Clinical Considerations for Cannabis Use

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Learning Objectives

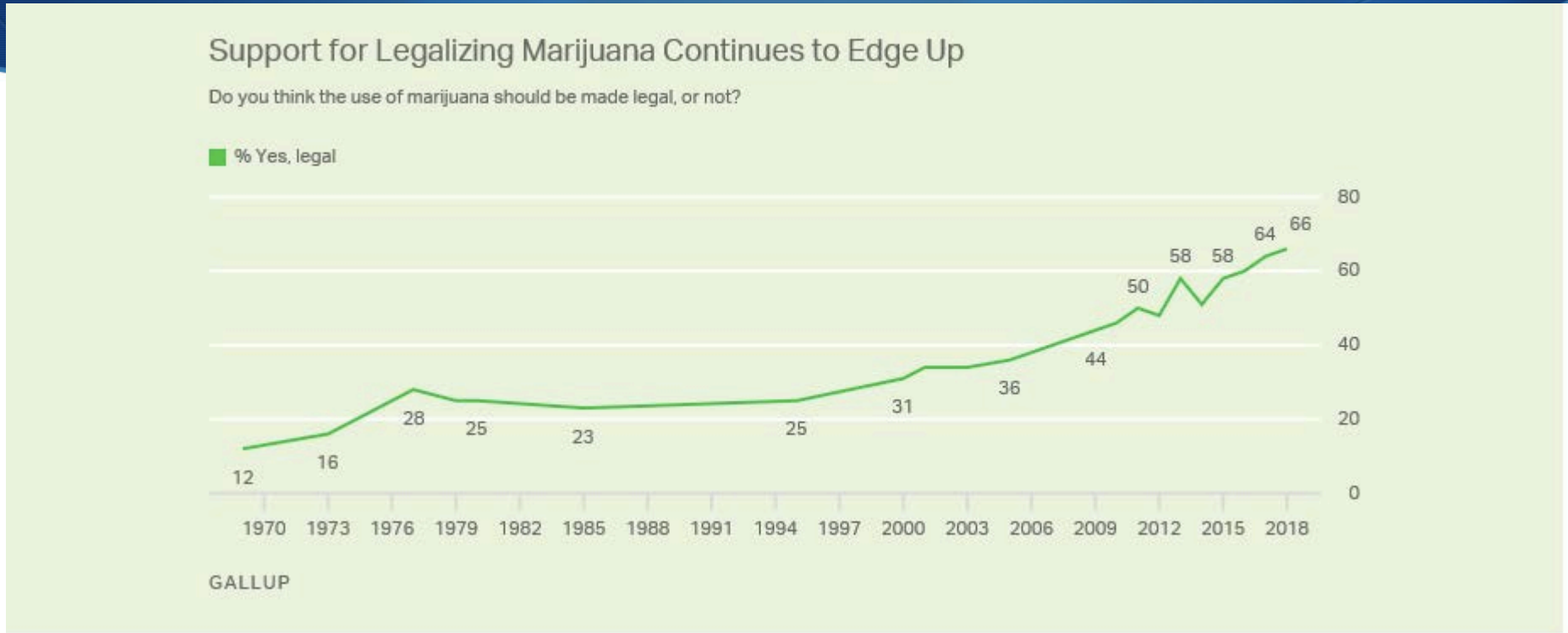
- Apply literature to determine potential benefits of cannabis products for future patients
- Identify clinically-relevant drug-drug interactions with THC and CBD, classifying them as pharmacodynamic or pharmacokinetic in nature

Baby Boomers on the Rise

- Currently 75.4 million baby boomers (born 1946-1964)
- By 2050, those ≥65 will be estimated at 83.7 million
- Grew up in a dynamic and changing world
  - Vietnam war
  - Civil rights movement
  - Sexual revolution
  - Women's liberation
  - Drugs

Potter SB. https://insight.factset.com/millennials-outnumber-baby-boomers-but-dont-count-them-out
Lloyd SL. *Gerontology and Geriatric Medicine*. https://doi.org/10.1177/2333721418781668

Perceptions are Changing



Adapted from Mccarthy J. Two in one Americans now support legalizing marijuana. Available at https://news.gallup.com/poll/243908/two-three-americans-support-legalizing-marijuana.aspx?g_source=link_NEWSV9&g_medium=TOPIC&g_campaign=item_&g_content=Two%2520in%2520Three%2520Americans%2520Now%2520Support%2520Legalizing%2520Marijuana

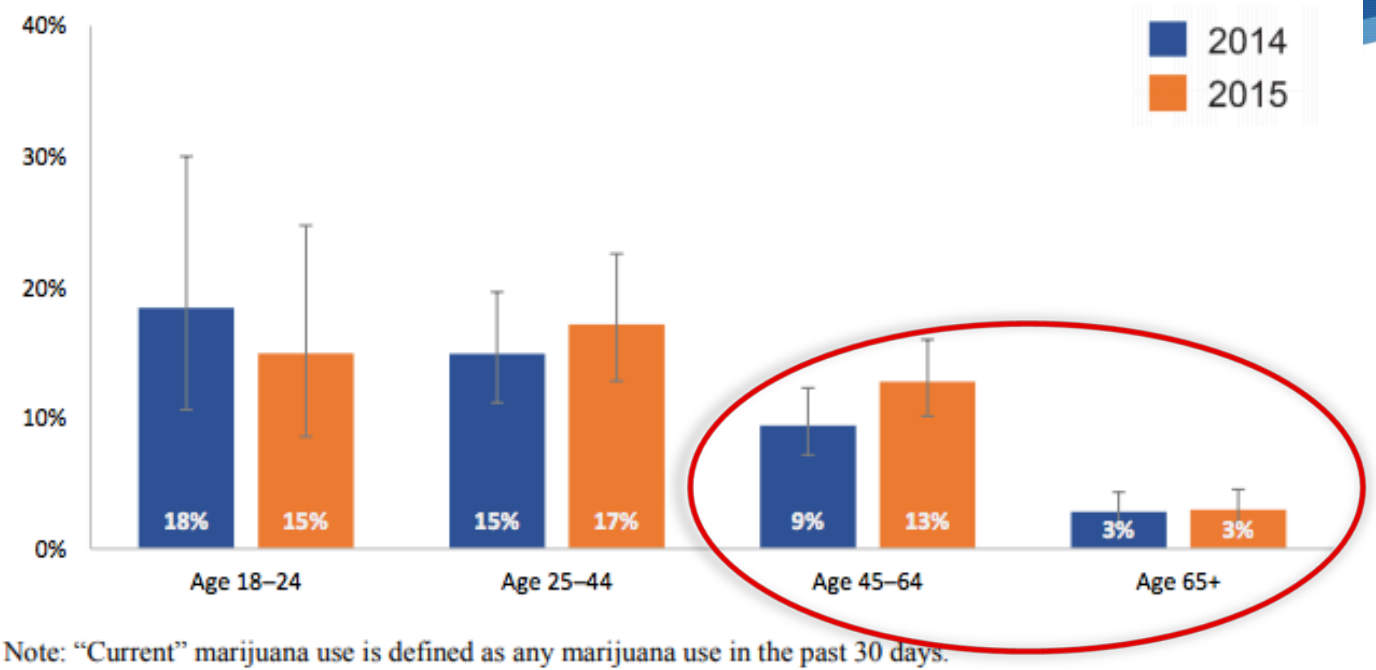
And so is the use…

Prevalence estimates for self-reported past-year cannabis use for adults 50 years and older, US 2003-2016

	2006/2007 (n=11,181)	2012/2013 (n=12,696)	% absolute change from 06/07 to 12/13	% relative change from 06/07 to 12/13	P-value
Prevalence of cannabis use	2.8	4.8	+2.0	+71.4	<0.001
Age group					
50-64	4.5	7.1	+2.6	+57.8	<0.001
65+	0.4	1.4	+1.0	+250.0	0.002
Gender					
Male	4.4	6.8	+2.4	+54.5	<0.001
Female	1.5	3.0	+1.5	+100.00	<0.001

Adapted from Han BH. Addiction. 2017 March;112(3):516-525. doi:10.1111/add.13670.

Figure 12. Current marijuana use among Oregon adults by age, 2014 and 2015

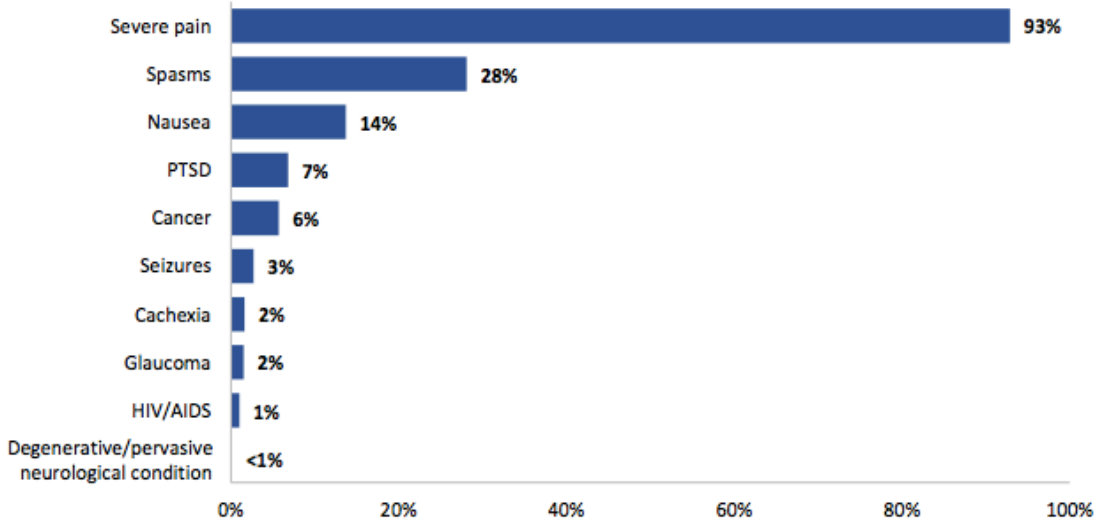


Note: "Current" marijuana use is defined as any marijuana use in the past 30 days.

Data source: Oregon Behavioral Risk Factor Surveillance System (2014 and 2015).

Why and what does this mean?

Figure 23. Oregon medical marijuana patient conditions, 2015



Data source: Oregon Medical Marijuana Program (OMMP) (October 2015 Statistical Snapshot).

What can be the effects ?

- Improved quality of life?
- Increased risk for falls?
- Reduced prescription medication use?
- Illicit drug use?
- Cost savings?
- Dependency/addiction?

Are marijuana and cannabis the same thing?

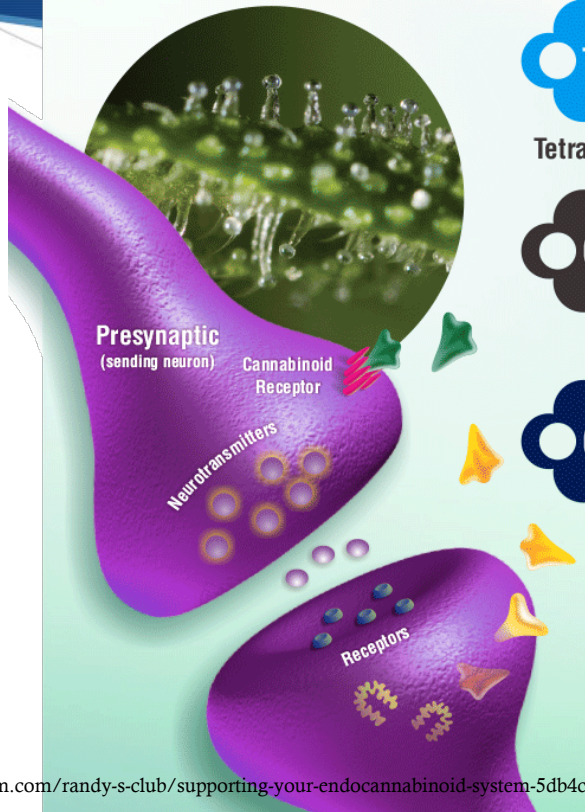
Cannabis… Marijuana… THC… CBD…

The Human Endocannabinoid System

CBD, CBN and THC fit like a lock and key into existing human receptors. These receptors are part of the endocannabinoid system which impact physiological processes affecting pain modulation, memory, and appetite plus anti-inflammatory effects and other immune system responses. The endocannabinoid system comprises two types of receptors, CB1 and CB2, which serve distinct functions in human health and well-being.

CB1 receptors are primarily found in the brain and central nervous system, and to a lesser extent in other tissues.

Receptors are found on cell surfaces



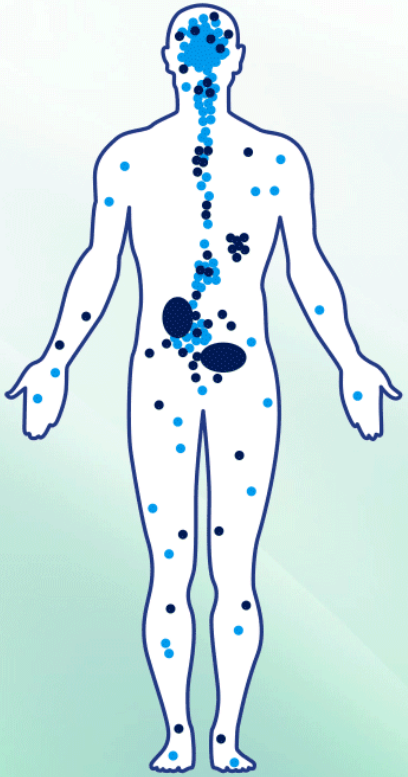
Tetrahydrocannabinol

Cannabidiol

Cannabinol

CBD does not directly "fit" CB1 or CB2 receptors but has powerful indirect effects still being studied.

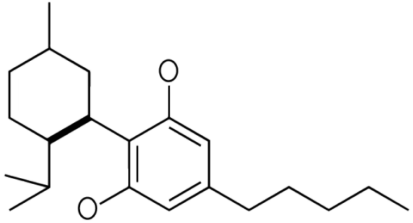
CB2 receptors are mostly in the perepheral organs especially cells associated with the immune system.

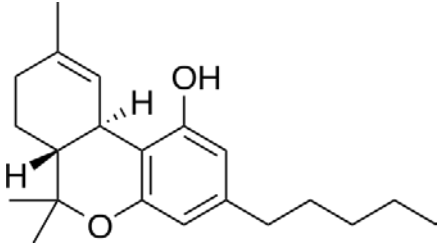


https://medium.com/randy-s-club/supporting-your-endocannabinoid-system-5db4c35d6037

source: www.the-human-solution.org

Cannabis





CBD	THC
No activity at CB1 or CB2 receptors	Activates CB1 & CB2 receptors

Bridgeman MB, Abazia DT. Medicinal Cannabis: History, Pharmacology, And Implications for the Acute Care Setting. *P T*. 2017;42(3):180-188.
https://kalytera.co/cbd/
https://en.wikipedia.org/wiki/Tetrahydrocannabinol

Effects	THC	CBD
Anticonvulsant	+	++
Muscle Relaxation	++	+
Psychoactive	++	--
Anxiolytic	--	++
Tachycardia	+	--
Appetite Stimulant	+	--
Antioxidant	+	++

Russo E. Medical Hypotheses. 2006;66:234-46.

Rx Products

- Dronabinol (Marinol) oral solution, capsules
  - Pure THC; CIII
- Nabilone
  - Synthetic analog of THC; CII
- Cannabidiol (Epidiolex) oral solution
  - Pure CBD; CV

Epidiolex (Cannabidiol)

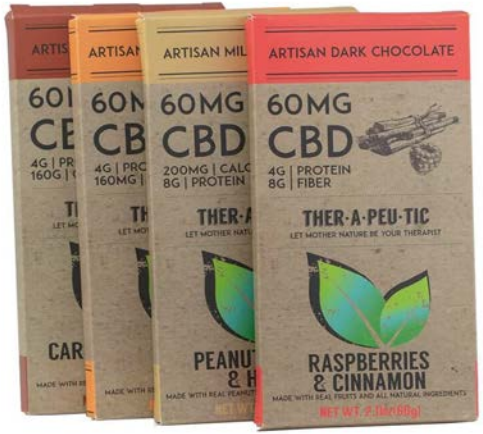
- Doses range from 2.5-10 mg/kg BID for seizures
  - Example: 75 kg male: 188 – 750 mg twice daily
  - Higher doses = higher efficacy, but more adverse effects
  - Recent FDA approval, so little-to-no data for safety or efficacy in older adults

Non-Rx CBD Products

https://keytocannabis.com/blogs/cannabis/which-kind-of-cbd-will-work-for-me

https://komonews.com/news/consumer/heres-what-you-should-know-about-using-cbd-products-for-pain-relief

https://www.bevnet.com/news/2018/green-rush-beverage-business-cbd-part-2

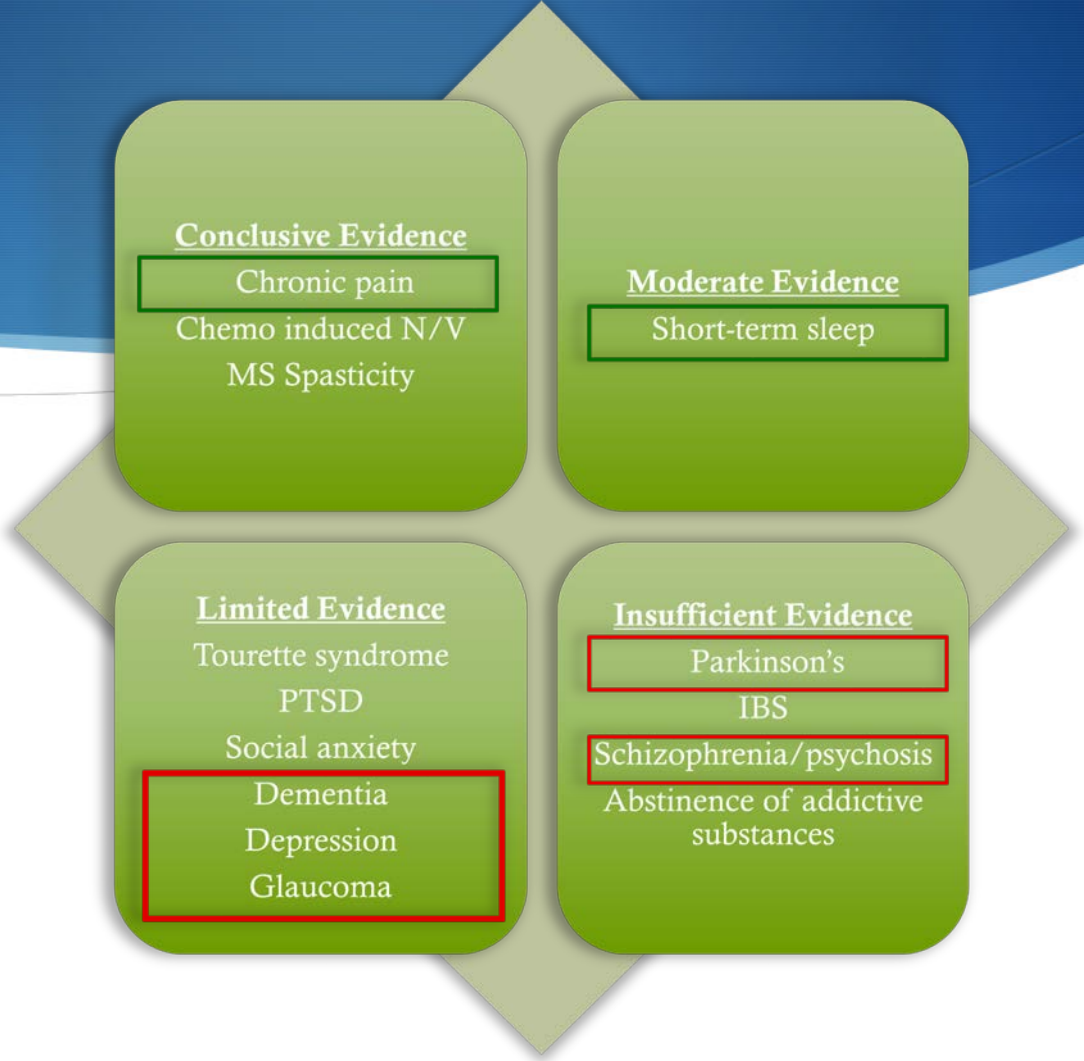


https://madebyhemp.com/product/therapeutic-cbd-chocolate/

What disease states are cannabis, THC, or CBD used for?

National Academies of Sciences, Engineering and Medicine

The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research (2017)



Parkinson's Disease

- Cannabinoids are neuroprotective hypothesis
  - Low CB1 receptors concentration in PD patients
- Majority of evidence available for levodopa-induced dyskinesia in Parkinson's disease
  - Three RCTs, 48 patients
  - Oral cannabis extract had no effect on dyskinesia
  - Some discrepancy in QOL outcomes
- Evidence for benefits are mostly anecdotal for improvement of pain, anxiety and sleep

More SV. Mol Neurodegener. 2015; 10: 17
Koeppel BS. Neurology. 2014 Apr 29;82(17):1556-63
Lim K. Clinical Psychopharmacology and Neuroscience 2017;15(4):301-312

Alzheimer's Dementia

- Pre-clinical research found THC to lower beta-amyloid levels
- 4 studies , 90 participants, unclear risk of bias
  - 2.5 mg dronabinol reduced disturbed behavior in 12 patients
  - THC capsule 0.75 – 4.5 mg/day, no effect seen
- How does cannabis affect the brain damage associated with dementia?
  - What about the anticholinergic effects of THC?

Cao C. Journal of Alzheimer's Disease, vol. 42, no. 3, pp. 973-984, 2014
Lim K. Clinical Psychopharmacology and Neuroscience 2017;15(4):301-312

Cannabis and Brain Development

- Greater decline in IQ (~6 points vs. never users) connected to persistent and younger age of use
  - Adult onset users did not experience a significant decline
  - Greatest impairment in executive functioning and processing speeds
- Relationship between early and heavy cannabis use and impairments in…
  - White matter integrity
  - Smaller whole brain and cortical grey matter volumes
  - Cognitive function
  - Increased risk of psychopathology
- Difficult to account of confounders in studies

Cannabis and Psychosis

- Insufficient evidence to support or refute use for schizophrenia and psychosis
  - Mixed evidence for impact on positive symptoms
  - Does not worsen negative symptoms
  - Potential improvement in cognitive function
- Perceived benefits outweigh risks for patients with psychosis
  - Improved sociability
  - Reduced anxiety
  - Improvement in medication side-effects
- Multiple studies have identified a correlation with cannabis use and development psychosis

The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study

Marta Di Forti, Diego Quattrone, Tom P Freeman, Giada Tripoli, Charlotte Gayer-Anderson, Harriet Quigley, Victoria Rodriguez, Hannah E Jongsma, Laura Ferraro, Caterina La Cascia, Daniele La Barbera, Ilaria Tarricone, Domenico Berardi, Andrei Szöke, Celso Arango, Andrea Tortelli, Eva Velthorst, Miguel Bernardo, Cristina Marta Del-Ben, Paulo Rossi Menezes, Jean-Paul Selten, Peter B Jones, James B Kirkbride, Bart PF Rutten, Lieuwe de Haan, Pak C Sham, Jim van Os, Cathryn M Lewis, Michael Lynskey, Craig Morgan, Robin M Murray, and the EU-GEI WP2 Group*

Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review

Theresa H M Moore, Stanley Zammit, Anne Lingford-Hughes, Thomas R E Barnes, Peter B Jones, Margaret Burke, Glyn Lewis

Dose response effect

- Greater risk with frequency of use
- Higher potency
- Younger age

In 2014, 20.2 million people had substance use disorder, 7.9 million also had a mental health disorder

Leaf image:https://www.istockphoto.com/photos/marijuana-leaf?sort=mostpopular&mediatype=photography&phrase=marijuana%20leaf
DNA image: https://www.medicalnewstoday.com/articles/320560.php
World image: http://weknowyourdreams.com/world.html
SAMHSA 2015. https://www.samhsa.gov/data/sites/default/files/NSDUH-FRR1-2014/NSDUH-FRR1-2014.pdf

Cannabis and Substance abuse

OR

Gateway image: https://www.recoveryfirst.org/blog/is-marijuana-a-gateway-drug/
Exit image: https://www.uline.com/Product/Detail/S-9959P/Warehouse-Signs/Exit-Sign-Plastic

Cannabis as an "Exit Drug"

- Harm reducing role?
  - Patient reported reductions in alcohol, illicit drug use and prescription medications with cannabis and return without
    - Higher rates of substitution seen with patients <40 yo, opportunity for education?
  - Binge drinking and fatal alcohol accidents reduced in states following approval of medical marijuana
  - Card carrying users demonstrated less risky behavior with alcohol, tobacco and other substances than non-card holders

Lucas P. Drug and Alcohol Review (2015) DOI: 10.1111/dar.12323
Anderson DM. J Law Econ 56: 333–369
Richmond MK. Journal of psychoactive drugs 47(1):1-9

December 18, 2018

States Move to Substitute Opioids With Medical Marijuana to Quell Epidemic

Rebecca Voelker, MSJ

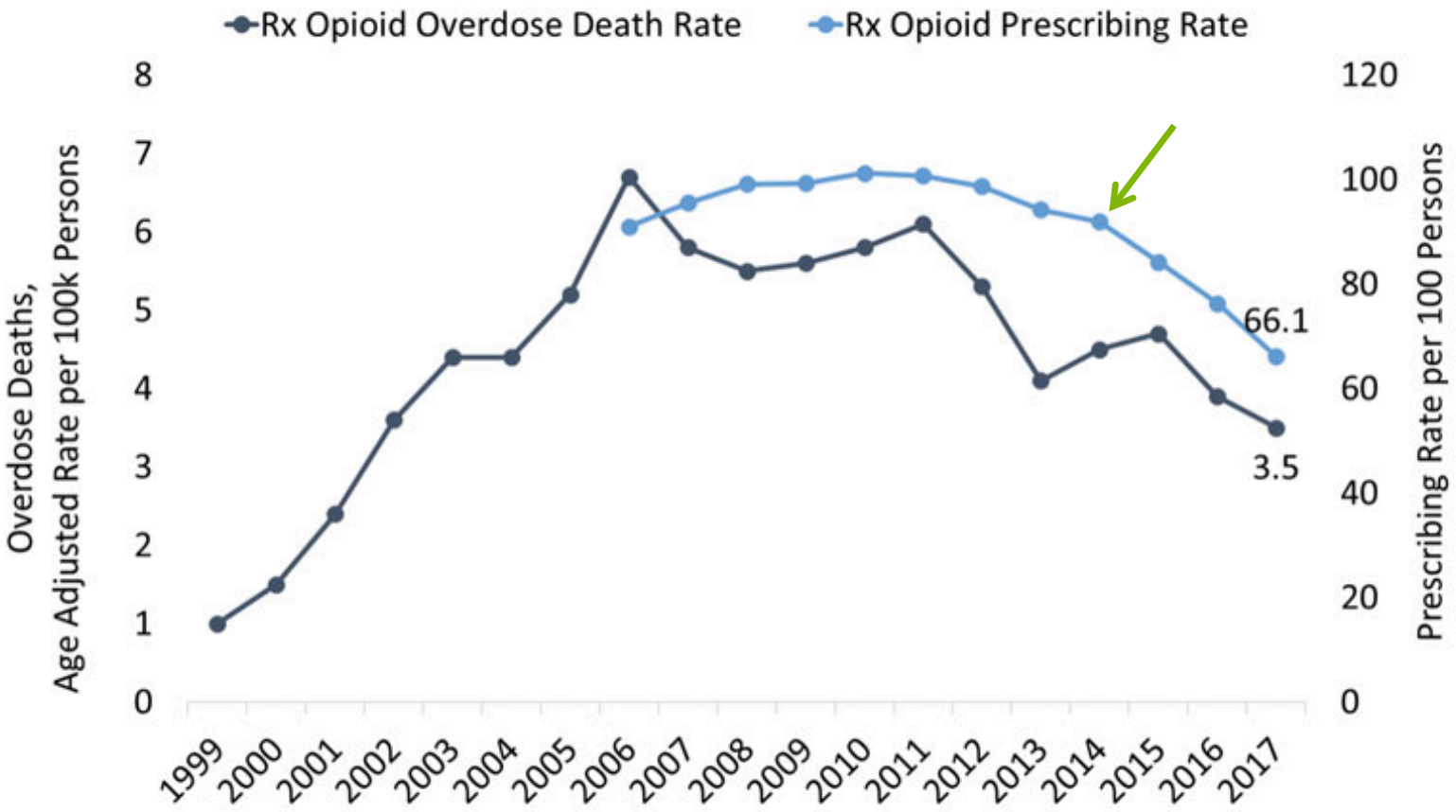
Article Information

JAMA. 2018;320(23):2408-2410. doi:10.1001/jama.2018.17329

New York and Illinois allow substitution of opioid prescription for marijuana with approved condition

- In light of evidence demonstrating almost 25% reduction in annual opioid overdose mortality in states with approved medical marijuana
- Following approved programs opioid prescriptions decreased
  - Medicare Part D: 2.11 mill. daily doses per year
  - Medicaid: 5.88% (medical), 6.38% (recreational)

Bachuber MA. *JAMA Intern Med.* 2014;174(10):1668-1673
Bradford AC. *JAMA Intern Med.* 2018;178(5):667-672
Wen H. *JAMA Intern Med.* 2018;178(5):673-679



NIH Oregon opioid summary. https://www.drugabuse.gov/opioid-summaries-by-state/oregon-opioid-summary

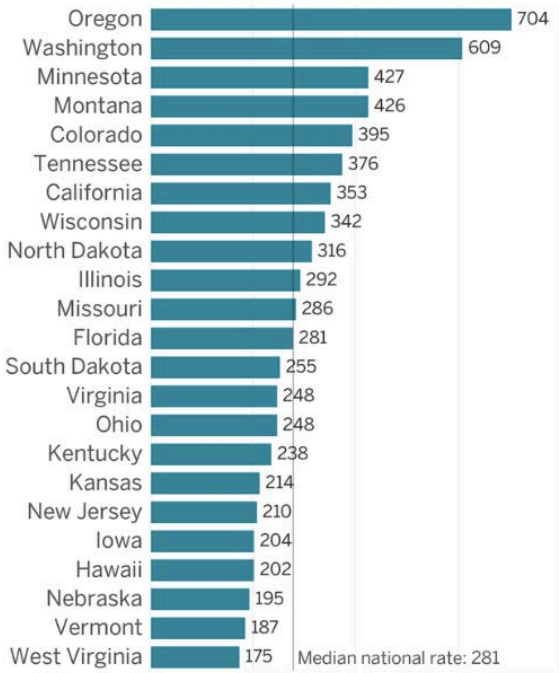
Oregon leads U.S. in seniors hospitalized for opioids

Updated Jul 7, 2017; Posted Jul 7, 2017

Oregon DOJ says opioid manufacturer targets senior citizens, lied to sell drugs in state

Posted Sep 13, 2018

2015 state rates of opioid-related hospital stays per 100,000 people age 65 and older



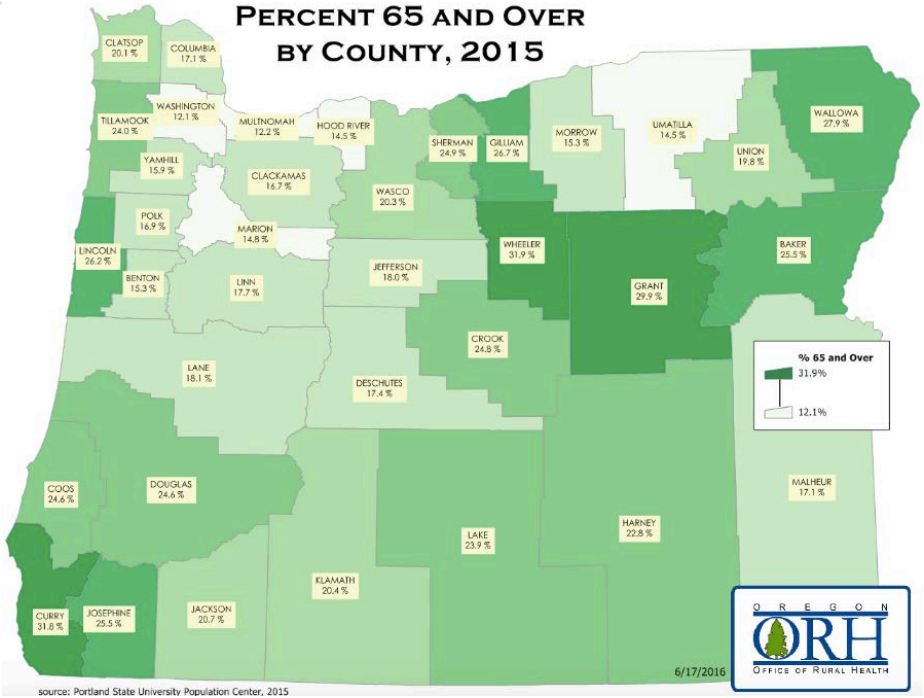
The median national rate for 2015 is based on data from 23 states. The remaining states and Washington, D.C., did not provide data.

Terry L. https://www.oregonlive.com/health/2017/07/oregon_has_top_rate_in_us_of_s.html
Harbarger M. https://www.oregonlive.com/health/2018/09/oregon_doj_says_opioid_manufac.html

What risks come with THC and CBD use?

Rural Oregonians?

- In 2017, estimated 670,000 people living in rural Oregon
  - 43% of those 65+ are living in rural areas
- Evidence suggests access to cannabis and other substances is similar to urban areas



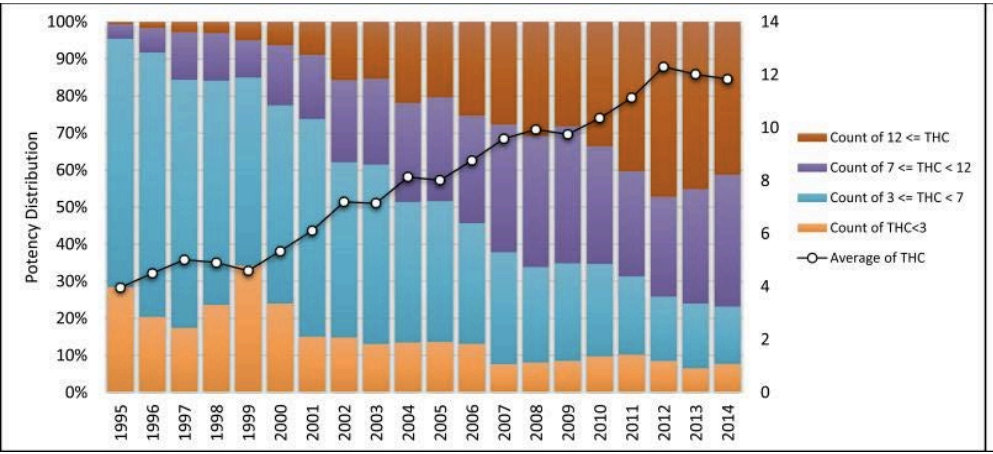
Considerations

- Remote locations
  - Access to emergency medical care
    - Higher rates of ED visits among users 50+ compared to none users
- Aggravation of comorbid conditions
  - Neurologic disorders
  - Discontinuation of medications
  - Cardiovascular concerns?
    - 20-100% increase in HR, case reports od MI associated with cannabis use
- What is the potency?

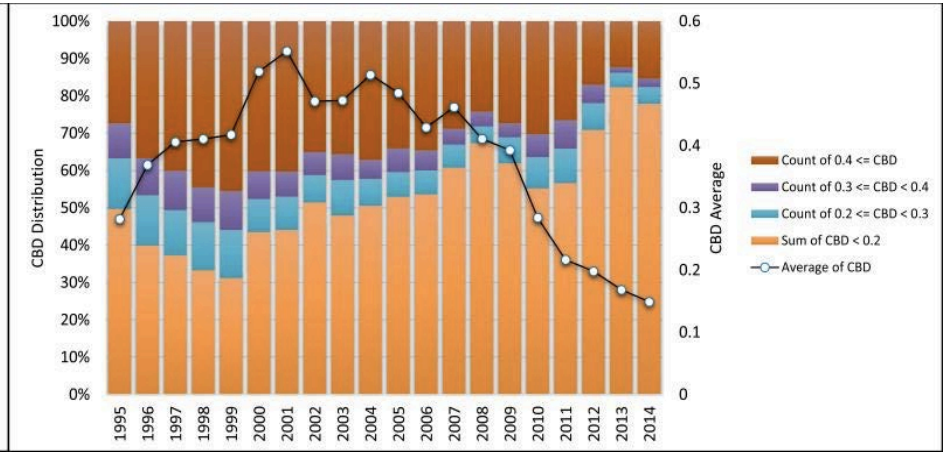
Goyle H. J Thorac Dis. 2017 Jul; 9(7): 2079–2092

Times Have Changed

- THC potencies have increased over past 20-30 years, up to 30% THC in some varieties



THC is on the rise



CBD is in decline

Pharmacokinetic Drug-Drug Interactions (DDIs)

- Pharmacokinetic DDI = alters the absorption, distribution, metabolism, or elimination of another drug
- CBD: Inhibits CYP3A4, CYP2C19, and CYP2D6
  - Decreases concentration of clopidogrel, decreases efficacy of stroke prevention
  - Increases concentration of citalopram, increases risk of QT prolongation
  - May have clinically relevant DDI with warfarin
- THC: substrate of CYP enzymes, pharmacokinetic DDIs less likely

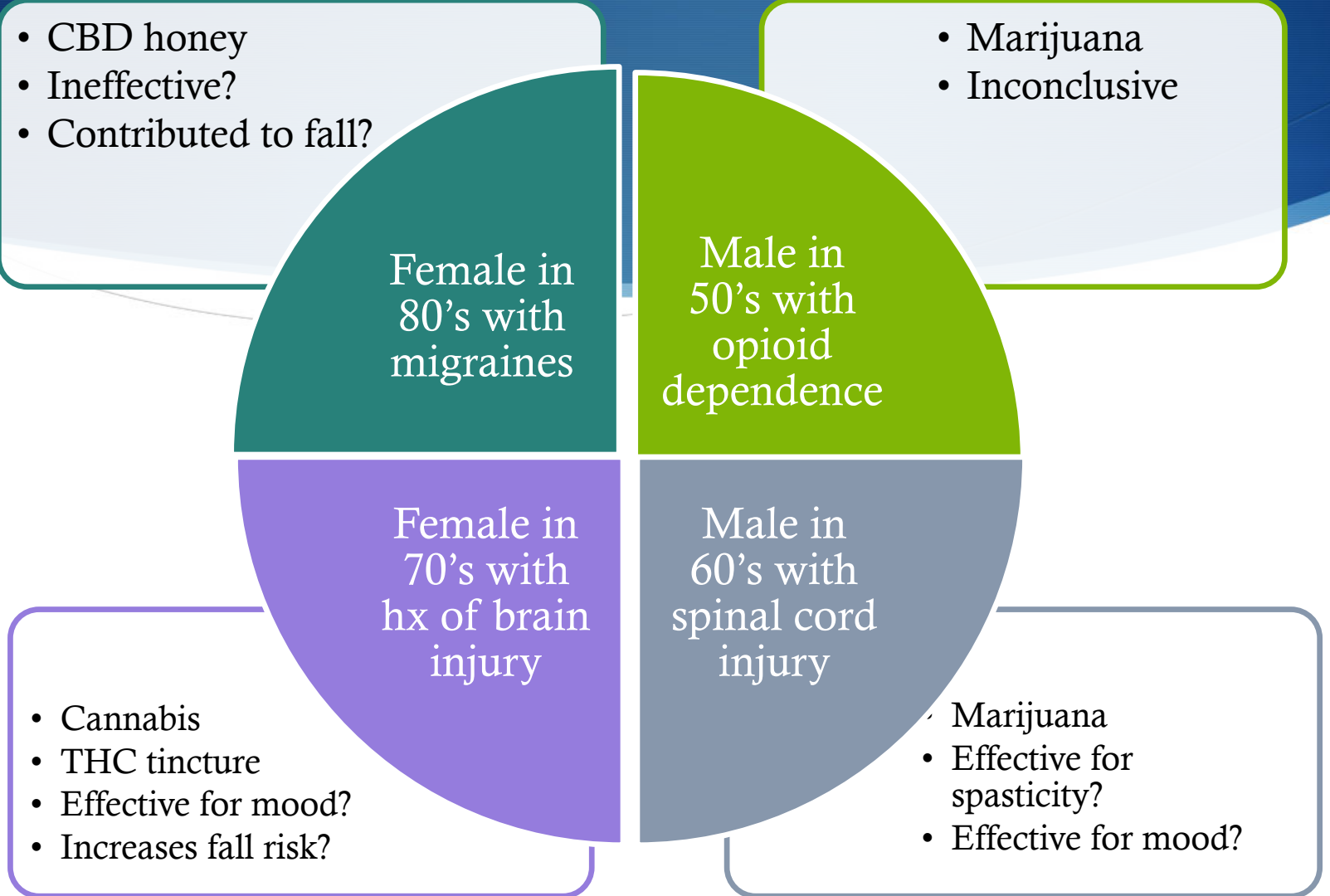
Pharmacodynamic Drug-Drug Interactions

- Pharmacodynamic DDIs = Drugs with similar side-effect profiles having a synergistic response
- CBD: Sedating
  - Increases fall risk
- THC: Anticholinergic, Psychoactive
  - DDI with cholinesterase inhibitors (used for dementia)
  - Could contribute to delirium?

Clinical experience with cannabis, THC, and CBD

Precautions for Patients

- FDA approval ≠ safety concerns and precautions
- Don't just "jump back in"
  - THC potencies are much higher today than in the past
- Driving under the influence is unsafe at any age, and with any cognitive impairing substance
- Be aware of increased risk for falls
- Speak with PCP before discontinuing any prescription medications


• CBD honey
• Ineffective?
• Contributed to fall?
• Marijuana
• Inconclusive
Female in 80's with migraines
Male in 50's with opioid dependence
Female in 70's with hx of brain injury
Male in 60's with spinal cord injury
• Cannabis
• THC tincture
• Effective for mood?
• Increases fall risk?
• Marijuana
• Effective for spasticity?
• Effective for mood?

Additional Discussion

- Any additional clinical experiences to share?
- Any clarifying questions or additional insights about DDIs?
- We welcome any further discussion on this topic!

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- Apply literature to determine potential benefits of cannabis products for future patients
- Identify clinically-relevant drug-drug interactions with THC and CBD, classifying them as pharmacodynamic or pharmacokinetic in nature