Cannabis: Clinical Applications and Updates

ANANTH SHENOY, MD FACP
OPTUM WASHINGTON
ANANTH.SHENOY@OPTUM.COM

New York Times Headlines Last Month

As America's Marijuana Use Grows, So Do the Harms

The drug, legal in much of the country, is widely seen as nonaddictive and safe. For some users, these assumptions are dangerously wrong.

By Megan Twohey, Danielle Ivory and Carson Kessler

The reporters are continuing to examine cannabis policies, use of the drug and the rise of the commercial market. If you have a story or information to share, please contact us here.

Published Oct. 4, 2024 Updated Oct. 7, 2024

A Patchwork of Cannabis Laws Creates Health Risks, Study Finds

A new report calls for public education and closing of legal loopholes to keep the public safe.

By Matt Richtel

Cannabis Has Become Upscale Chic. I Miss the Old Red-Eyed Stoners.

Widespread legalization has created a polished new market for cannabis products — one that's trendy, spalike and weirdly unfun.

By Erin Somers

Oct. 1, 2024

Help me guide this talk

- Who has had patients ask them about cannabis use?
- Who has treated patients for complications of cannabis use?
- What is your level of comfort with answering questions about cannabis?

Overview of Today's Talk

- Federal Law, State Law
- Pharmacology of Cannabinoids
- Evidence Basis and Applications
- Adverse Effects
  - Cannabis Hyperemesis
- Patient Guidance
- Questions

I have no financial disclosures but will be discussing Cannabis which remains a Schedule I substance and off label uses of it

Clinical Scenarios

- 55 year old patient with painful diabetic neuropathy and chronic kidney disease is seeing you in clinic.

  "My daughter suggested I try this CBD extract under my tongue for my pain, what do you think?"

- 75 year old patient with severe degenerative joint disease and pain in their hands and feet, on chronic opiate therapy.

  "My spouse wants me to try smoking marijuana for my pain. Is this safe and will it help?"

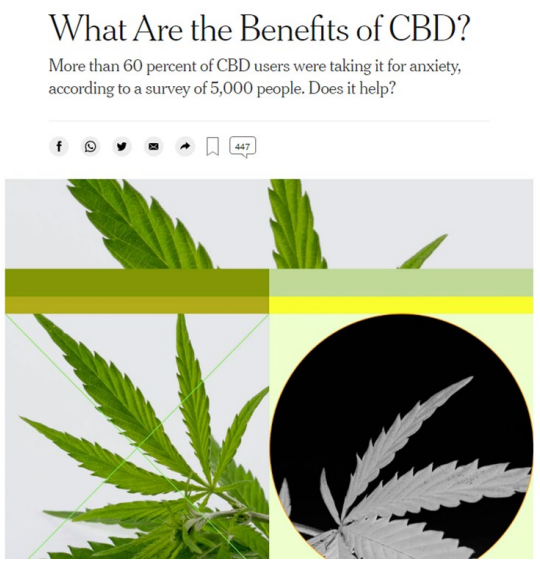
  "Can you prescribe it?"

Legality

Cannabis and US Federal Law

- **Cannabis remains Schedule I substance**
- Under the Agriculture Improvement Act of 2018, Hemp (Less than 0.3% d9-tetrahydrocannabinol [THC] by weight) is **no longer a controlled substance**
- So…Cannabidiol (CBD) without THC is "legal"
  - Available OTC!

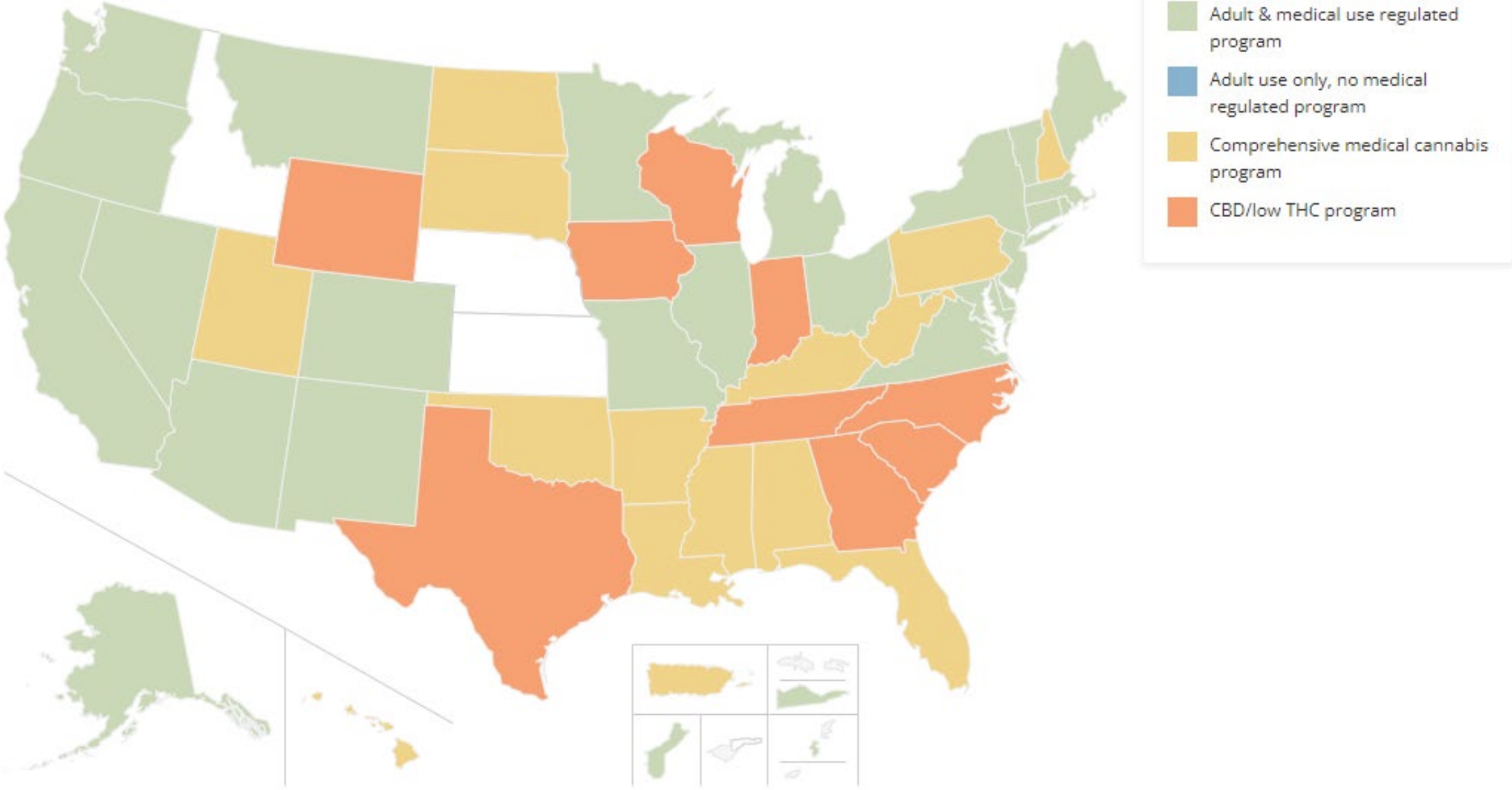
https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-including-cannabidiol-cbd#relatedinfo


What Are the Benefits of CBD?

More than 60 percent of CBD users were taking it for anxiety, according to a survey of 5,000 people. Does it help?

https://www.nytimes.com/2019/10/16/style/self-care/cbd-oil-benefits.html

Cannabis Laws by State



https://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx

Medicinal Use in Washington (since 1998)

- Clinicians (ARNP,DO,MD,ND,PA) may provide a patient with an approved condition an **authorization** to use marijuana for medicinal purposes
  - **This is NOT a prescription**
  - Must document thorough history and exam
    - Including any substance misuse/abuse with risk assessment tool
    - Review Prescription Drug Monitoring Program database
    - Document treatment plan, discussion of risks and alternative options
  - Should have 3 hours of appropriate CME (the state website links to a 4 hour CME course)
  - This process is an **attestation** that the clinician agrees the patient meets the state requirements for the medicinal authorization => it is NOT a recommendation to use marijuana

Source: Washington State DOH Medical Marijuana

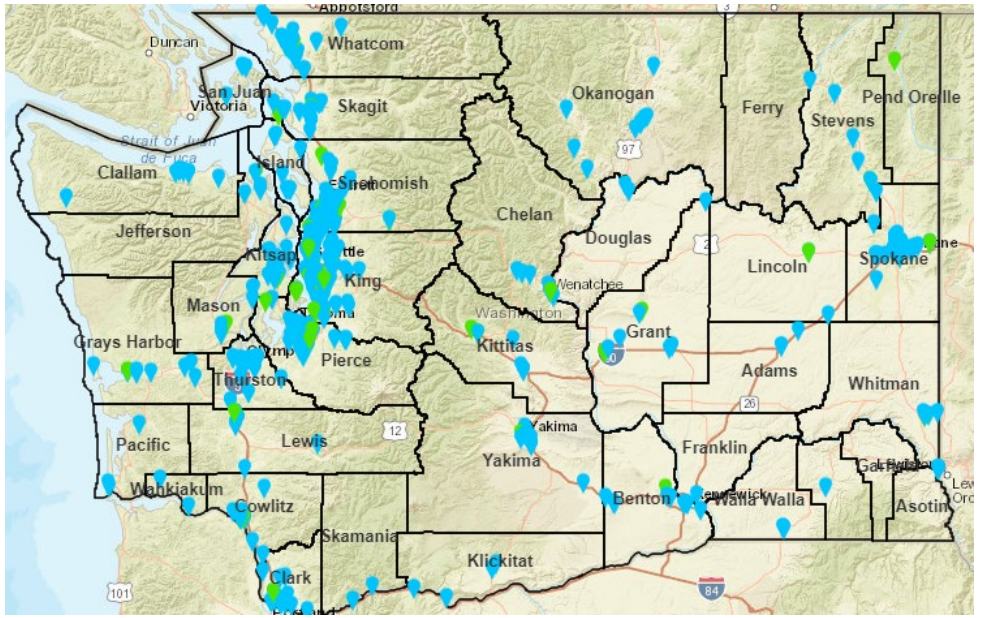
Medicinal Use in Washington

Approved conditions

- Cancer, human immunodeficiency virus (HIV), multiple sclerosis, epilepsy or other seizure disorder, or spasticity disorders.
- **Intractable pain**, limited for the purpose of this chapter to mean pain unrelieved by standard medical treatments and medications.
- Glaucoma, either acute or chronic, limited for the purpose of this chapter to mean increased intraocular pressure unrelieved by standard treatments and medications.
- Crohn's disease with debilitating symptoms unrelieved by standard treatments or medications.
- Hepatitis C with debilitating nausea or intractable pain unrelieved by standard treatments or medications.
- **Diseases,** including anorexia, **which result in** nausea, vomiting, wasting, appetite loss, cramping, seizures, muscle spasms, or spasticity, when these symptoms are unrelieved by standard treatments or medications.
- Chronic renal failure requiring hemodialysis.
- Posttraumatic stress disorder.
- Traumatic brain injury.

Recreational Use in Washington (2012)

- Age 21+
- Can purchase limited quantity from licensed retailers
  - ~2000 issued licenses => there are lots of dispensaries!
  - $1.5B in sales in 2021
- Tax revenue $555M in 2021



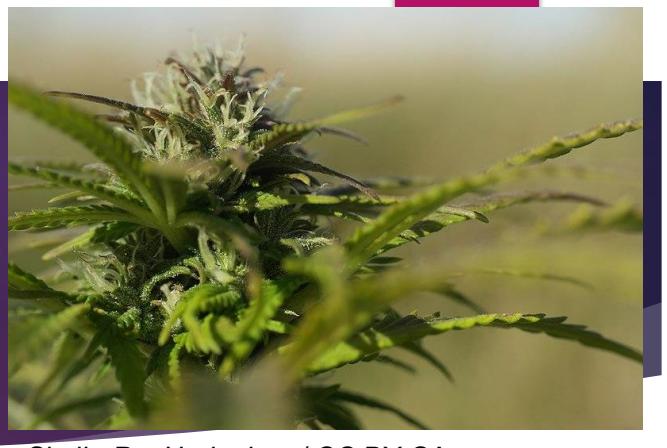
Source: Washington State Liquor and Cannabis Board

So Why Medical Authorization?

- Patients can have a limited number of plants and register in a state database (WA)
- Patients can possess higher quantities of marijuana products (WA)
- No Sales Tax
- Higher quality standard (WA)
- To purchase in other states that do Not have recreational access
- Legitimacy?

Pharmacology and Therapeutics

Cannabinoids



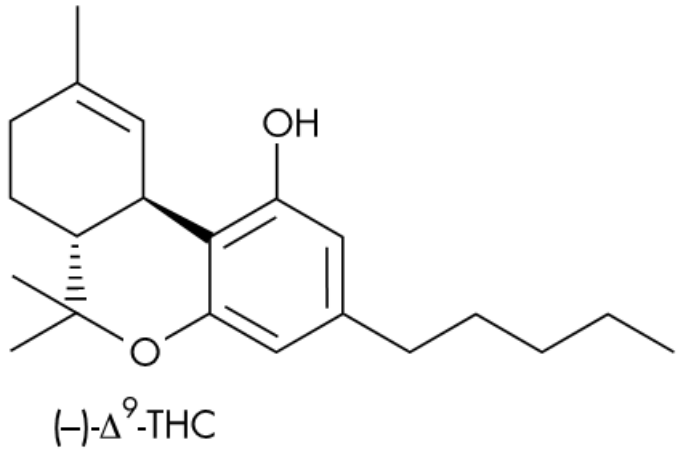
Skalle-Per Hedenhös / CC BY-SA
(https://creativecommons.org/licenses/by-sa/4.0)

Plants – C.sativa (hemp), C.indica

Target - Endogenous signaling system

Numerous active chemical compounds

- Δ9-tetrahydrocannabinol (THC)
  - Psychoactive, anti-emetic, analgesic properties
- Cannabidiol (CBD)
  - Anti-inflammatory, anxiolysis, analgesic, anti-epileptic



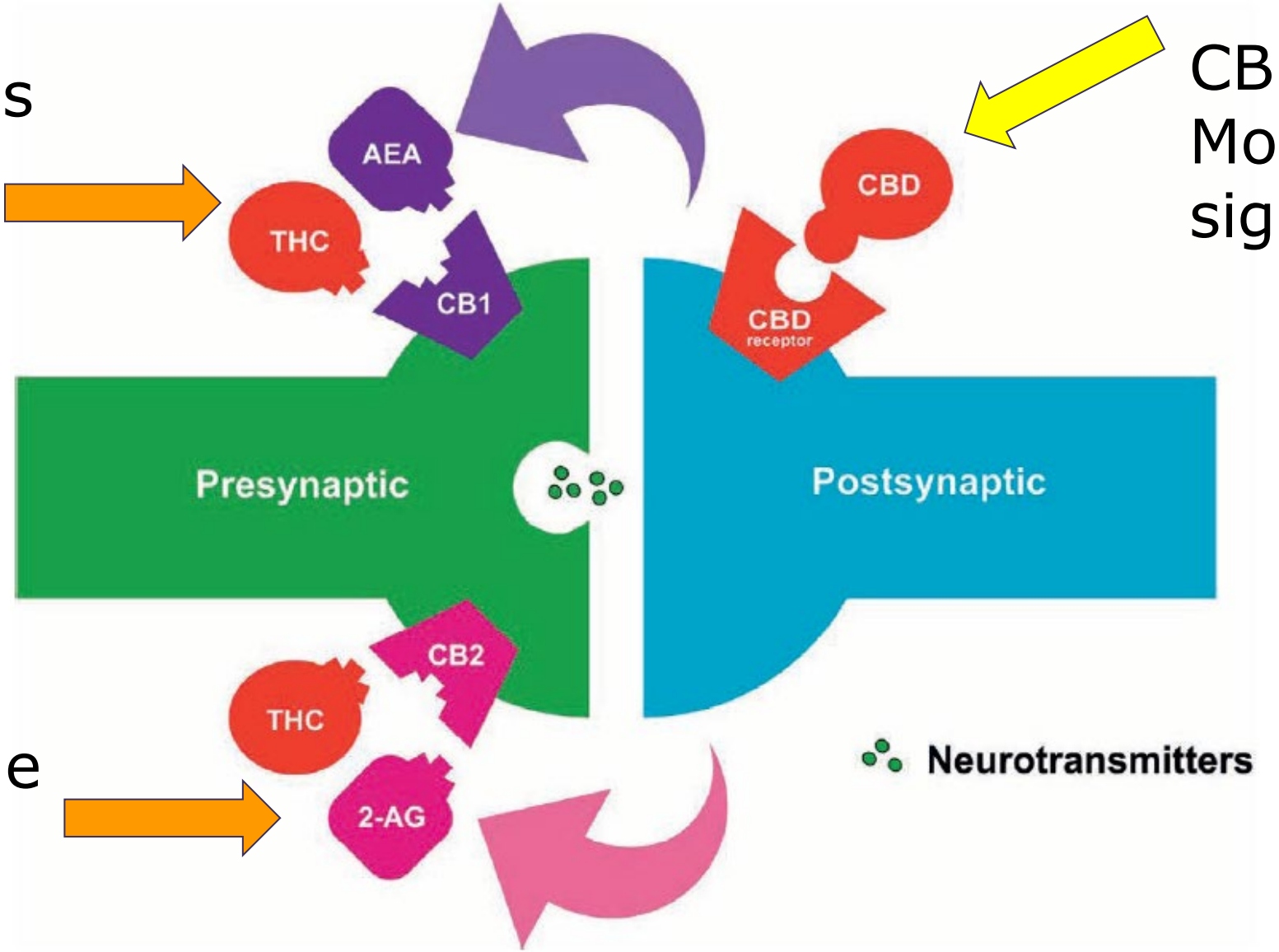
(–)-Δ^9-THC

PMID: 28050136

Biochemical Targets of Cannabinoids

CB1 – Nervous system / Widespread

CBD – Modulating signaling



CB2 – Immune system

Shenoy 2022, VM Bulletin

Pharmaceutical Cannabinoids

- THC compounds
  - Dronabinol (Marinol, Syndros), Nabilone* (Cesamet)
  - For anorexia, nausea and vomiting
- CBD compounds
  - Cannabidiol (Epidiolex)
  - For refractory childhood epilepsy syndromes
- Combined CBD+THC (1:1)
  - Nabiximols oral spray (THC+CBD)
  - Not approved in USA

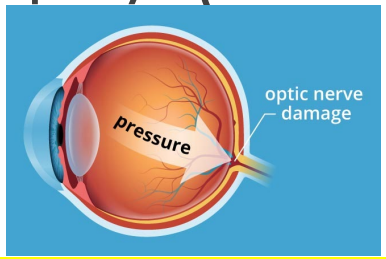
So, what is the Evidence?

Indications with various levels of Support

Chronic pain
Nausea, Vomiting
Spasticity

These Photos by Unknown Author is licensed under CC BY-SA

Anorexia
Intractable Epilepsy (Pediatrics)*
Insomnia*
Glaucoma*



In general – small sample sizes, significant risk for bias, limited quality of studies, *Will not be reviewing these today

PMID: 26103030, 28182367

Chronic Pain

- Cancer
- Neuropathic
- Diabetic Peripheral
- HIV
- MS related
- Rheumatoid arthritis
- Fibromyalgia
- Chronic generalized pain

Primarily compared to **placebo**

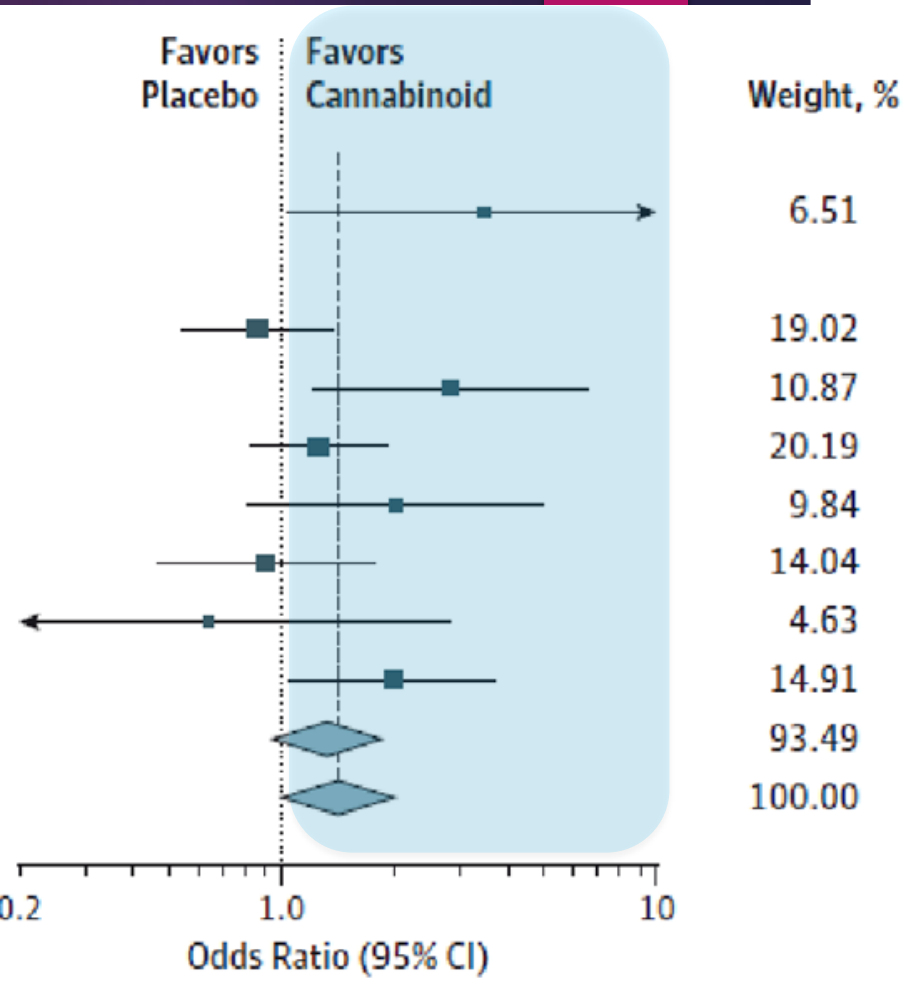
Different agents studied

- Inhaled and oral cannabis
- Dronabinol
- Nabilone
- Nabiximols*

- Patient blinding very challenging
- Often patients on other analgesics (including opiates)

PMID: 26505059, 26103030, 26103031, 28050136, 28182367

Improvement in Pain With Cannabinoid vs Placebo by Study	Cannabinoid Events		Placebo Events		Odds Ratio (95% CI)	Weight, %
	No.	Total No.	No.	Total No.		
Tetrahydrocannabinol (smoked)						
Abrams et al,[77] 2007	13	25	6	25	3.43 (1.03-11.48)	6.51
Nabiximols						
GW Pharmaceuticals,[22] 2005	54	149	59	148	0.86 (0.54-1.37)	19.02
Johnson et al,[69] 2010	23	53	12	56	2.81 (1.22-6.50)	10.87
Langford et al,[65] 2013	84	167	77	172	1.25 (0.81-1.91)	20.19
Nurmikko et al,[76] 2007	16	63	9	62	2.00 (0.81-4.96)	9.84
Portenoy et al,[67] 2012	22	90	24	91	0.90 (0.46-1.76)	14.04
Selvarajah et al,[70] 2010	8	15	9	14	0.63 (0.14-2.82)	4.63
Serpell et al,[88] 2014	34	123	19	117	1.97 (1.05-3.70)	14.91
Subtotal $I^2=44.5\%$, ($P=.0.94$)	241	660	209	660	1.32 (0.94-1.86)	93.49
Overall $I^2=47.6\%$, ($P=.0.64$)	254	685	215	685	1.41 (0.99-2.00)	100.00



- Moderate improvement in pain scores (>=30%)
- Trend towards improvement with higher dose, inhaled cannabis
- Side effects often limiting higher dosing
- Larger effect seen in non-cancer pain

PMID 26103030

Reduced opioid use?

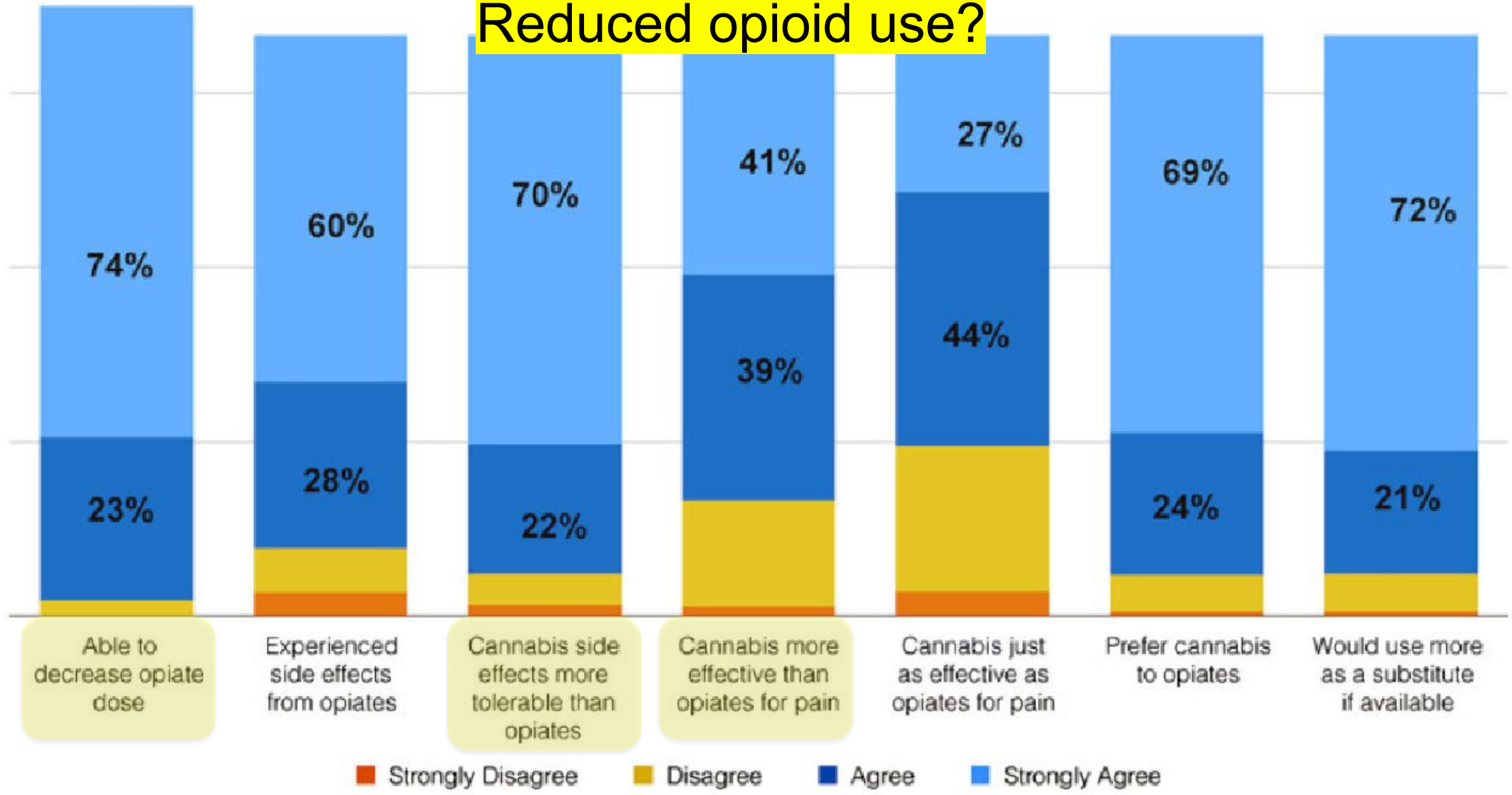
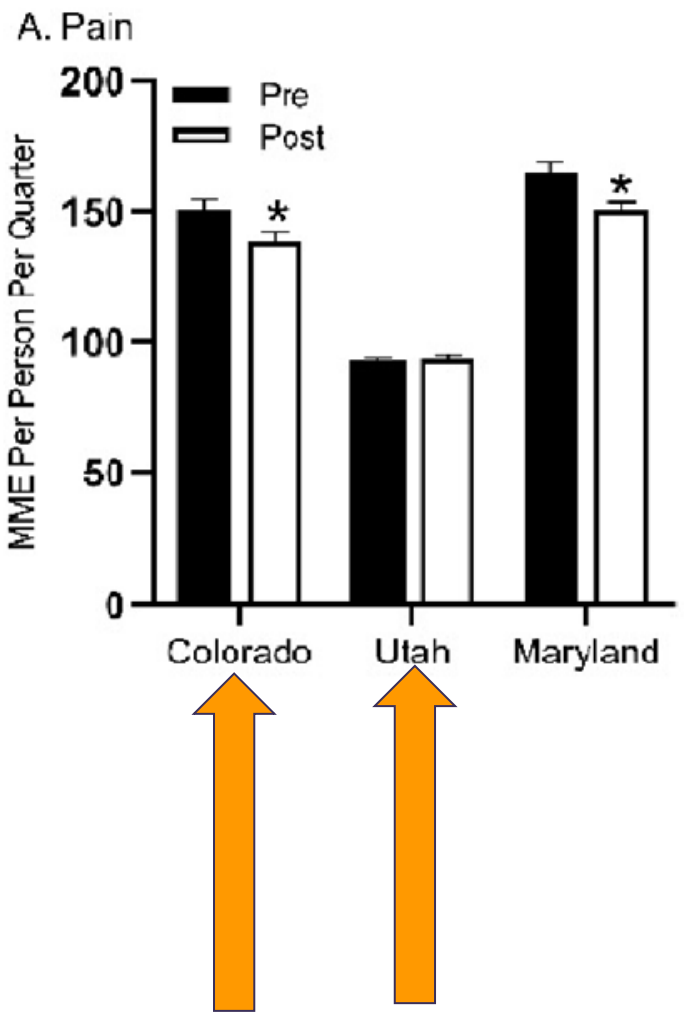
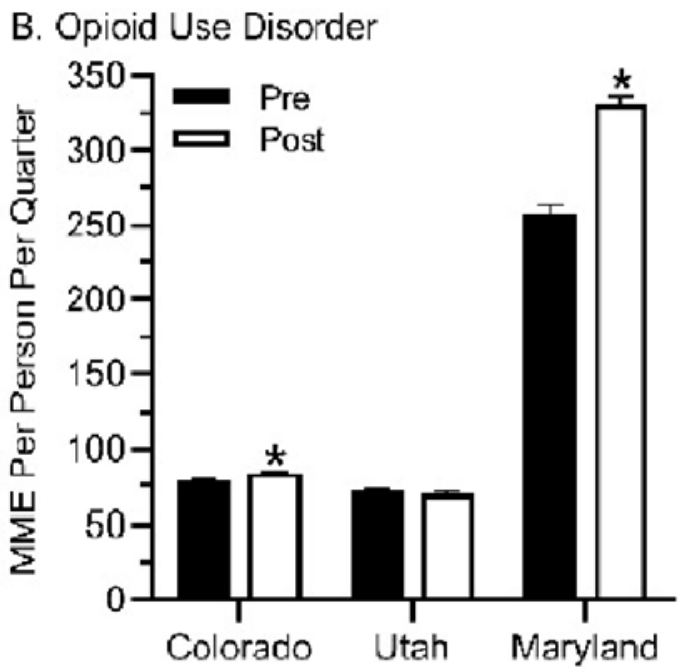


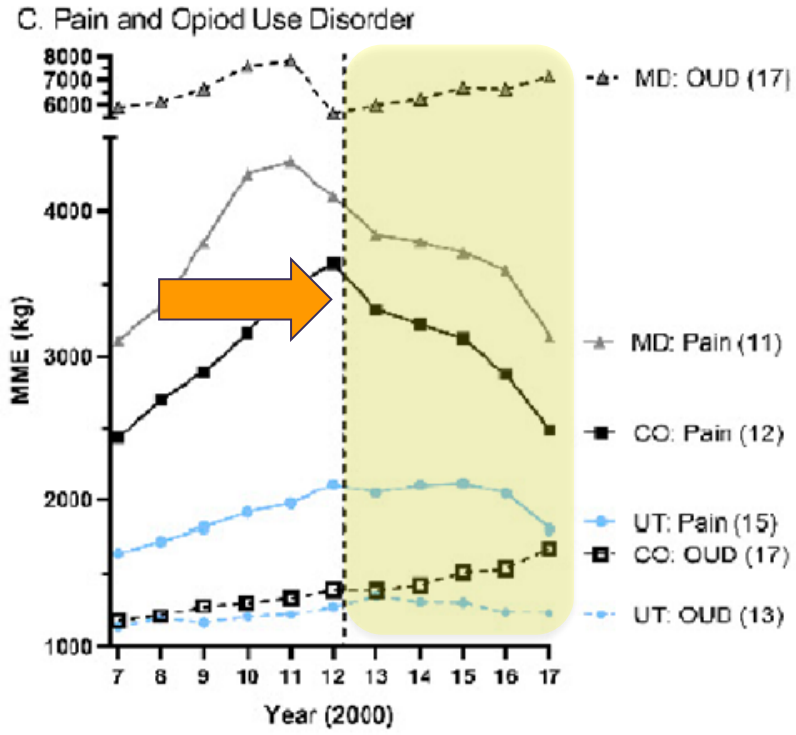
FIG. 2. Use of cannabis as a substitute/in conjunction with opioid-based pain medication ($n = 828$).

PMID 28861516

Reduced Opiate Prescriptions?







PMID 32392702

Nausea and Vomiting

Chemotherapy induced

- Compared to placebo, prochlorperazine, metoclopramide, domperidone, chlorpromazine
- Comparable / superior efficacy
- More side effects, but patient preferred
- The anxiolytic properties may be a component

*Surprisingly, poor studies and small sample sizes, dated

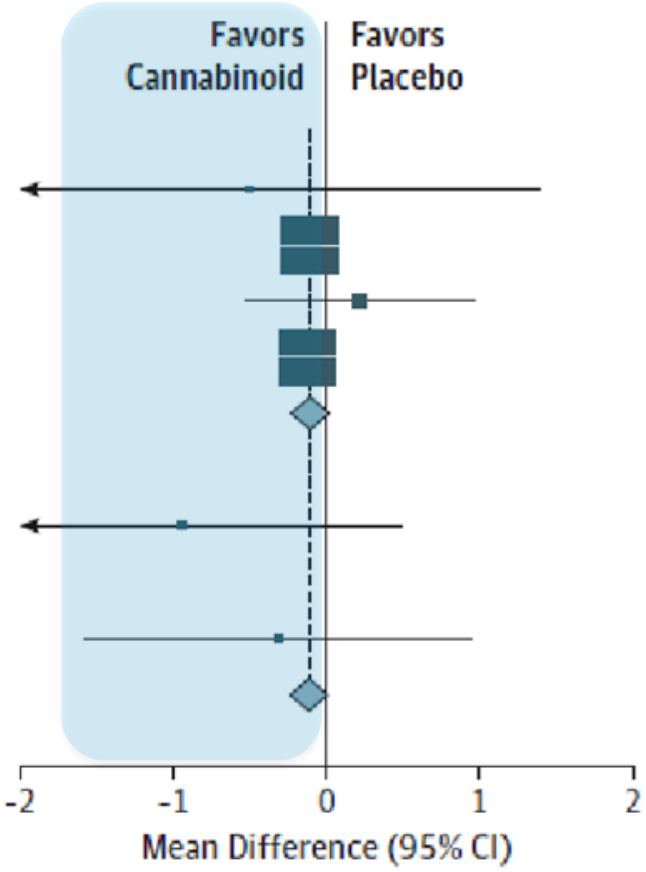
PMID: 26561338

Spasticity

Multiple Sclerosis and Paraplegia related spasticity

- Improved subjective symptoms and trend towards improvement on physical exam

Score Change With Cannabinoid vs Placebo by Study	Cannabinoid		Placebo		Mean Difference (95% CI)
	No. of Patients	Mean (SD) Score Change	No. of Patients	Mean (SD) Score Change	
Nabiximols					
Collin,[125] 2010	156	-3.3 (9.25)	160	-2.8 (7.81)	-0.50 (-2.39 to 1.39)
Collin,[127] 2007	114	-.64 (.56)	63	-.53 (.58)	-0.11 (-0.29 to 0.07)
Wade,[129] 2004	73	-.37 (2.51)	70	-.59 (2.04)	0.22 (-0.53 to 0.97)
Berman,[87] 2007	40	-.13 (.43)	44	-.01 (.42)	-0.12 (-0.30 to 0.06)
Subtotal $I^2 = 0.0\%$, ($P = .0.82$)	383		337		-0.11 (-0.23 to 0.02)
Dronabinol					
Zajicek,[131] 2003	197	-1.86 (7.95)	207	-.92 (6.56)	-0.94 (-2.37 to 0.49)
Tetrahydrocannabinol/cannabidiol					
Zajicek,[131] 2003	207	-1.24 (6.6)	207	-.92 (6.56)	-0.32 (-1.59 to 0.95)
Overall $I^2 = 0.0\%$, ($P = .80$)	590		544		-0.12 (-0.24 to 0.01)



PMID 26103030, 28182367

Anorexia in Cancer, HIV/AIDS

Dronabinol and Cannabis studied in **HIV/AIDS, cancer cachexia**

- Compared to placebo and megestrol acetate in both disease categories
- Very mixed results
- **Superior** to placebo in weight gain, appetite, body fat in HIV/AIDS
- Comparable to megestrol acetate, no additional benefit with combination

Of **reduced benefit in cancer** – not statistically significant

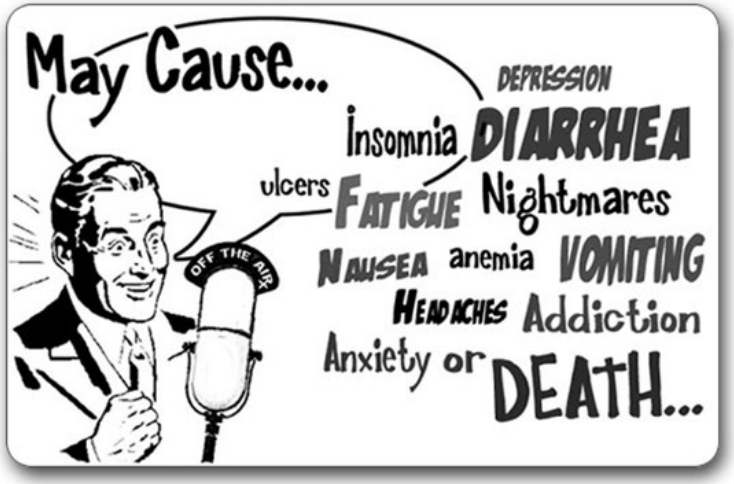
PMID: 28050136, 26103030, 26103031

Adverse Effects

Adverse Effects

Acute – Dose dependent

- Gastrointestinal
- Neurological
- Behavioral
- Anticholinergic



PMID 26103030, 28182367

Chronic – Dose/Frequency dependent

- **Gastrointestinal**
- Pulmonary
- Cognitive => caution with adolescents
- Psychosis
- Dependency, Withdrawal
- Prenatal risk
- Unclear => Infertility, Cancer (testicular)

Schizophrenia

- **More frequent use associated with schizophrenia and psychosis**
  - Daily use with HR 3.6
  - Over 5-year period in a study

PMID: 26785806

Withdrawal and Dependency

Dependency (~6% with chronic use)

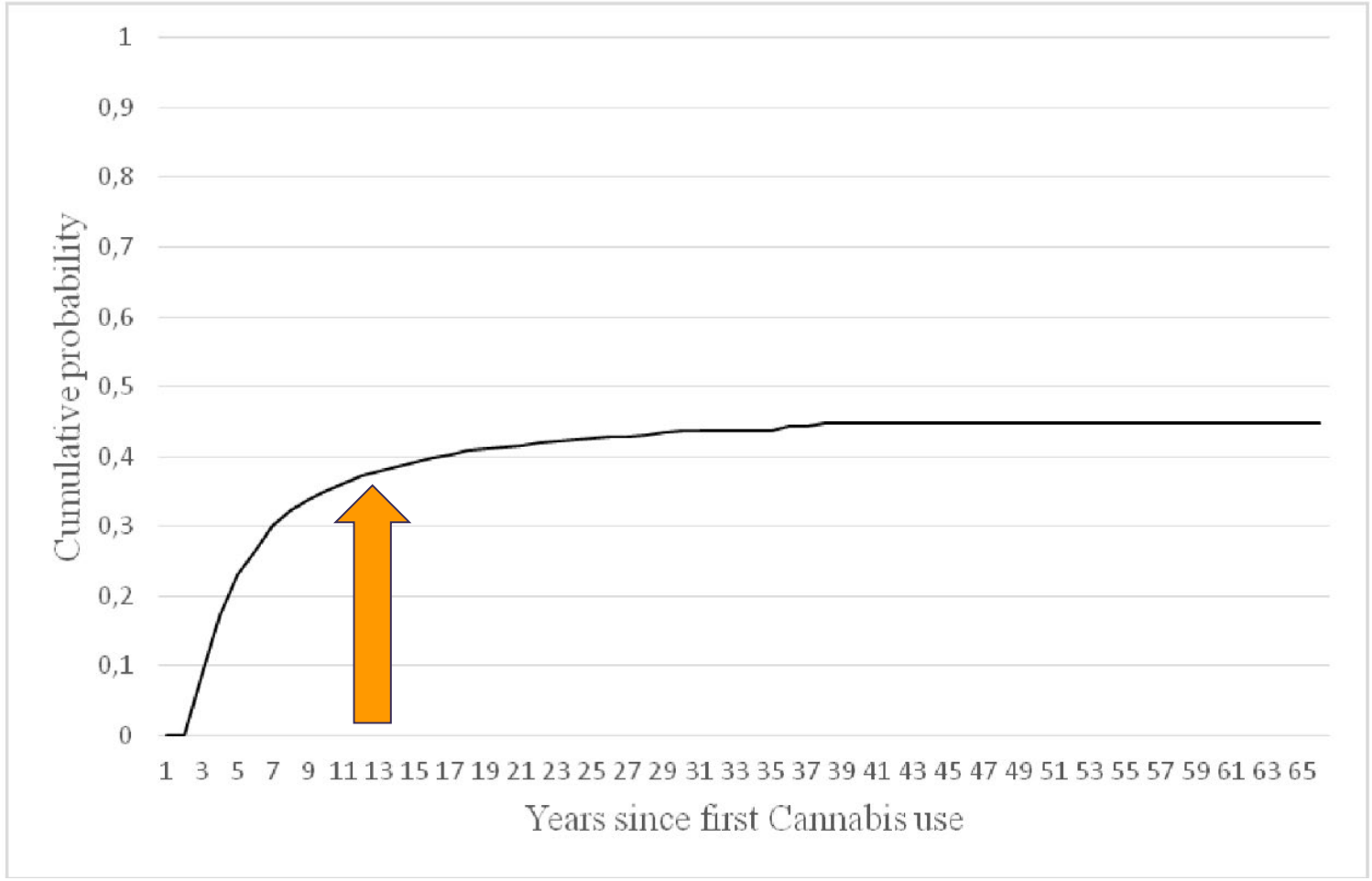
- Treatment – Cognitive Behavioral and Family Based Therapy
- N-acetyl cysteine?

Withdrawal Symptoms (days to weeks)

- Irritability/anger/aggression
- Anxiety, Depressed mood
- Insomnia
- Appetite changes
- Abd.pain, tremor, sweating, chills, headache
- Benzodiazepines, Gabapentin for symptoms, avoid SSRI/SNRIs

PMID: 27776623

Gateway drug?



- Difficult to elucidate relationship – confounders
- Association with other illicit substances – **44%**

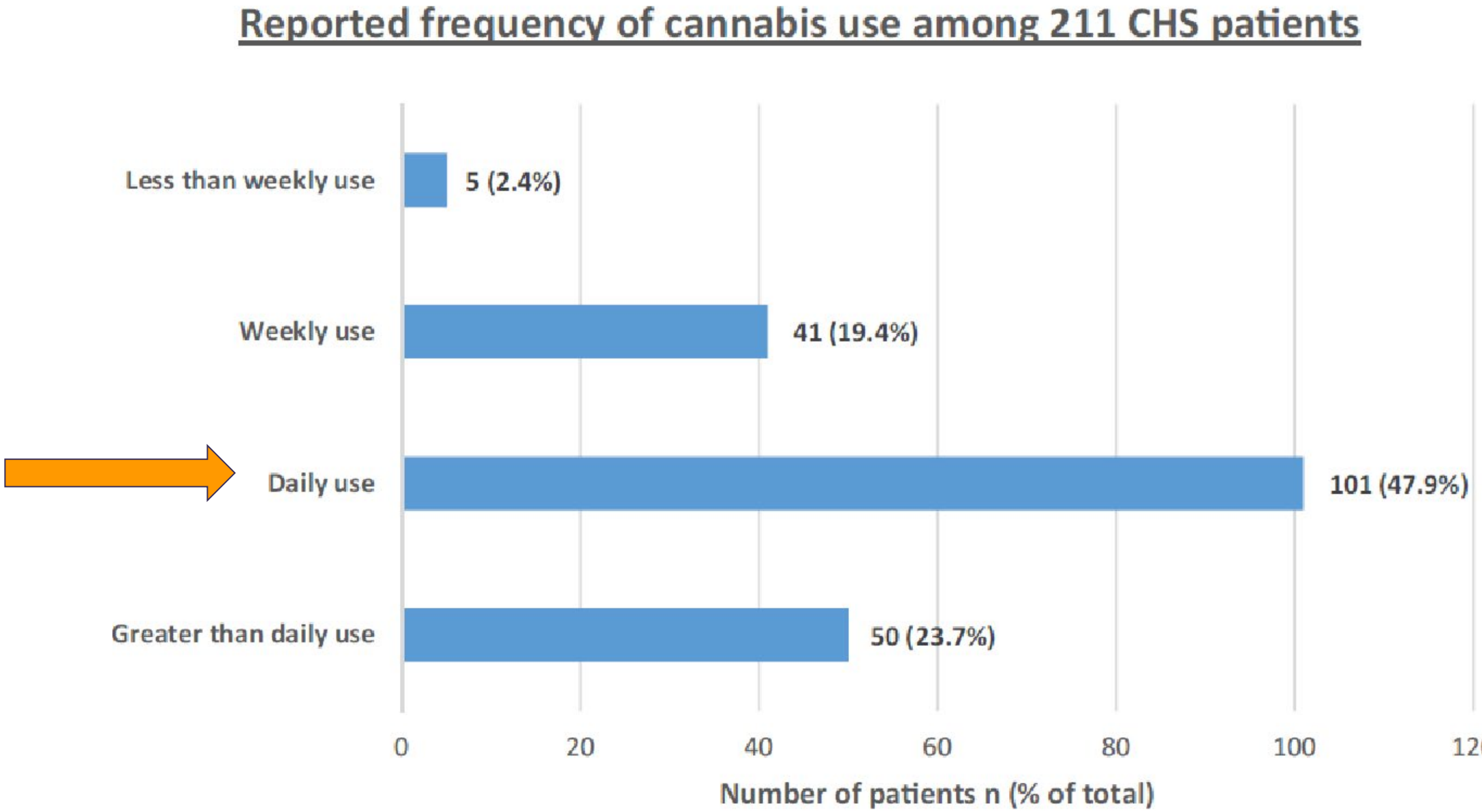
PMID: 25168081

Cannabis Hyperemesis Syndrome

- Incidence unclear (? 1%)
- Cyclic nausea, vomiting and abdominal pain
- Associated with daily use
- Crave hot showers for relief of symptoms
- Can persist for weeks-months after use (cannabinoids are lipophilic)

PMID: 22150623, 28000146

Cannabis Hyperemesis Syndrome (CHS)



Cannabis Hyperemesis Syndrome

- Mechanism - Delayed gastric emptying?
  - Slow release from adipose tissue
  - High levels of THC?
- Treatment: Abstinence!
  - Symptomatic relief
    - Haloperidol
    - Topical Capsaicin

PMID: 22150623, 28000146

Patient Counseling Harm Reduction

Contraindication/Cautions

This Photo by Unknown Author is licensed under CC BY-ND

- Avoid before age **25**
- Avoid in pregnancy
- Avoid with Family history of schizophrenia/psychosis, bipolar
- Avoid in history of substance abuse/dependency
- Caution in cardiac and pulmonary disease
- Caution with CYP450 inhibitors (2C9, 3A4)
- Do NOT drive after use

PMID: 27308872, 28050136

Pharmacokinetics of Cannabinoids

Route of Cannabis Administration

	Oral (edible)	Sublingual	Inhalation
Bioavailability	Low 2-10%	Medium 10%	High 25%
Onset	1-2 hours	0.5-1 hours	Minutes
Duration	Long 8-12 hours	Medium 2-4 hours	Medium 2-4 hours

PMID: 27466748, 28050136

Pharmacokinetics

- **Long half life** (lipophilic)
  - Variable duration and effect
- Metabolites can persist for **weeks** in adipose tissue
- Metabolized by cytochrome P450 system => primarily **2C9**
  - THC can **inhibit** 2C9, 3A4

PMID: 28050136

Guidance for patients?

- Consider **1:1** ratio of **THC to CBD**
  - Might increase THC if targeting nausea
  - Might increase CBD if avoiding psychotropic effects
- Start low, go slow
- Vapor/inhalation and sublingual easier to titrate
  - 1 puff or drop, wait 30mins, reassess and re-dose if needed
- May defer to dispensary?

PMID: 28050136

Clinical Scenarios

- 55 year old patient with painful diabetic neuropathy.

  "My daughter suggested I try this CBD extract under my tongue for my pain, what do you think?"

  - Reasonable to try
  - Likely safe (will need to review other medications)
  - Sublingual absorption probably more effective route

- 75 year old patient with severe DJD and COT

  "Smoking marijuana for my pain. Is this safe and will it help?"

  - Less clear benefit – but again, may be reasonable?
  - Smoking caries risks and consider more side effects
  - Try sublingual or edible instead?

  "Will you prescribe it?"

  - No, we cannot prescribe this - but could do attestation

Authorization Process - Washington

- Patient in-person appointment*, history and physical!
- If you agree, document the following:
  - Discussed other management options
  - Assessed potential benefit with marijuana
  - Advised regarding risk
  - Reviewed additional necessary evaluations and treatments
  - Specified duration (up to 12 months)
  - Updated treatment plan as appropriate
- Complete authorization form on tamper resistant paper
- **Patient then takes form** to Medical Dispensary, meets with Certified Consultant who registers in state database, gets card

Source: Washington State DOH Medical Marijuana

Physician Statement for Medical Use of Marijuana Registry Applicant

I, _____, state that I personally examined _____
(Physician's Name) (Applicant's Name)

on _____ and that the examination took place in the context of a bona fide physician-patient relationship;
(Date of examination)

and that _____ has a debilitating medical condition qualifying under AS 17.37.070.
(Applicant's Name)

I have considered other approved medications and treatments that might provide relief, that are reasonably available to the patient, and that can be tolerated by the patient, and have concluded that the patient might benefit from the medical use of marijuana.

Physician's Signature: _____ **Date:** _____

Physician's License Number: _____

The physician must either be licensed to practice medicine in the state of Alaska or must be an officer in the regular medical service of the armed forces of the United States or the United States Public Health Service while in the discharge of their official duties, or while volunteering services without pay or other remuneration to a hospital, clinic, medical office, or other medical facility in Alaska.

In Summary

- Cannabinoids include THC, CBD and have different properties
- There is potentially a role for cannabinoids in Chronic pain, Chemotherapy induced nausea/vomiting, Spasticity, Anorexia
- **Contraindicated** in those with risk of psychosis, adolescents/young adults, pregnancy, substance dependency
- Easier to titrate doses with inhaled and sublingual forms, consider 1:1 mixture of THC to CBD
  - Increase THC ratio to target appetite, nausea, pain
  - Increase CBD ratio to increase anxiolysis, pain
- Titrate to lowest dose that gives symptom relief

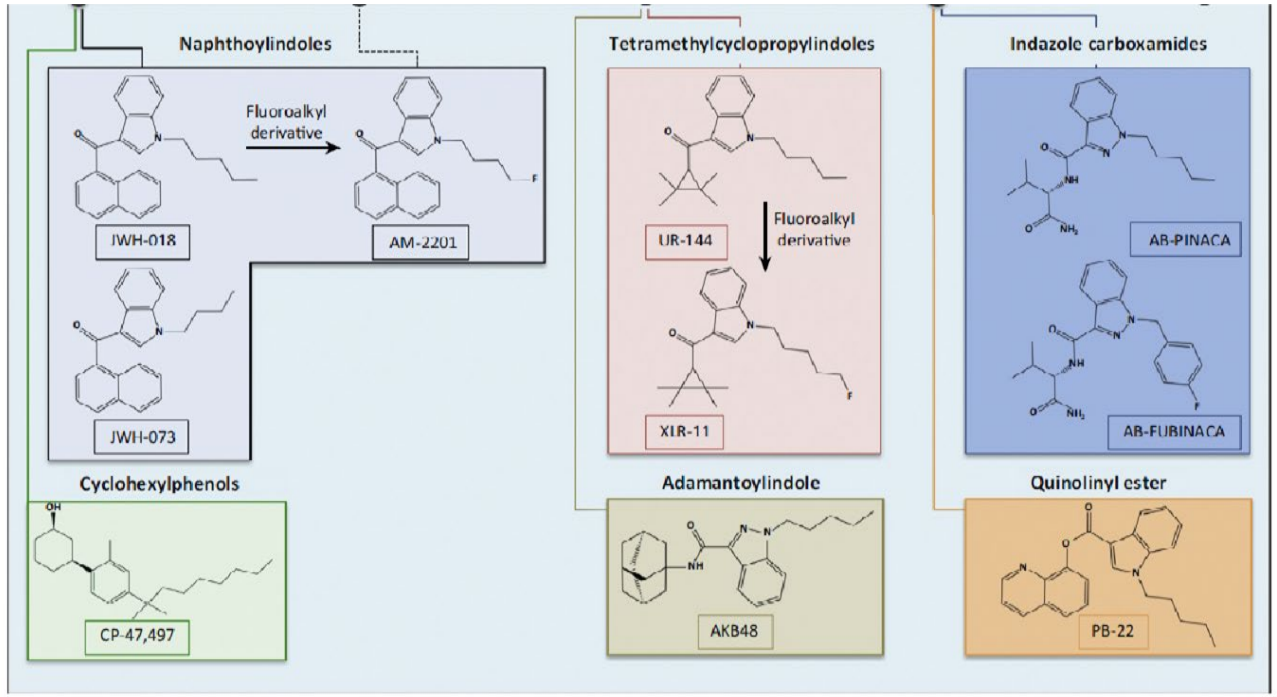
Thank you! Questions?

Email: Ananth.Shenoy@optum.com

K2 and Spice

K2 and Spice

- Synthetic cannabinoids
  - Deceptive marketing
- ***Significant*** chemical ***variability*** and ***effects***



PMID: 28162792

K2/Spice

- More potent – higher receptor affinity
- Wide range of adverse effects
  - **Fatalities**
  - Seizures, Cardiac, Renal failure

http://cullmantoday.com/2015/04/21/7-fatalities-linked-synthetic-cannabis-spice-k2/

PMID: 28162792

K2/Spice

Skirting edge of **legality**

[illegible]	[illegible]	[illegible]	[illegible]

PMID: 28162792

References

1. Andreae MH. Inhaled Cannabis for Chronic Neuropathic Pain: A Meta-analysis of Individual Patient Data. J Pain. 2015 Dec;16(12):1221-1232. doi: 10.1016/j.jpain.2015.07.009. Epub 2015 Sep 9. PMID: 26362106

2. Brents LK. Marijuana, the Endocannabinoid System and the Female Reproductive System. Yale J Biol Med. 2016 Jun 27;89(2):175-91. eCollection 2016 Jun. PMID: 27354844

3. Cather JC, Cather JC. Cannabidiol primer for healthcare professionals. Proc (BaylUniv Med Cent). 2020 Jul 6;33(3):376-379. eCollection 2020 Jul. PMID: 32675954

4. Efficacy and adverse effects of medical marijuana for chronic noncancer pain: Systematic review of randomized controlled trials. Deshpande A, Mailis-Gagnon A, Zoheiry N, Lakha SF.Canadian Family Physician. 2015 Aug; 61(8): e372-e381 PMID: 26505059

5. Donvito G. The Endogenous Cannabinoid System: A Budding Source of Targets for Treating Inflammatory and Neuropathic Pain. Neuropsychopharmacology. 2018 Jan;43(1):52-79. Epub 2017 Aug 31. PMID: 28857069

6. du Plessis SS, Agarwal A, Syriac A. Marijuana, phytocannabinoids, the endocannabinoid system, and male fertility. J Assist Reprod Genet. 2015 Nov;32(11):1575-88. Epub 2015 Aug 16. PMID: 26277482

7. Ebbert JO, Scharf EL, Hurt RT. Medical Cannabis. Mayo Clin Proc. 2018 Dec;93(12):1842-1847. PMID: 30522595

8. ElSohly MA. Changes in Cannabis Potency Over the Last 2 Decades (1995-2014): Analysis of Current Data in the United States. Biol Psychiatry. 2016 Apr 1;79(7):613-9. Epub 2016 Jan 19. PMID:26903403

9. Everson EM. Post-Legalization Opening of Retail Cannabis Stores and Adult Cannabis Use in Washington State, 2009-2016. Am J Public Health. 2019 Sep;109(9):1294-1301. Epub 2019 Jul 18. PMID: 31318588

10. Evins AE. The effect of marijuana use on the risk for schizophrenia. J Clin Psychiatry. 2012 Nov;73(11):1463-8. PMID: 23218162

11. Fitzcharles MA, Eisenberg E. Medical cannabis: A forward vision for the clinician. Eur J Pain. 2018 Mar;22(3):485-491 Epub 2018 Jan 29. PMID: 29377381

12. Hill KP. Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems: A Clinical Review. JAMA. 2015 Jun 23-30;313(24):2474-83. Erratum in: JAMA. 2016 Sep 6;316(9):995. PMID: 26103031

13. Huang YH. An epidemiologic review of marijuana and cancer: an update. Cancer Epidemiol Biomarkers Prev. 2015 Jan;24(1):15-31. PMID: 25587109

14. Jikomes N, Zoorob M. The Cannabinoid Content of Legal Cannabis in Washington State Varies Systematically Across Testing Facilities and Popular ConsumerProducts. Sci Rep. 2018 Mar 14;8(1):4519. Erratum in: Sci Rep. 2020 Aug 27;10(1):14406. PMID: 29540728

References

15. Marijuana Use in the Immediate 5-Year Premorbid Period is Associated with Increased Risk of Onset of Schizophrenia and Related Psychotic Disorders. Kelley ME. Schizophrenia research. 2016 Jan 17; 171(1-3): 62-67PMC [article] PMCID: PMC4929616, PMID: 26785806

16. Kropp Lopez AK. Prescription Opioid Distribution after the Legalization of Recreational Marijuana in Colorado. Int J Environ Res Public Health. 2020 May 7;17(9). pii: E3251. doi: 10.3390/ijerph17093251. PubMed [citation] PMID: 32392702, PMCID: PMC7246665

17. Le Bec PY, Fatséas M, Denis C, Lavie E, Auriacombe M. [Cannabis and psychosis:search of a causal link through a critical and systematic review]. Encephale.2009 Sep;35(4):377-85. doi: 10.1016/j.encep.2008.02.012. Epub 2008 Jul 9. Review.French. PubMed [citation] PMID: 19748375

18. A user's guide to cannabinoid therapies in oncology.Maida V, Daeninck PJ. Current Oncology. 2016 Dec 21; 23(6): 398-406. PMID: 28050136

19. Mondello E. Cannabinoids and spinal cord stimulation for the treatment of failed back surgery syndrome refractory pain. J Pain Res. 2018 Sep 6;11:1761-1767. doi: 10.2147/JPR.S166617. eCollection 2018.PubMed [citation] PMID: 30233233, PMCID: PMC6134407

20. National Academies of Sciences, Engineering, and Medicine, Health and Medicine Division, Board on Population Health and Public Health Practice, Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. Washington (DC): National Academies Press (US);2017 Jan 12. PMID: 28182367

21. Nugent SM. The Effects of Cannabis Among Adults With Chronic Pain and an Overview of General Harms: A Systematic Review. Ann Intern Med. 2017 Sep 5;167(5):319-331. doi: 10.7326/M17-0155. Epub 2017 Aug 15. Review. PubMed [citation] PMID: 28806817

22. Orhurhu V. Cannabis Use in Hospitalized Patients with Chronic Pain. Adv Ther. 2020 Aug;37(8):3571-3583. doi: 10.1007/s12325-020-01416-9. Epub 2020 Jul 6. Review. PubMed [citation] PMID: 32632850, PMCID: PMC7370966

23. Reiman A, Welty M, Solomon P. Cannabis as a Substitute for Opioid-Based Pain Medication: Patient Self-Report. Cannabis Cannabinoid Res. 2017 Jun 1;2(1):160-166. doi: 10.1089/can.2017.0012. eCollection 2017. PMID: 28861516, PMCID: PMC5569620

24. Roffman R. Legalization of cannabis in Washington State: how is it going? Addiction. 2016 Jul;111(7):1139-40. doi: 10.1111/add.13247. Epub 2016 Jan 18. PubMed [citation] PMID: 26781325

25. Schrot RJ, Hubbard JR. Cannabinoids: Medical implications. Ann Med. 2016;48(3):128-41. doi: 10.3109/07853890.2016.1145794. Epub 2016 Feb 25. Review. PubMed [citation] PMID: 26912385

26. Slawek D, Meenrajan SR, Alois MR, Comstock Barker P, Estores IM, Cook R. Medical Cannabis for the Primary Care Physician. J Prim Care Community Health. 2019 Jan-Dec;10:2150132719884838. doi: 10.1177/2150132719884838. Review. PubMed [citation] PMID: 31646929

27. Smith LA, Azariah F, Lavender VT, Stoner NS, Bettiol S. Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy. Cochrane Database Syst Rev. 2015 Nov 12;(11):CD009464. doi: 10.1002/14651858.CD009464.pub2. Review. PubMed [citation] PMID: 26561338

References

28. Sorensen CJ, DeSanto K, Borgelt L, Phillips KT, Monte AA. Cannabinoid Hyperemesis Syndrome: Diagnosis, Pathophysiology, and Treatment-a Systematic Review. J Med Toxicol. 2017 Mar;13(1):71-87. doi: 10.1007/s13181-016-0595-z. Epub 2016 Dec 20.

Review. PubMed [citation] PMID: 28000146, PMCID: PMC5330965

29. Cannabinoids and glaucoma. Tomida I, Pertwee RG, Azuara-Blanco A. The British Journal of Ophthalmology. 2004 May; 88(5): 708-713

PMC [article] PMCID: PMC1772142, PMID: 15090428, DOI: 10.1136/bjo.2003.032250

30. Walitt B, Klose P, Fitzcharles MA, Phillips T, Häuser W. Cannabinoids for fibromyalgia. Cochrane Database Syst Rev. 2016 Jul 18;7:CD011694. doi: 10.1002/14651858.CD011694.pub2. Review. PubMed [citation] PMID: 27428009

31. Walther L, Gantner A, Heinz A, Majić T. Evidence-based Treatment Options in Cannabis Dependency. Dtsch Arztebl Int. 2016 Sep 30;113(39):653-659. doi:10.3238/arztebl.2016.0653. Review. PubMed [citation] PMID: 27776623, PMCID:PMC5098026

32. Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, Keurentjes JC, Lang S, Misso K, Ryder S, Schmidlkofer S, Westwood M, Kleijnen J.Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. JAMA. 2015 Jun 23-30;313(24):2456-73. doi: 10.1001/jama.2015.6358. Review. Erratum in: JAMA.2015 Aug 4;314(5):520. JAMA. 2015 Aug 25;314(8):837. Erratum in: JAMA. 2015 Dec 1;314(21):2308. JAMA. 2016 Apr 12;315(14):1522. PubMed [citation] PMID: 26103030

33. Perisetti A, Gajendran M, Dasari CS, Bansal P, Aziz M, Inamdar S, Tharian B, Goyal H. Cannabis hyperemesis syndrome: an update on the pathophysiology and management. Ann Gastroenterol. 2020 Nov-Dec;33(6):571-578. doi: 10.20524/aog.2020.0528. Epub 2020 Sep 16. PMID: 33162734; PMCID: PMC7599351.