Benefits and Risks of Cannabis in Cancer Symptom Management

Brant Hager, MD

Associate Professor of Psychiatry

University of New Mexico

Disclosure

- No conflicts of interest to disclose

Learning Objectives

By the end of this talk, I hope you can:

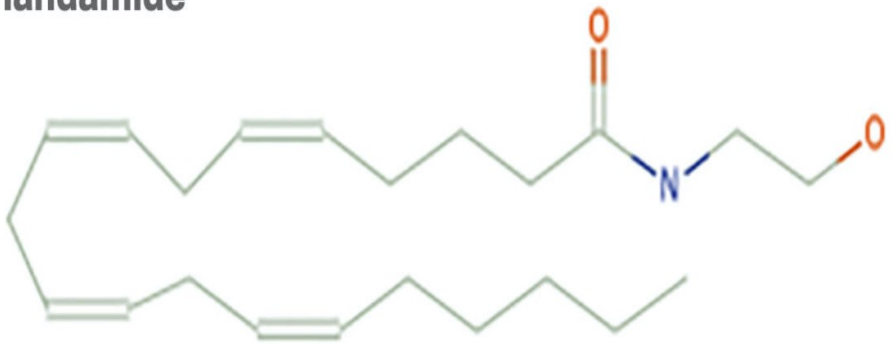
- Appreciate the body's natural cannabinoid system
- Understand some of the active components of cannabis and how they may work
- Describe the potential role of cannabinoids in cancer therapeutics

Points of Departure

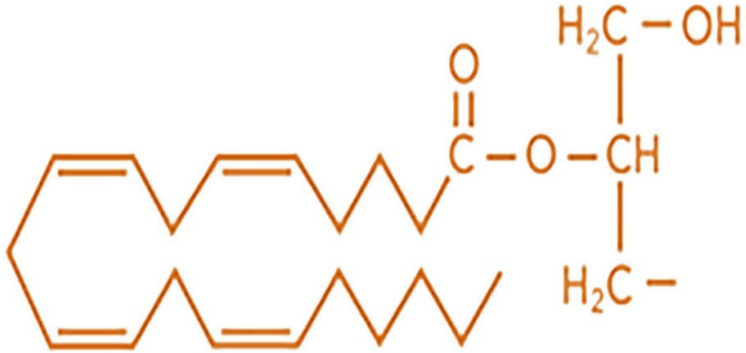
- A lot of cannabis-related literature focuses on its risks as a recreational or use disorder substance
- Some cannabis-related literature focuses on its therapeutic uses
- Similarities and differences remain unclear between people who use cannabis recreationally vs. medically
- Most studies of therapeutic uses of cannabis utilize pharmaceutically prepared cannabinoids
- Cannabinoid content of medical cannabis preparations differs from that of researched preparations
- Cannabinoids other than THC and CBD remain underrepresented in therapeutic literature
- Terpenes remain underrepresented in therapeutic literature

Our Bodies Have a Natural Cannabinoid System

Anandamide



2-Arachidonoylglycerol (2-AG)



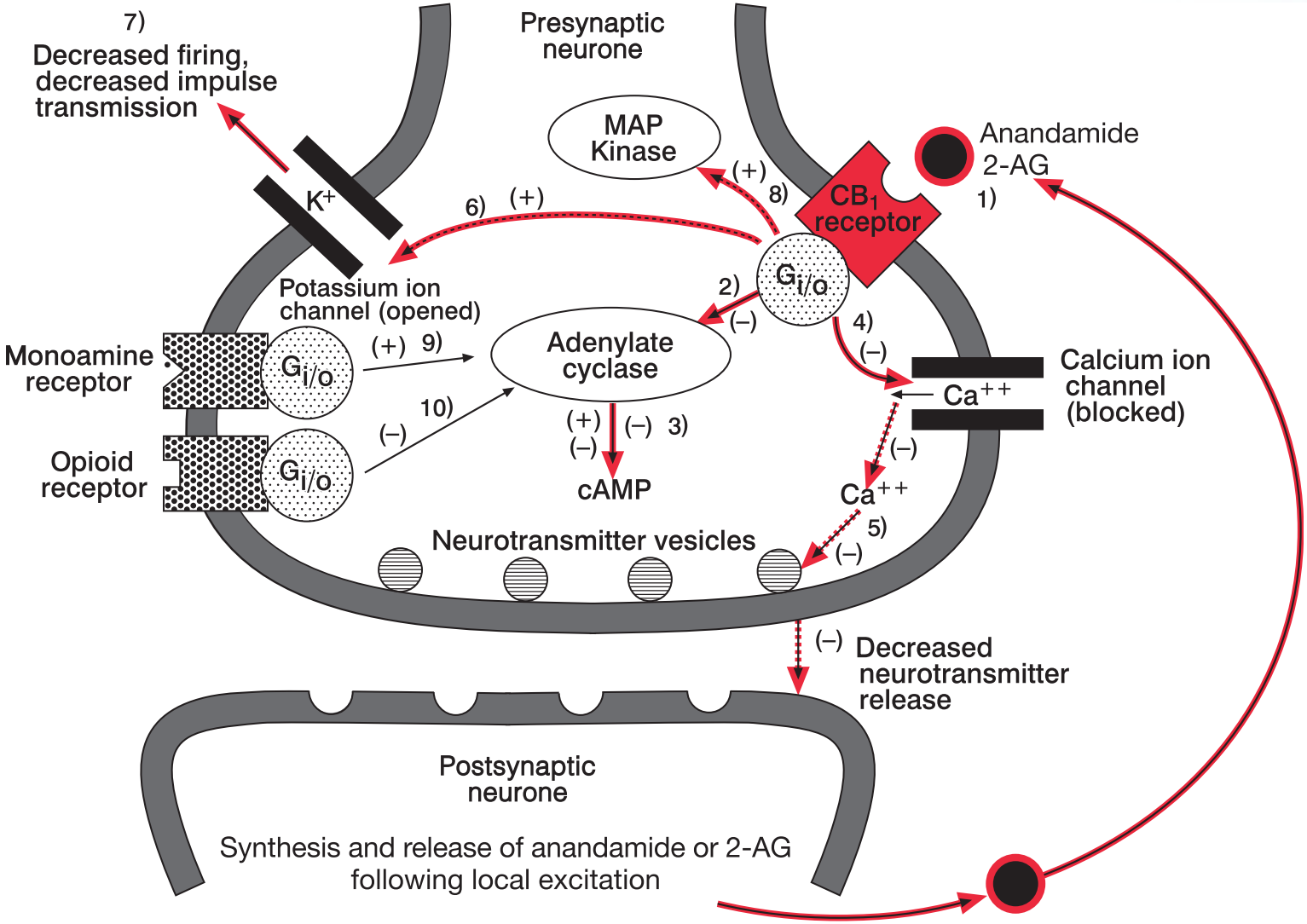
https://curepharmaceutical.com/blog/the-role-of-the-endocannabinoid-system-in-the-human-body/

Our Bodies Have a Natural Cannabinoid System

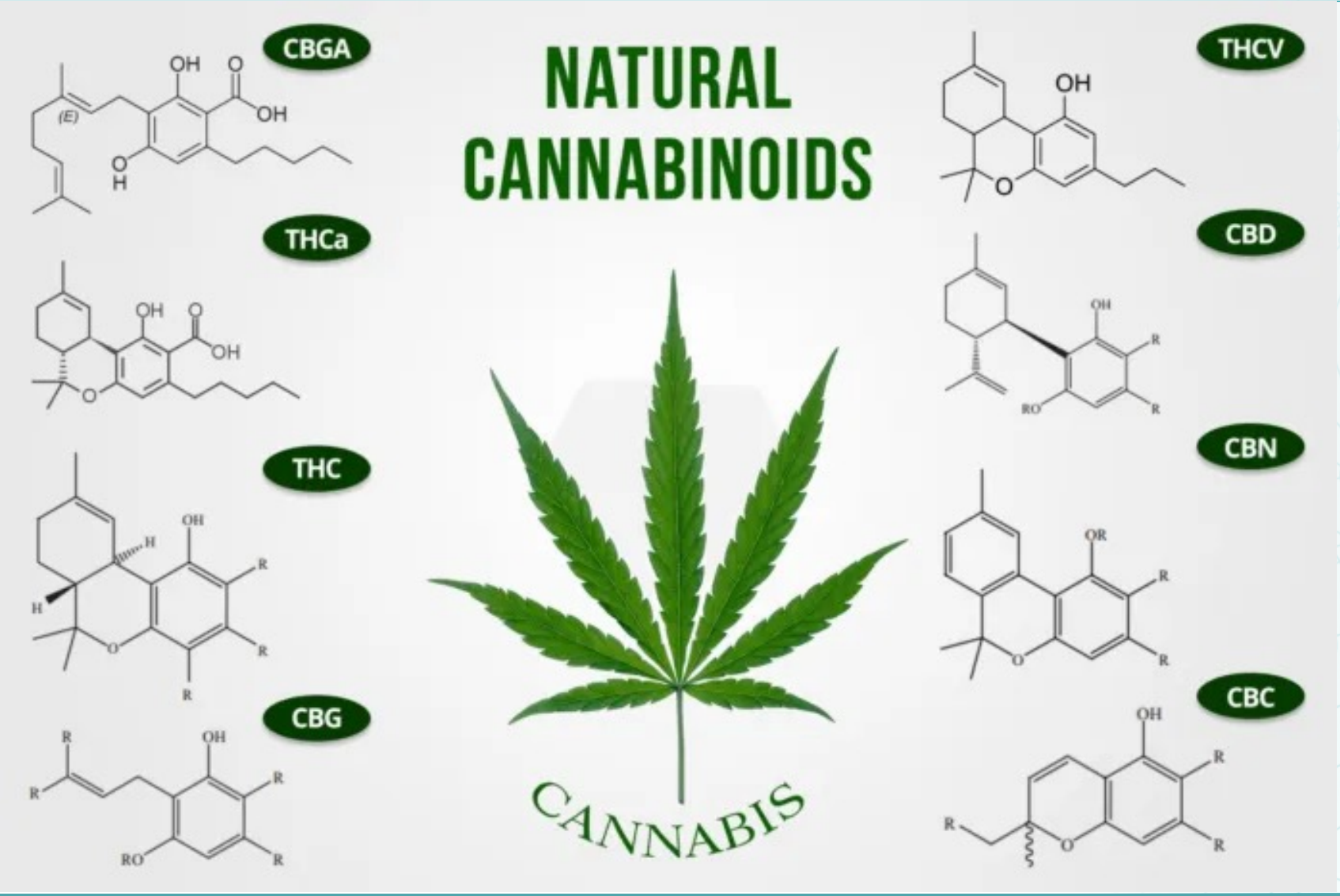
- Cannabinoid-1 (CB1) Receptor
  - Found in brain, spinal cord, nerves, fat, liver, pancreas, muscle
  - Stimulated by anandamide and 2AG
- Cannabinoid-2 (CB2) Receptor
  - Found on immune cells (also in brain and spinal cord, but role unclear)
  - Stimulated by anandamide and 2AG
- TRPV Receptor
  - Found on pain sensing nerves
  - Stimulated by smaller amounts of anandamide
  - Inhibited by larger amounts of anandamide

Ashton 2015, Piomelli 2015, Palazzo 2010

Our Body's Natural Cannabinoid System Helps Balance Nerve Function



Cannabis is Not a Single Drug



https://www.encore-labs.com/cannabinoids-beyond-thc-and-cbd

Cannabis is Not a Single Drug

https://www.northislandgazette.com/columns/cannabis-corner-terpenes-demystified/

Different Cannabinoids Have Different Effects

- THC
  - Partially stimulates CB1 and CB2
  - Has intoxicating effects
- CBD
  - Blocks CB1 / CB2 stimulators
  - Increases anandamide
  - Stimulates serotonin 1 receptors
  - No known intoxicating effects
- Other Cannabinoids
  - No known intoxicating effects
- Terpenes
  - Various effects, some activating, some sedating

Piomelli 2015, Bih 2015, Devinsky 2014, Russo 2011

Cannabinoids Have Potential Benefits

- THC or THC-CBD mixtures have evidence for treating
  - Chronic pain
  - Chemotherapy related nausea and vomiting
  - Multiple sclerosis related spasticity
- CBD has evidence for treating schizophrenia
  - CBD being studied as potential treatment for bipolar depression
- Small doses of THC may have cognitive benefits in bipolar
- Cannabis effects on PTSD are unclear
  - Small dose THC at night may help with PTSD sleep disturbance
  - Small trial of smoked cannabis in PTSD showed no difference between active and placebo cannabis
  - Cannabis use may be associated with worsened course of PTSD

Whiting 2015, LaFrance 2020

Cannabinoids Have Potential Benefits

- THC Potential Positives
  - Euphoria
  - Calmness
  - Appetite increase
  - Sociability increase
  - Time perception alteration
  - Color perception heightened

Cannabinoids Have Potential Harms

- THC Potential Negatives
  - Impairment of cognition, judgement, motor coordination
  - Panic
  - Paranoia, hallucinations
  - Red eyes, dry mouth, tachycardia
  - Cannabis withdrawal
    - Irritability, anger, aggression
    - Nervousness, anxiety
    - Insomnia, disturbed dreams
    - Appetite decrease
    - Restlessness
    - Depressed mood
    - Abdominal pain, tremors, sweating, fevers, chills, headache
- THC and CBD may interact with other medicines

Recreational Cannabis Use Has Potential Harms

- 9% of first-time recreational cannabis users go on to develop cannabis use disorder
- Recreational cannabis use at baseline associated with increased risk of developing
  - Alcohol use disorder 2-5x risk
  - Tobacco use disorder 2x risk
  - Opioid use disorder 2x risk
  - Major depressive disorder 2x risk
  - Bipolar disorder 3x risk
  - Schizophrenia 2-3x risk

SAMHSA 2017, Lopez-Quintero 2011, Stinson 2006, Gorelick 2021

Recreational Cannabis Use Has Potential Harms

- Lower birth weight in offspring
- Increased attention and behavioral problems in offspring
- Poorer cognitive, academic, vocational outcomes
- 2x increased risk MVA
- Increased risk heart attack around time of smoking
- Increased risk stroke around time of smoking
- Exacerbation of schizophrenia, bipolar disorder, depression
- 2-5 x increased risk suicide

Hall 2015; Wilkinson 2015; National Academies of Sciences 2017

Pharmaceutical THC Has Potential Harms

Individual AEs		
Dizziness	41 (4243)	5.09 (4.10-6.32)
Dry mouth	36 (4181)	3.50 (2.58-4.75)
Nausea	30 (3579)	2.08 (1.63-2.65)
Fatigue	20 (2717)	2.00 (1.54-2.62)
Somnolence	26 (3168)	2.83 (2.05-3.91)
Euphoria	27 (2420)	4.08 (2.18-7.64)
Depression	15 (2353)	1.32 (0.87-2.01)
Vomiting	17 (2191)	1.67 (1.13-2.47)
Diarrhea	17 (2077)	1.65 (1.04-2.62)
Disorientation	12 (1736)	5.41 (2.61-11.19)
Asthenia	15 (1717)	2.03 (1.35-3.06)
Drowsiness	18 (1272)	3.68 (2.24-6.01)
Anxiety	12 (1242)	1.98 (0.73-5.35)
Confusion	13 (1160)	4.03 (2.05-7.97)
Balance	6 (920)	2.62 (1.12-6.13)
Hallucination	10 (898)	2.19 (1.02-4.68)
Dyspnea	4 (375)	0.83 (0.26-2.63)
Paranoia	4 (492)	2.05 (0.42-10.10)
Psychosis	2 (37)	1.09 (0.07-16.35)
Seizures	2 (42)	0.91 (0.05-15.66)

Whiting 2015

Proposed Cautions for Medical Cannabis Use

- High sensitivity to adverse effects
- Cannabis use disorder
- Schizophrenia
- Bipolar disorder
- Suicidality
- Use prior to full neurodevelopment
- Pregnancy
- PTSD
- Depression
- Non-cannabis substance use disorder
- High cardiovascular risk
- High cerebrovascular risk
- Chronic bronchitis (for smoked preparations)

Cannabis Use in Cancer Therapeutics

Symptom	Conclusion
Nausea and vomiting	There is evidence that cannabis or cannabis-derived products can alleviate chemotherapy-induced nausea and/or vomiting, and an inhalable form could be better for patients unable to retain oral medications. However, most data are from the 1980s, and cannabis has not been compared with modern anti-emetic regimens.
Anorexia and loss of appetite	Medical cannabis and THC specifically, have led to increased appetite in humans and laboratory animals, mostly in noncancer contexts thus far.
Pain	Research is promising for relieving pain acutely from various sources including cancer, perhaps even to reduce the dose of opiates. However, pain surfaces *via* many different mechanisms and it is not yet clear what contexts in which cannabis could have an analgesic effect.
Chemotherapy-induced peripheral neuropathy	Evidence is promising from studies in people with HIV, trauma/surgery, and diabetes as well as cancer-related animal models, but there is not yet evidence in humans with cancer.
Gastrointestinal distress	There are promising data from research in patients with inflammatory bowel disease, but none yet in patients with cancer. Diarrhea can also be a side effect of cannabis use.
Cognitive impairment	There have not been studies with cannabis for cancer-related cognitive problems. Recreational users and patients report acute complaints in memory, attention, and executive function, though long-term effects are unclear. Some studies suggest potential benefits, especially from cannabidiol.
Anxiety and depression	Most research to date is epidemiological and results are unclear.
Sleep disorders and fatigue	Very few studies have been conducted, but limited evidence suggests that cannabis is promising for alleviation of clinical sleep disorders (not yet in patients with cancer).
Cardiac, metabolic, and bone health toxicities	Too few studies have been conducted to make conclusions recommending or discouraging cannabis for these purposes.

Kleckner 2019

Do Cannabinoids Treat Cancer?

- In vitro and animal models demonstrate anti-cancer properties of several cannabinoids in several cancers
  - Increased cancer cell death
  - Increased cancer cell differentiation
  - Decreased cancer cell invasion
  - Decreased cancer cell vascular supply
  - Cancer cell cycle arrest
- Human clinical trials are early in their development
  - www.clinicaltrials.gov
- In contrast: heavy recreational cannabis associated with small increase in risk of testicular cancer

Abrams 2015

Summary

- Our body's natural cannabinoid system serves to maintain nerve balance and regulate immune function
- THC and CBD alter the body's natural cannabinoid system, resulting in both potential positive and negative effects
- Pharmaceutical THC, and to a lesser extent medical cannabis, have evidence for a variety of cancer-related therapeutic uses
- Anti-cancer effects of cannabis require human study
- Cannabinoid preparations, including medical cannabis, have benefits and risks, like any other medicine
- I encourage collaboration with your health care providers

References

- Abrams DI, Guzman M. Cannabis in cancer care. Clin Pharmacol Ther 2015;97(6):575-586
- Allen GM, Finley CR, Ton J, et al. Systematic review of systematic reviews for medical cannabinoids: pain, nausea and vomiting, spasticity, and harms. Canadian Family Physician 2018;64: e78-94
- American Psychiatric Association. Diagnostic and Statistical Manual, 5th Edition. 2013, Arlington
- Ashton CH, Moore PB. Endocannabinoid system dysfunction in mood and related disorders. Acta Psychiatr Scand 2011;124:250-261
- Bachhuber MA, Saloner B, Cunningham CO, et al. Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. JAMA Intern Med 2014;174:1668-1673
- Bih CI, Chen T, Nunn AVW, et al. Molecular targets of cannabidiol in neurological disorders. Neurotherapeutics 2015;12:699-730
- Blanco C, Hasin, D, Wall M, et al. Cannabis use and risk of psychiatric disorders: prospective evidence from a US national longitudinal study. JAMA Psychiatry 2016;73:388-395
- Broyd SJ, van Hell HH, Beale C, et al. Acute and Chronic Effects of Cannabinoids on Human Cognition – a systematic review. Biol Psychiatry 2016;79:557-567
- Devinsky O, Cilio MR, Cross H, et al. Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. Epilepsia 2014;55(6):791-802
- Enthover WTM, Roelofs PDDM, Dey RA, et al. Non-steroidal anti-inflammatory drugs for chronic low back pain. Cochrane Database Sys Rev 2016;2: DOI: 10.1002/14651858.CD012087.
- Duehmke RM, Derry S, Wiffen PJ, et al. Tramadol for neuropathic pain in adults. Cochrane Database Syst Rev 2017;6: DOI: 10.1002/14651858.CD003726.pub4.
- Epstein DH, Preston KL. No evidence for reduction of opioid-withdrawal symptoms by cannabis smoking during a methadone dose taper. Am J Addiction 2015;24:323-328

References

- Franklyn AM, Eibl JK, Gauthier GJ, et al. The impact of cannabis use on patients enrolled in opioid agonist therapy in Ontario, Canada. PLoS ONE 2017;12: e0187633
- Fusar-Poli P, Crippa JA, Bhattacharyya S, et al. Distinct effects of delta-9-tetrahydrocannabinol and cannabidiol on neural activation during emotional processing. rch Gen Psychiatry 2009;66(1):95-105
- Gorelick DA. Cannabis use disorder: epidemiology, comorbidity, health consequences and medico-legal status. UpToDate, accessed 3/21/2021
- Hall W. What has research over the past two decades revealed about the adverse health effects of recreational cannabis use? Addiction 2014;110:19-35
- Huhn M, Tardy M, Spineli LM, et al. Efficacy of pharmacotherapy and psychotherapy for adult psychiatric disorders: a systematic review and meta-analysis. JAMA Psychiatry 2014;71(6):706-715
- Kho KH, van Vreeswijk MF, Simpson S, et al. A meta-analysis of electroconvulsive therapy efficacy in depression. J ECT 2003;19(3):139-147
- Kleckner A, Kleckner IR, Kamen CS, et al. Opportunities for cannabis in supportive care in cancer. Ther Adv Med Oncol 2019; doi: 10.1177/1758835919866362
- Leucht S, Hierl S, Kissling W, et al. Putting the efficacy of psychiatric and general medicine medication into perspective: review of meta-analyses. BJP 2012;200:97-106
- Lopez-Quintero C, Perez de low Cobos J, Hasin DS, et al. Probability and predictors of transition from from first use to dependence on nicotine, alcohol, cannabis, and cocaine: results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). Drug Alcohol Dep 2011;115:120-130
- Lorenzetti V, Solowij N, Yucel M. The role of cannabinoids in neuroanatomic alterations in cannabis users. Biol Psychiatry 2017;79:e17-e31
- Lunn MPT, Hughes RAC, Wiffen PJ. Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. Cochrane Database Syst Rev 2014;1: DOI: 10.1002/14651858.CD007115.pub3.

References

- National Academies of Sciences, Engineering, and Medicine. The health effects of cannabis and cannabinoids: the current state of evidence and recommendations for research. 2017, Washington, DC
- Nielsen S, Sabioni P, Trigo JM, et al. Opioid-sparing effect of cannabinoids: a systematic review and meta-analysis. Neuropsychopharmacology 2017;42:1752-1765
- Nugent SM, Morasco BJ, O,Neil ME, et al, The effects of cannabis among adults with chronic pain and an overview of general harms.: a systematic review. Ann Intern Med 2017;167:319-331
- Olfson M, Wall M, Liu SM, et al. Cannabis use and risk of prescription opioid use disorder in the United States.
- Palazzo E, Luongo L, Novellis V, et al. The role of cannabinoid receptors in the descending modulation of pain. Pharmaceuticals 2010;3:225-2673
- Piomelli D. Neurobiology of Marijuana, in Galanter M, Kleber HD, Brady KT. The American Psychiatric Publishing Textbook of Substance Abuse Treatment, 2015 American Psychiatric Association, Arlington, VA
- Piomelli D, Weiss S, Boyd G, et al. Cannabis and the opioid crisis. Cannabis and Cannabinoid Research 2018;3.1: http://online.liebertpub.com/doi/10.1089/can.2018.29011.rtl
- Richardson JD. Cannabinoids modulate pain by multiple mechanisms of action. J Pain 2000;1:2-14
- Russo E. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. Br J Pharmacol 2011;163:1344-1364

References

- SAMHSA. Results from the 2016 survey on drug use and health: detailed tables. Center for Behavioral Health Statistics and Quality. 2017, Rockville, MD
- Sherif M, Radhakrishnan R, D'Souza DC, et al. Human laboratory studies on cannabinoids and psychosis. Biol Psychiatry 2016;79:526-538
- Skosnik PD, Cortes-Briones JA, Hajos MA. It's all in the rhythm: the role of cannabinoids in neural oscillations and psychosis. Biol Psychiatry 2016;79:568-577
- Stinson FS, Ruan WJ, Pickering R, et al. Cannabis use disorders in the USA: prevalence, correlates and co-morbidity. Psychological Medicine 2006;36:1447-1460
- Venegas H, Vazquez E, Tortorici V, NSAIDs, opioids, cannabinoids, and the control of pain by the central nervous system. Pharmaceuticals 2010;3 doi:10.3390/ph3051335
- Vigil JM, Stith SS, Adams IM, et al. Associations between medical cannabis and prescription opioid use in chronic pain patients: a preliminary cohort study. PLoS One 2017;12: e0187795
- Weitzman L, Daya L, Brill S, et al. Cannabis analgesia in chronic neuropathic pain is associated with altered brain connectivity. Neurology 2018;921:1285-1294
- Whiting PF, Wolff RF, Deshapnde S, et al. Cannabinoids for medical use: a systematic review and meta-analysis. JAMA 2015;313(24):2456-2473
- Wilkinson ST, Stefanovics E, Rosenheck RA. Marijuana use is associated with worse outcomes in symptom severity and violent behavior in patients with posttraumatic stress disorder. J Clin Psychiatry 2015;76(9):1174-1180