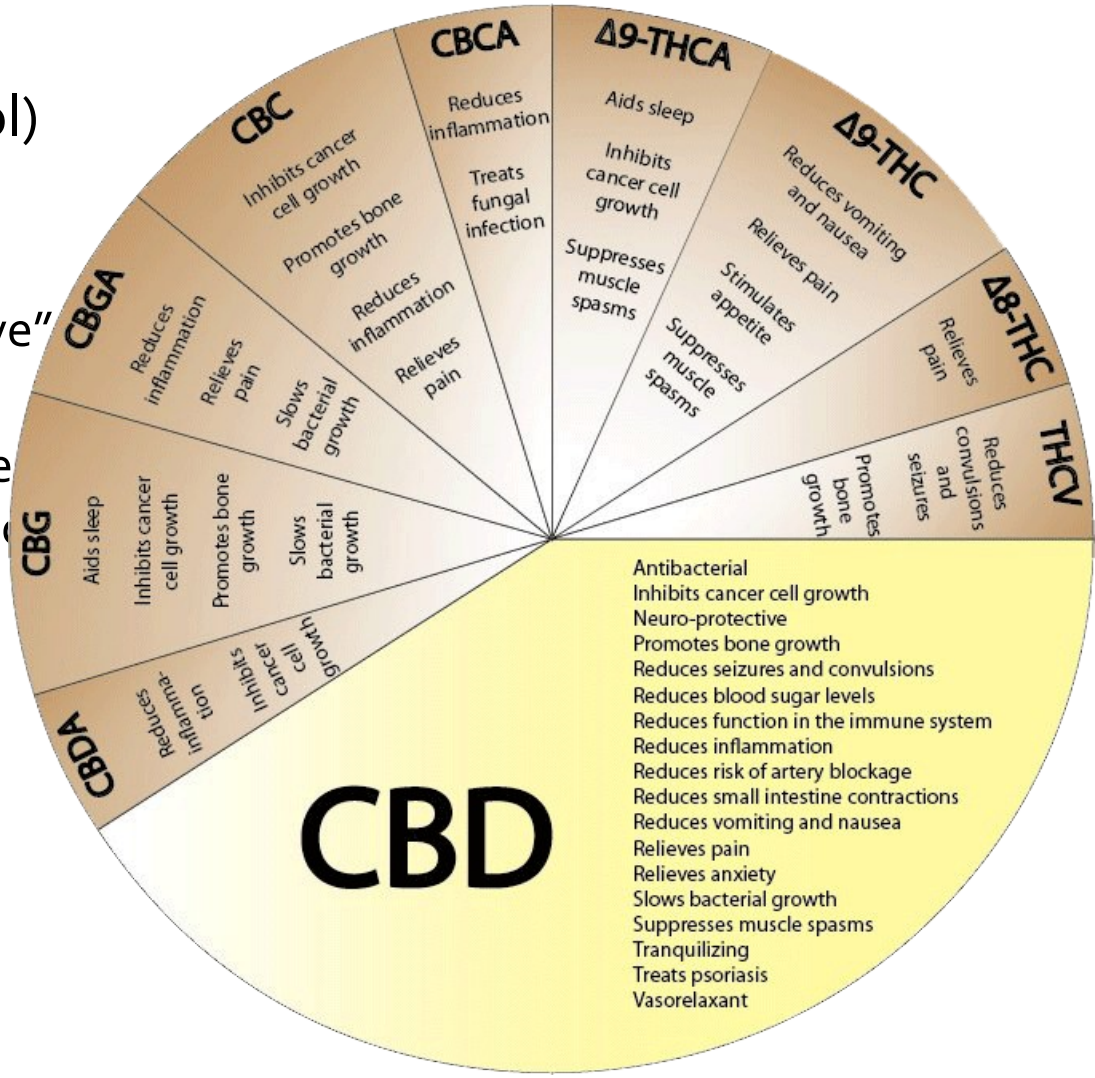
- CB1 receptor
  - Primarily in brain
  - Memory, processing, movement, pain
- CB2 receptor
  - Primarily in other organs and cells
  - Modulates inflammation and immune cell functions



Atakan Z, Ther Adv Psychopharmacology, 2012

Marijuana Composition

- THC (tetrahydrocannabinol)
  - Most common molecule in cannabis
  - Responsible for "psychoactive" effects
  - Triggers release of dopamine (happy and addictive chemi
- CBD (cannabidiol)
  - Second most common molecule in cannabis
  - Lessens effects of THC
  - Medical benefit



Atakan Z, Ther Adv Psychopharmacology, 2012

Marijuana Plants

- Majority of marijuana on market is from two plants
  - Cannabis sativa
    - THC content ~23.7%
    - CBD content ~0.1%
  - Cannabis indica
    - THC content ~19.6%
    - CBD content ~0.2%
- Percentages have shifted with genetic engineering of strains
  - Generally toward high THC

Erowid.org
Leafly.com

Marijuana Effects

- Intoxication
  - Altered senses
  - Dissociation
  - Mood swings
  - Movement impairment
  - Challenges problem solving
  - Memory impairment
  - Fast heart rate
  - Hallucinations/psychosis (high dose)
  - Delusions (high dose)
- Withdrawal
  - Uncommon except with chronic use
  - Can last up to 2-4 days
    - 6 weeks in long term use
  - Lack of interest
  - Cyclic vomiting
  - Headaches/pain/stiffness
  - Cravings
  - Appetite suppression
  - Fatigue/lethargy
  - Impatience/annoyance
  - Residual hallucinations (high dose)

NIDA Marijuana Fact Sheet

How Do You Use It?

- Smoking/vaping
  - Most common method
  - Onset of high = seconds/minutes
  - Peak effects ~ 30 minutes
  - "Come down" ~ 1-3 hours
  - Specific effects depend on temperature or vape
- Dabbing
  - Flash vaporization of hash oils
  - Similar pharmacokinetics of smoking/vaping above
  - Increased effects due to elevated THC content of oils
- Edibles
  - All kinetics delayed
  - Onset of high = 30-120 minutes
  - Peak effects ~ 2-4 hours
  - "Come down" ~ 5-8 hours
  - Significant differences in amount entering blood stream (20-40%)
- Topical products?
  - Does not enter bloodstream
  - May target CB receptors in skin
  - Most benefit appears to be from application

Erowid.org
Atakan Z, Ther Adv Psychopharmacology, 2012

FDA Approved Products

- Cannabidiol (Epidiolex®)
  - Treatment of seizures associated with
    - Lennox-Gastaut Syndrome (LGS)
    - Dravet Syndrome (DS)
    - Tuberous Sclerosis Complex (TSC)
- Dronabinol (Marinol®, Syndros®)
  - Anorexia associated with Acquired Immune Deficiency Syndrome (AIDS)
  - Nausea/vomiting associated with cancer chemotherapy, treatment failure
- Nabilone (Cesamet®)
  - Nausea/vomiting associated with cancer chemotherapy, treatment failure

Epidiolex. Package inert. Greenwich Biosxiences, Inc. 2020
Marinol. Package insert. ThePharmaNetwork, LLC. 2019
Syndros. Package insert. Benuvia Therapeutics, Inc. 2021
Cesamet. Package insert. Bausch Health US LLC. 2020

Symptoms Discussed

- Nausea/vomiting
- Appetite stimulation
- Glaucoma
- Epilepsy
- Pain management
- Anxiety/PTSD

Nausea/vomiting

- Three clinical trials in chemotherapy patients
  - No antiemetic effect, pts receiving chemotherapy after dronabinol failure
  - Significant antiemetic effect after high-dose methotrexate
  - Another small study had benefit from both oral and smoked THC
- No direct comparison with newer medications we use regularly
- ASCO 2017 antiemetic guidelines
  - "Evidence remains insufficient to recommend for prevention or treatment"
- Evidence of benefit – **LOW**

Chang AE et al, Cancer, 1981
Chang AE et al, Ann Intern Met, 1979
Musty RE et al, Journal of Cannabis Therapeutics, 2001
Duran M et al, Br J Clin Pharmacol, 2010
Hesketh PJ et al, J Clin Oncol, 2017

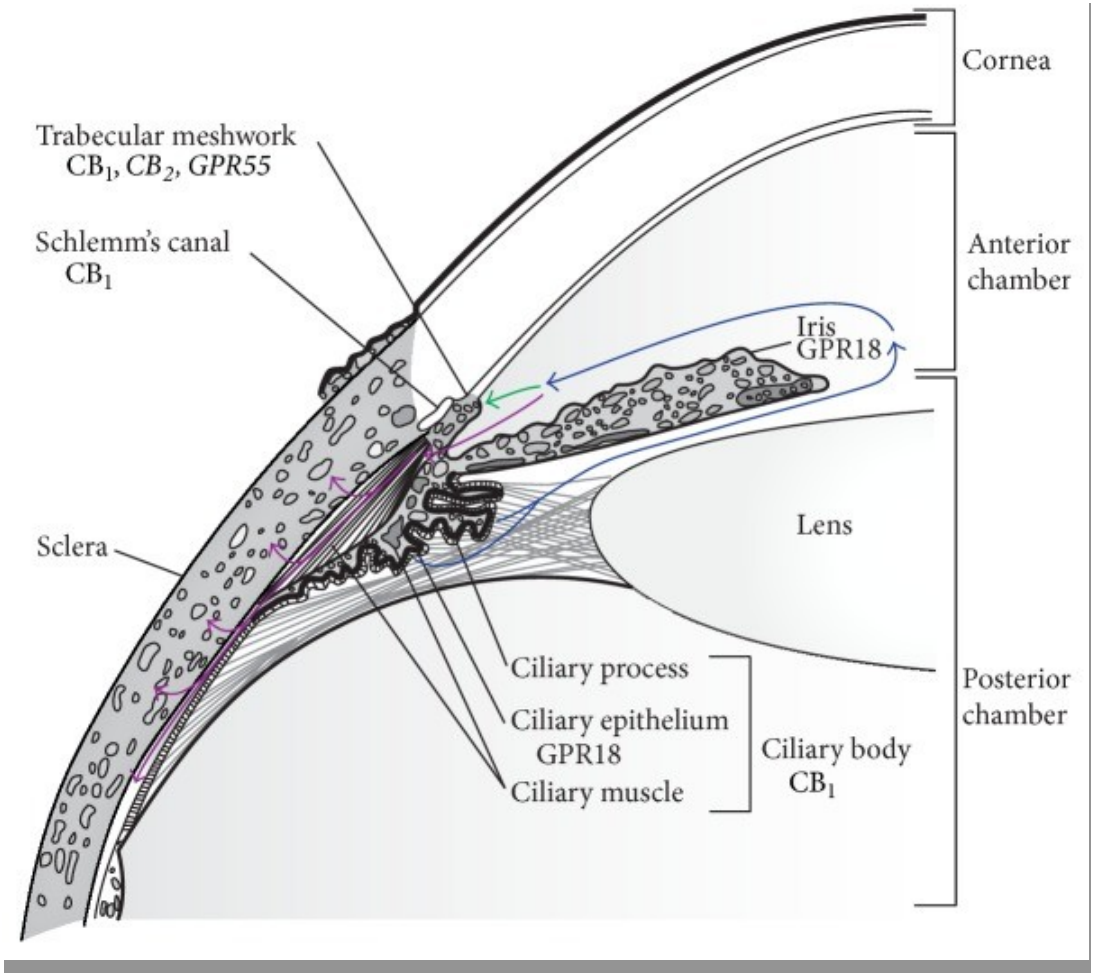
Appetite Stimulation

- Four trials related to oral THC
  - Three studies found improvements in hunger outcomes
  - One active control study (dronabinol vs megestrol vs both)
    - Appetite increased 75%, weight increased 11% in megestrol group
    - Appetite increased 49%, weight increased 3% in dronabinol group
    - Combined group was similar to monotherapy megestrol
- Cannabis led to increased in calorie intake in 1980s studies
- One 2006 study demonstrated no benefit of oral cannabis
- No published studies of inhaled cannabis on appetite
- Evidence of benefit – **LOW/MODERATE**

Brisbois TD et al, Ann Oncol, 2011
Jatoi A et al, J Clin Oncol, 2002
Turcott JG et al, Support Care Cancer, 2018
Foltin RW et al, Pharmacol Biochem Behav, 1986
Foltin RW et al, Appetite, 1988
Strasser F et al, J Clin Oncol, 2006
Regelson W et al, The Pharmacology of Marihuana, 1976

Glaucoma

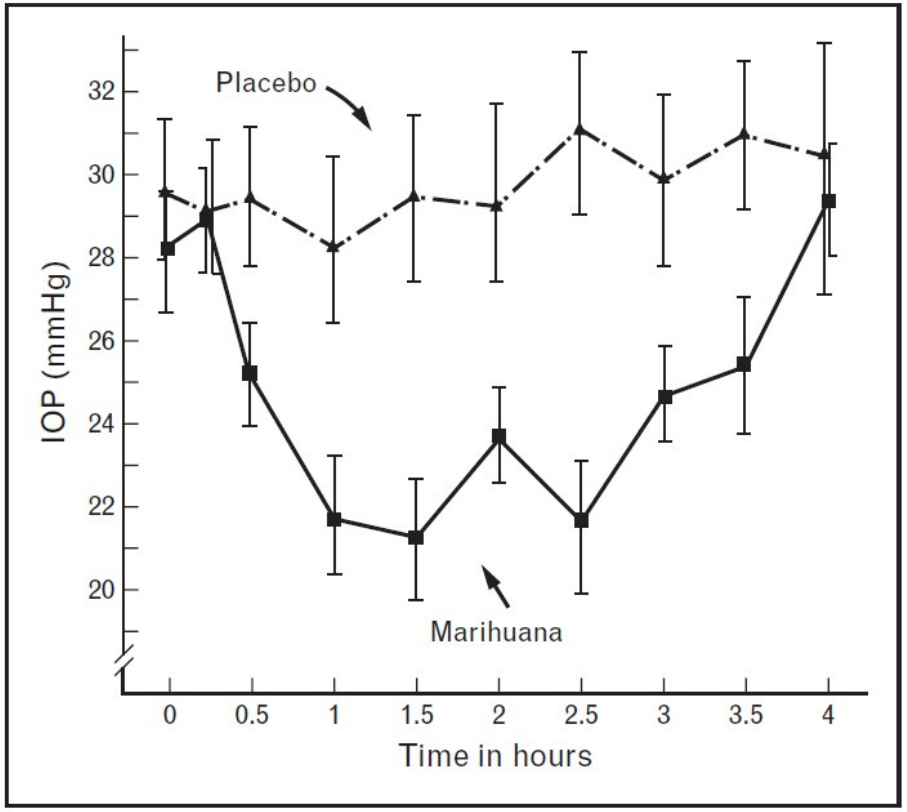
- How does it work?
  - Decreases pressure in the eye
  - Increases outflow of fluid



Cairns EA et al. Neural Plasticity. 2016

Glaucoma, cont.

- Decrease average pressure from 28 mmHg to 22 mmHg
  - Normal pressure 8-21 mmHg
  - Note: did not hit normal level
- Duration of effect ~3.5 hours
  - 6-8 times per day dosing
- Adverse effects
  - Fast heart rate
  - Dizziness upon standing
  - Possible mental health effects
- Evidence for the benefit - **LOW**



Novack GD, Curr Opin Opthalmol, 2016
Merritt JC, Opthalmology, 1980

Epilepsy

- Open-label treatment-resistant trial (failed multiple drugs)
  - 214 patients with child-hood onset
  - Decrease in seizures by 36.5% per month
- 2016 Studies
  - Open-label study where 49% on CBD has ≥50% improvement in seizure control
  - Second study of 81 patients (39 adults) showed durable effect
- Tuberous sclerosis complex (TSC)
  - 1-7 anti-epileptic drugs at baseline
  - Median reduction in weekly seizure frequency was 48.8%

Devinsky O et al. Lancet Neurology. 2016
Szaflarski JP et al. AES 70th annual meeting abstract: 2016
Hess EJ et al. Epilepsia. 2016

Epilepsy, cont.

- Febrile Infection-Related Epilepsy Syndrome (FIRES)
  - 6 of 7 patients in a case series had improvement of seizure frequency and duration
- Remember – FDA approved product exists (Epidiolex®)
- Evidence for benefit:
  - CBD – **HIGH**
  - Whole plant – **LOW/MODERATE**

Gofshteyn JS et al. Journal of Child Neurology. 2017
Devinsky O et al, N Engl J Med, 2018
Thiele EA et al, Lancet, 2018
Lattanzi S et al. Epilepsia, 2020

Pain

- Two studies of THC
  - One study of 15-20mg of THC demonstrate pain relief
  - One study showed 10mg THC = 60mg codeine
- Nabiximols (THC:CBD, Sativex®, not in US) extract vs THC alone studied
  - Combination treatment provided pain relief
  - 1-10 sprays per day showed benefit in opioid-treated chronic pain patients
- Nabilone patients experienced improvement in pain, anorexia, depression and anxiety
  - Decreased opioid, NSAIDs, and other medication requirements

Calignano A et al, Nature, 1998
Fields HL et al, Nat Med, 1998
Noyes R et al, J Clin Pharmacol, 1975
Noyes R et al, Clin Pharmacol Ther, 1975
Portenoy RK et al, J Pain, 2012
Maida V et al, J Support Oncol, 2008

Pain, cont.

- Doses hard to quantify for cannabis plant
- Study from 2011 showed added benefit with morphine
  - Average pain score lower at day 5
- Two trials with inhaled cannabis and neuropathy
  - Pain scores significantly reduced
  - Also shown with HIV-induced neuropathy
- Nabiximols also tried with nerve pain
  - No difference between placebo and treatment
- Evidence for benefit - **HIGH**

Abrams DI et al, Clin Pharmacol Ther, 2011
Wilsey B et al, J Pain, 2013
Winsey et al, J Pain, 2008
Andreae MH et al, Data J Pain, 2015
Lynch ME et al, J Pain Symptom Manage, 2014

PTSD

- 2015 study examined efficacy from 46 published articles
  - Suggested overall decrease in PTSD symptoms
- 2 studies of nabilone
  - Nightmares decreased in 72% of patients
  - Reduced nightmare in 10 treatment-resistant military patients
- THC- open-label, 10 patients on THC
  - Symptom severity improvement
  - Better sleep quality
  - Decreased nightmares
- Note: studies presented here are short-term use

Mizrachi zer-aviv T et al. Behavioral Pharmacology. 2016
Jetly R et al. Psychoneuroendocrinology. 2015
Yarnell S, Prim Care Companion CNS Disord, 2015

PTSD, cont.

- When we look at longer term studies…
- Study of 2276 Veterans with PTSD
  - Cannabis use was associated with
    - More severe symptoms
    - More violent behavior
    - More alcohol/drug use
  - Stoppers and never users had lowest scores
- 432 Veteran study
  - Cannabis use resulted in less change in PTSD scores 4 months after treatment
- Evidence for benefit:
  - Short term, as needed use – **MODERATE/HIGH**
  - Daily/chronic use – **LOW (may cause harm)**

Haney M et al, Neuropsychopharmacology, 2016
Bonn-Miller MO et al, Psychol Addict Behav, 2011

Key Take-Aways

- There are many different components to marijuana
  - Research targets whole plant, specific cannabinoids, etc.
- Important to identify intoxication/withdrawal effects
- Evidence for use varies greatly
  - Disease state
  - What's researched (see previous slides)
  - Definition of outcome
  - Can find pro/con articles for most everything

Questions?

Jeremy Daniel, PharmD, BCPS, BCPP
Associate Professor, SDSU College of Pharmacy and Allied Health Professions
Adjunct Clinical Associate Professor, USD Sanford School of Medicine
Clinical Pharmacist, Avera Behavioral Health Center
President, South Dakota Society of Health-Systems Pharmacists
May 26, 2021