



# **Reefer Madness Revisited: Taking the Insanity Out of Medical Cannabinoids**

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## Disclosure

- Dr. Schatman is a consultant with Salix Pharmaceuticals
- Dr. Schatman has no other conflicts of interest, although he is a veteran of 34 Grateful Dead/Dead and Company concerts



# Learning Objectives

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- Describe the political issues surrounding the legalization of medical marijuana
- Recognize the obstacles to conducting high-quality medical cannabinoid research in the United States
- Discuss how to modify your medical marijuana authorization patterns based on legal realities and empirical data

# What the Heck is “Medical Marijuana”?!?!?!?

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- Lots of questions to be asked...
- Lengthy history in the US
  - ❖ California became the first state to legalize MM in 1996
- Currently there are MM laws in 33 states plus DC

Berk J, Gould S. States where marijuana is legal. Business Insider, January 1, 2020. Available at: <https://www.businessinsider.com/legal-marijuana-states-2018-1>.

- Individual states’ medical marijuana laws are incredibly heterogeneous – varying widely in terms of process of obtaining, limits on possession, rules regulating dispensaries, allowable medical conditions, and every other parameter

# What is Medical Marijuana?

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- In the eyes of the pro-marijuana zealots, ALL marijuana is “medical”
- In the eyes of the FDA, NO marijuana is “medical”
- Perhaps the truth falls somewhere in between....
- CSA (1970) made cannabis a Schedule I drug – “drugs with no currently accepted medical use and a high potential for abuse”

US Drug Enforcement Administration. Drug Scheduling. Available at: <http://www.justice.gov/dea/druginfo/ds.shtml>

- Remains federally “illegal”

# What is Medical Marijuana?

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- Is it legal or illegal?
- Should it be legal?
- Is it safe?
- Is there an evidence basis for efficacy?
- If it's sold in a dispensary, should it therefore be considered "medical"?
- If it's "medical", can it be abused?

# So Let's Complicate Things Even More....

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- What constitutes “recreational marijuana”?
- Again, to the FDA, legal recreational marijuana doesn't exist
- However, tell this to the good citizens of:

- ❖ Washington
- ❖ Colorado
- ❖ Alaska
- ❖ Oregon
- ❖ California
- ❖ Nevada
- ❖ DC
- ❖ Massachusetts
- ❖ Maine
- ❖ Vermont
- ❖ Michigan
- ❖ Illinois

Berk J, Gould S. States where marijuana is legal. Business Insider, January 1, 2020. Available at: <https://www.businessinsider.com/legal-marijuana-states-2018-1>.



# The Future of Recreational Pot?

■ Predictions for possible legalization in 2020 for more states, including:

- ❖ New York
- ❖ New Jersey
- ❖ Connecticut
- ❖ New Mexico
- ❖ Arizona
- ❖ Montana
- ❖ Pennsylvania
- ❖ Florida

Smith J. Marijuana Business Daily, January 13, 2020.



# Politics

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- 2014 – Congress passes the Rohrabacher–Blumenauer amendment, defunding the DOJ from enforcement of federal law in MM states

Lopez G. Vox, May 30, 2014.

- Must be renewed every fiscal year to stay in effect

McCoy JJ. New Frontier Data, March 17, 2018. Available at: <https://newfrontierdata.com/marijuana-insights/rohrabacher-blumenauer-what-are-the-stakes-revisited/> .

- Has been successfully renewed each year – attached to the federal budget bill
- Every time a budget agreement can't be reached, federal protection of states' laws is threatened
- And the DOJ can theoretically run wild....

# Cannabinoids

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- Marijuana contains over 100 cannabinoids

Welling MT, et al. Med Cannabis Cannabinoids. 2019;2:1–13.

- $\Delta^9$ -tetrahydrocannabinol (THC) – the principle psychoactive constituent of cannabis
- Gets all of the press – good and bad
- Recreational marijuana – goal is to maximize THC
- Seems to be the goal of “medical marijuana” as well.....
- Higher THC fetches a higher price in dispensaries

# THC:CBD Ratio

- What kinds of ratios do we see in medical and non-medical cannabis?
- Recent study of THC & CBD (medical and recreational) 2008-2017

Chandra S, et al. Eur Arch Psychiatry Clin Neurosci. 2019;269(1):5-15.

- ❖ THC levels doubled (8.9% in 2008, 17.1% in 2017)
- ❖ CBD levels decreased from 0.37% in 2008 to 0.14% in 2017
- ❖ THC:CBD ratio increase from 23:1 in 2008 to 104:1 in 2017
- ❖ Importance of the ratio: “CBD is nonintoxicating and has been found to offset several, harmful effects of  $\Delta^9$  -THC, including memory impairment and psychotic-like symptoms”

# THC:CBD Ratio

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- ❖ Authors conclude, “These trends in the last decade suggest that cannabis is becoming an increasingly harmful product”
  - The THC:CBD ratio is not examined in most studies
- Vindenes V, Morland J. Increasing plant concentrations of THC and implications on health related disorders. In: Handbook of Cannabis and Related Pathologies: Biology, Pharmacology, Diagnosis, and Treatment. Academic Press, 2017. pp. 24-32.
- Ability to understand the THC:CBD ratio and the impact of breeding the CBD out of cannabis is essential to understanding its health risks

# Synthetic THC

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- Available as a Schedule III drug (dronabinol) since 1985
- Nabilone - (Schedule II) –A synthetic THC analogue – also FDA-approved in 1985
- Common side effects include drowsiness, unsteady gait, dizziness, inability to focus thoughts, confusion, mood changes, delusions, and hallucinations – tolerability dubious

WebMD. Drugs and medications: Marinol oral. <http://www.webmd.com/drugs/drug-9308-Marinol+Oral.aspx?drugid=9308&drugname=Marinol+Oral&pagenumber=6>.

- Recent study: Dronabinol did NOT increase oxycodone analgesic effects, but did increase oxycodone “drug liking” and cognitive impairment

Babalonis S, et al. Psychopharmacology (Berl). 2019 Nov;236(11):3341-3352.

# Safety Issues Associated with Marijuana

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- The myriad safety concerns identified are thought to be due primarily to THC; more THC means more risks

Rømer Thomsen K, et al. Exp Clin Psychopharmacol. 2019;27(4):402-411.

- Smoking remains the most common route of administration

Spindle TR, et al. Curr Opin Psychol. 2019;30:98-102.

- 2018 review – pulmonary effects are even worse than we'd thought – "Marijuana Lung"

Leb JS, et al. Chronic Obstr Pulm Dis. 2018;5:81-83.

- Heavy smoking of MJ found to result in voice disorders

Meehan-Atrash J, et al. JAMA Otolaryngol Head Neck Surg. 2019[Epub ahead of print].

- Tars from smoked marijuana contain more carcinogens than do those from tobacco

Wu TC, et al. N Engl J Med. 1988;318:347-351.

# Physical Safety Issues

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- Vaporization is safer than smoking – fewer toxicants emitted

Spindle TR, et al. J Anal Toxicol. 2019;43:233–258.

- Cardiovascular risk: Increased likelihood among young MJ users (18-39) of arrhythmia and stroke

Desai R, et al. Medicina (Kaunas). 2019;55(8):E438.

- Systematic review – Increases rates of acute myocardial infarction, including in individuals with no cardiac risk factors

Patel RS, et al. Trends Cardiovasc Med. 2019[Epub ahead of print].

- Predicts acute myocardial infarction even in adolescents (15-22)

Patel RS, et al. J Adolesc Health. 2020;66(1):79-85.

- Cannabis use recently linked to stress-related cardiomyopathy

Ma L, et al. Curr Cardiol Rep. 2019;21(10):121.



# Physical Safety Issues

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- Systematic review – MJ use increased risk of both acute coronary syndrome and chronic cardiovascular disease

Richards JR, et al. Clin Toxicol (Phila). 2019;57(10):831-841.

- Increased duration of marijuana use is associated with increased risk of death from hypertension

Yankey BA, et al. Eur J Prev Cardiol. 2017;24(17):1833-1840.

- Heavy users had greater prevalence of cardiovascular risk factors (hypertension, diabetes, obesity, tobacco smoking, human immunodeficiency virus, alcohol, and cocaine abuse)

Chami T, Kim CH. Mayo Clin Proc. 2019;94(8):1647-1649.

- Immunosuppressive – Reduces T-Cell activation

Costiniuk CT, Jenabian MA. AIDS. 2019; 33(15):2273-2288.

# Physical Safety Issues

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## ■ Cannabinoid Hyperemesis Syndrome

- ❖ Characterized by a syndrome of cyclic vomiting, abdominal pain and compulsive showering in some habitual users

- ❖ Symptoms alleviated with cessation of use

Venkatesan T, et al. Neurogastroenterol Motil. 2019;31 Suppl 2:e13606.

- ❖ As many as 3.3 million cases in the US annually

Chocron Y, et al. BMJ. 2019;366:l4336.

- ❖ Fatal cases now being reported

Nourbakhsh M, et al. J Forensic Sci. 2019;64(1):270-274.

- ❖ Average case hospitalized 3.2 days, at average cost of almost \$23,000 dollars

Madireddy S, et al. Cureus. 2019;11(8):e5502.

# Physical Safety Issues

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- Drugged driving – 96% of cases involve cannabis

Bonar EE, et al. Addict Behav. 2018;78:80-84.

- Rapid increases in blood THC → delayed decrease in vigilance and driving performance empirically established

Hartley S, et al. Clin Chem. 2019;65(5):684-693.

- Drugged driving continues to increase, with increases associated with more traffic fatalities

Chung C, et al. Inj Epidemiol. 2019;6(1):3.

- In the 5 years after recreational legalization in WA & CO, fatal crashes increased there – unlike in non-legalization states

Aydelotte JD, et al. Accid Anal Prev. 2019;132:105284.

# Physical Safety Issues

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- Perhaps the issue is that users of MJ have been found to have greater perceived safety than those who don't

Borodovsky JT, et al. Prev Med. 2020;131:105956.

- Pregnancy – Use of marijuana among pregnant women increasing “dramatically”.

Nelson R. Am J Nurs. 2019;119(10):16-17.

- Recent study found 22.6% of pregnant women positive for THC

Howard DS, et al. J Addict Med. 2019;13(6):436-441.

- Cannabis use associated with preterm birth, placental abruption, lower Apgar scores, higher rates of NICU admissions

Corsi DJ, et al. JAMA. 2019;322(2):145-152.

- Likelihood of stillbirth or miscarriage 12 times higher among women using MJ during pregnancy

Coleman-Cowger VH, et al. Neurotoxicol Teratol. 2018;68:84-90.

# Physical Safety Issues

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## ■ Addiction

- ❖ Not as severe as opioid or benzo addiction
- ❖ Abrupt cessation results in irritability, insomnia, anorexia

Haney M, et al. Neuropsychopharmacology 2013;38:1557-1565.

## ■ Perceived barrier to quitting MJ – fear of severe withdrawal symptoms

Peraza N, et al. Addict Behav. 2019;90:164-170.

## ■ When used hs, withdrawal's impact on sleep is particularly problematic

Choi S, et al. J Clin Neurophysiol. 2020;37(1):39-49.

## ■ MJ use associated with decreased sleep efficiency and altered sleep architecture

Drazdowski TK, et al. J Am Coll Health. 2019[Epub ahead of print].

Gordon HW. J Addict Res (OPAST Group). 2019;3(2):1-18.

# Cognitive Safety Issues

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- We've known about chronic MJ use and its impact on diminution of grey matter in the brain for years

Block RI, et al. Neuroreport 2000;11:491-496.

- Of particular concern in the developing brain
- Executive functioning deficits associated with MJ dependence

Manza P, et al. Cereb Cortex. 2019[Epub ahead of print].

- Myriad studies and review indicate that chronic MJ use results in cognitive deficits
  - ❖ Long-term and short-term

# Cognitive Safety Issues

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- Long-term deficits include (from a 2020 narrative review of systematic reviews and meta-analyses):
  - ❖ Learning
  - ❖ Memory
  - ❖ Abstraction/Executive Functioning
  - ❖ Attention
  - ❖ Motor Skills
  - ❖ Verbal/Language

Kroon E, et al. *Addiction*. 2020;15(3):559-572

- Cognitive deficits appear to be worse when cannabis users are under stress

Zhao W, et al. *J Psychiatry Neurosci*. 2020;45(2):88-97.

# Mental Health Risks

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- Most studied issue has been early-onset psychosis and recovery from it in marijuana users
- MJ-Psychosis association recognized back to the 1950s
- One third to one half of new cases of psychosis in London & Amsterdam linked to daily high-potency MJ use

Ames F. J Ment Sci. 1958;104(437):972-999.

Hawkes N. BMJ. 2019;364:1290.

- ❖ Development of psychosis is particularly problematic in patients using ultra-high-THC wax dabs, oils, and other concentrates

Schauer GL, et al. Drug Alcohol Depend. 2020[Epub ahead of print].



# Mental Health Risks – Psychosis

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- Cannabis use by schizophrenics is associated with failure of anti-psychotic medications

Arsalan A, et al. Psychiatry Res. 2019;278:242-247.

- ❖ As well as is adherence to anti-psychotic medications

Murray RM, et al. Schizophr Res. 2020[Epub ahead of print].

- Extended abstinence from MJ doesn't seem to reverse symptoms in cannabis-dependent schizophrenics

Rabin RA, et al. Schizophr Res. 2018;194:55-61.

- Increases risk of violence in patients with psychotic disorders

Lamsma J, et al. Psychol Med. 2019[Epub ahead of print].

# Mental Health Risks - Anxiety

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- The acute induction of anxiety associated with THC cannot be ignored
- Early studies found an anxiolytic effect of MJ

Sethi BB, et al. Biol Psychiatry 1986;21:3-10.

- Recent research suggests that cannabis-induced cortisol hyporesponsiveness is responsible for panic symptoms

Petrowski K, Conrad R. Psychopathology. 2019;52(1):26-32.

❖ However, this may have much to do with Indica vs. Sativa strains

- Longitudinally, reduction of MJ use is associated with decreased anxiety

Ouellette MJ, et al. Can J Addict. 2019;10(3):30-37.

# Mental Health Risks - Anxiety

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- PTSD – Once thought to be “treatable” with cannabis
- However chronic MJ use has been found to impair fear extinction, and make users oblivious to threat cues

Papini S, et al. J Abnorm Psychol. 2017;126:117-124.

Blair RJR, et al. J Child Adolesc Psychopharmacol. 2019;29(7):526-534.

- MJ use strongly predicts dropout from therapeutic treatment of PTSD

Bedard-Gilligan M, et al. Psychol Addict Behav. 2018;32(3):277-288.

- Recent study – In military personnel, MJ increases the severity of PTSD and its use is associated with increased suicidal ideation

Allan NP, et al. Depress Anxiety. 2019; 36(11):1072-1079.

# Cannabidiol (CBD)

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- Contrary to popular belief, THC is not the most relevant cannabinoid for medical application

Pacher P, et al. Annu Rev Pharmacol Toxicol. 2019[Epub ahead of print].

- CBD was first isolated in 1934

Robson P. Br J Psychiatry 2001;178:107-115.

- First synthesized in 1967, first easily useable form in 1985

Baek SH, et al. Tetrahedron Lett. 1985;26:1083-1086.

- Ignored for many years
- Seen as something limiting the amount of THC marijuana plant could potentially contain

# CBD

- Of no interest to recreational users....and tragically, for many medical users
- Initially described as “non-psychotropic”
- However, produces anxiolysis through increasing serotonergic transmission....and reverses allodynia

De Gregorio D, et al. Pain 2019;160(1):136–150.

- Appears to have a mild antidepressant effect for those with low levels of serotonin

Sales AJ, et al. Mol Neurobiol. 2019;56(2):1070-1081.

- More appropriately called “non-euphoriant”

Russo EB. Ther Clin Risk Manag. 2008;4:245-259.

# CBD Safety Profile

- Safety profile had been believed to be well-established

Cunha JM, et al. Pharmacol. 1980;21:175-185.

Devinsky O, et al. Lancet Neurol. 2016;15:270–278.

McGuire P, et al. Am J Psychiatry 2018;175:225-231.

- Ultra-high dosages may have hepatic implications

Ewing LE, et al. Molecules. 2019;24(9). pii: E1694.

Huestis MA, et al. Curr Neuropharmacol. 2019;17(10):974-989.

- The Director of NIDA wrote, “CBD appears to be a safe drug”

Volkow N. Huffington Post July 23, 2015.

- Dosing? We’re clueless... No associations found between CBD dose and patient-reported benefits

Gulbransen G, et al. BJGP Open. 2020[Epub ahead of print].

- Attenuates the “high” caused by THC at 8:1 CBD:THC ratio

Kim PS, Fishman M. Curr Pain Headache Rep. 2017;21(4):19.

# CBD Availability

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- Despite its safety profile and the impossibility of abusing it, CBD from whole plant MJ is still considered a Schedule I drug
- Other than recently FDA-approved Epidiolex
- Has been available in all medical marijuana states
- 13 states had the wisdom to legalize it without MM legalization
- New changes in the law allow for CBD from the hemp plant

Traynor K. Am J Health Syst Pharm. 2018;75:1088-1089.

McGarrell SL, Maguire TC. National Law Rev., December 20, 2018. Available at:

<https://www.natlawreview.com/article/2018-farm-bill-signed-law-includes-major-changes-involving-hemp>.

# CBD Legal Status

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- Hemp plant is in the same genus as MJ, but contains, by definition and law, <0.3% THC content

Shannon S, et al. Perm J. 2019;23:18-041.

- THC will not show up in standard UDT immunoassays
- Now most commonly used for stress relief, relaxation, and sleep improvement

Wheeler M, et al. Subst Use Misuse. 2020[Epub ahead of print].

- Due to lack of regulation, FDA found that many CBD products contain little to no CBD, in marked contrast to their labeled amounts

White CM. J Clin Pharmacol. 2019;59(7):923-934.



# CBD and Pain

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- Much of the existing supportive data is preclinical
- CBD is anti-inflammatory to cultured skin fibroblasts

Gęgotek A, et al. Cells. 2019;8(9). pii: E995.

- Attenuation of early phase inflammation by cannabidiol prevents pain and nerve damage in osteoarthritis

Philpott HT, et al. Pain 2017; 158:2442-2451.

- Relevance for back pain: CBD has anti-inflammatory effects on rat nucleus pulposus cells – needs further study

Chen J, et al. Mol Med Rep. 2016;14:2321-2327.

## More CBD Research

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- Reduces chemotherapy-related peripheral neuropathy, and does so to an even greater degree when combined with low-dose morphine

Brenneman DE, et al. J Mol Neurosci. 2019;68(4):603-619.

Harris HM, et al. Med Cannabis Cannabinoids 2018;1:54–59.

- Safety established when co-administered with fentanyl

Manini AF, et al. J Addict Med. 2015;9:204-210.

- Enhances fracture healing

Apostu D, et al. Drug Metab Rev. 2019;51(4):498-523.

# More CBD Research

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- Animal model - Protective effects on lesion-induced intervertebral disc degeneration

Silveira JW, et al. PLoS One 2014;9:e113161.

- Animal model – synergistic with morphine

Rodríguez-Muñoz M, et al. Mol Brain. 2018;11(1):51.

- But we have to watch the preclinical researchers and their sneaky lab animals...

# Rat Cheating on a Forced-Swim Test

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# CBD and Pain - Clinical

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- In humans, CBD studies are scant and of limited quality
  - ❖ CBD relieved somatoform symptoms, including chronic pain, and improved QOL in young girls attributed to the human papillomavirus vaccine

Palmieri B, et al. Isr Med Assoc J. 2017;19:79-84.
  - ❖ Effective for reducing chronic pain in kidney transplant patients

Cunettia L, et al. Transplantation Proc. 2018;50:461-464.
  - ❖ Decreased anxiety and improved sleep scores

Shannon S, et al. Perm J. 2019;23:18-041.
- Paucity of recent CBD and pain studies indicative of the need to standardize what's sold as "CBD"

# Marijuana and Pain Research

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- Extremely difficult to do in the US
  - All NIDA-funded MM research currently has to use low-grade MJ grown at the U of Mississippi for NIDA
  - 3 dose strengths available
    - ❖ Low potency (1.29% THC)
    - ❖ Moderate potency (3.53%)
    - ❖ High potency (7%)
- Reardon S. Nature. 2019;569(7755):172.
- Why is this a problem?

# Marijuana and Pain Research

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- Oil or wax dabs available at many dispensaries have THC contents greater than 90%!!!!

- ❖ Concentrates account for 28.5% of sales in Washington's recreational cannabis market

Davenport S. Int J Drug Policy. 2019[Epub ahead of print].

- Medical marijuana products sold in dispensaries are higher in THC than that sold on the streets

Bidwell LC, et al. Addict Behav Rep. 2018;8:102-106.

- Recent breakthrough – NIDA has approved a 13.4% THC MJ for research

# Edibles

- THC dosing in edibles has been described as “insane” by toxicologists

Gussow L. Emerg Med News 2014;36:24.

- Edibles are infused with almost pure THC
- They typically take 30-90 minutes to take effect, reach their peak in 3 hours, and can last for up to hours

Noble MJ, et al. Clin Toxicol (Phila). 2019;57(8):735-742.

- Thus, they don't allow for titration due to a lack of immediate effect
- Labeling of constituents' contents is generally inaccurate, impossible to understand

Tsutaoka B, et al. Clin Pediatr (Phila). 2018;57(2):227-230.

Hammond D. Int J Drug Policy. 2019[Epub ahead of print].



# Edibles

- Edibles are more likely to result in ED presentations for intoxication, acute psychiatric symptoms, and cardiovascular symptoms than inhaled MJ

Volkow ND, Baler R. Ann Intern Med. 2019;170(8):569-570.

- Myocardial infarction

Saunders A, Stevenson RS. Can J Cardiol. 2019;35(2):229.e1-229.e3.

- In Colorado, the only deaths definitively associated with cannabis use involved edibles

Monte AA, et al. Ann Intern Med. 2019;170(8): 531–537.



# Science vs. “Religion”

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- Medical marijuana advocates tend not to let the data get in the way of their opinions
- Try discussing potential harms of MM on Twitter....
- “There is none so blind as those who will not see...”



# MM and Pain Research – What DO We Know?

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- Is it effective for chronic pain?
- Depends on the properties of the marijuana being used and one's definition of “effective”
- It also depends upon goals of treatment
  - ❖ Is analgesia sufficient, even if it incapacitates the patient?
- It also depends on the medical indication
- E.g., opioids are effective for many types of pain, but not for neuropathic pain

# MM and Pain Research

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- Neuropathic pain – a number of studies demonstrate analgesia, but requires higher dosages – which result in cognitive deficits

Wilsey B, et al. J Pain 2008;9:506–521.

Ellis RJ, et al. Neuropsychopharmacology 2009;34:672-680.

Ware MA, et al. CMAJ 2010;182:E694-701.

Wallace MS, et al. J Pain 2015;16:616-627.

Wilsey B, et al. J Pain 2016;17:982-1000.

- 2013 study using low-dose (1.29% THC) MJ – limited efficacy for neuropathic pain, without significant cognitive effects

Wilsey B, et al. J Pain 2013;14:136-148.

# MM and Pain Research

- Conclusions of MJ for neuropathic pain:
  - ❖ Weak evidence as effective in terms of analgesia at higher doses
  - ❖ Cognitive side effects are dose-related
  - ❖ Never studied head-to-head against gabapentinoids
  - ❖ Gabapentinoids also have dose-related cognitive side effects
  - ❖ Research needed on MM with significant CBD content as well
  - ❖ Research needed on the types of MJ actually carried in dispensaries (25%+ THC)
- Recommendation: Consider as a last option for neuropathic pain
- Strongest evidence – May be for MS-related spasticity

Murff HJ. Ann Intern Med. 2017;167:JC62.

Urits I, et al. Curr Pain Headache Rep. 2019;23(8):59.

# MM and Pain Research

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- Musculoskeletal pain and arthritis – “Evidence is Needed”

Perrot S, Trouvin AP. Joint Bone Spine. 2019;86(1):1-3.

- Rheumatic conditions – no evidence for efficacy

Fitzcharles MA, et al. J Rheumatol. 2019;46(5):532-538.

- Fibromyalgia – Israeli study hopeful, but inconclusive

Sagy I, et al. J Clin Med. 2019 Jun 5;8(6). pii: E807.

- Headache – MJ interferes with botulinum toxin for migraines

Chan TLH, Zhang N. Can J Neurol Sci. 2019;46(6):785-786

- Cancer pain – “Nabiximols and THC have no effect on pain, sleep problems and opioid consumption in patients with cancer pain with insufficient pain relief from opioids”

Häuser W, et al. Schmerz. 2019;Oct;33(5):424-436.



# MM and Opioids

- The most compelling evidence basis for MJ in treating chronic pain was for its opioid-sparing effect

Boehnke KF, et al. J Pain 2016;17:739-744.

- Medical cannabis laws were associated with lower opioid overdose mortality rates

Bachhuber MA, et al. JAMA Intern Med. 2014;174:1668-1673.

- This has reversed itself over time

Shover CL, et al. Association between medical cannabis laws and opioid overdose mortality has reversed over time. Proc Natl Acad Sci U S A. 2019;116(26):12624–12626.

- Recent data indicate that recreational legalization does not influence compliance with opioid therapy

Lo S-Y, et al. Am J Med. 2019;132(3):347-353.

- Synergistic with opioids? Likely urban myth...

# MM and Opioids

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- Not associated with lower prescription rates and dosages of Schedule II opioids

Liang D, et al. Addiction. 2018;113(11):2060-2070.

- “Cannabis use appears to increase rather than decrease the risk of developing nonmedical prescription opioid use and opioid use disorder”

Olfson M, et al. Am J Psychiatry. 2018;175(1):47-53.

- “Multivariable analyses indicated that medical cannabis use was significantly associated with risk of prescription opioid misuse”

Nugent SM, et al. Gen Hosp Psychiatry. 2018;50:104-110.

- Cannabis use associated with “non-medical” use of opioids

Gillespie NA, et al. Addiction. 2019;114(12):2229-2240



# MM and Opioids

- Similarly, medical marijuana users more likely to use prescription drugs – including opioids – non-medically

Caputi TL, Humphreys K. J Addict Med. 2018;12(4):295-299.

- Perioperative opioid use is significantly higher in MJ-users despite lower subjective pain scores

Bauer FL, et al. Perm J. 2018 Jul 19;22.

- Medical and non-medical cannabis use increase risk of prescription opioid use disorders

Liang D, et al. Drug Alcohol Rev. 2019;38(6):597-605.

- Predictive of a 2.5-fold increase in the rate of opioid aberrancy

DiBenedetto DJ, ... Schatman ME, et al. Pain Med. 2018;19:1997-2008.

# MM and Opioids

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- MJ use associated with higher prescription opioid use following traumatic musculoskeletal injury

Bhashyam AR, et al. J Bone Joint Surg Am. 2018;100(24):2095-2102.

- Alcohol and cannabis misuse issues recently found to relate to severity of opioid dependency and opioid misuse in chronic pain patients

Roger AH, et al. Int J Behav Med. 2019;26(5):569-575.c

Twardowski MA, et al. J Am Osteopath Assoc. 2019[Epub ahead of print].

- Methodologic issue with new studies claiming that states with MML laws see lower death tolls from opioid ODs – Don't take into account dramatic decreases in overall opioid prescribing

# “Watcha Smoking, Dude?”

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- To talk about “medical marijuana” as a single entity is ridiculous
- We need to be discussing “medical **marijuanas**”
- Indica or sativa? – 2 separate species, usually in a hybrid form
- Indicas empirically established as preferable for pain management, but cause more sedation than sativas

Cohen NL, et al. J Stud Alcohol Drugs 2016;77(3):515-520.

## Treatment Recommendation

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- “The Medicinal Cannabis Treatment Agreement: Providing Information to Chronic Pain Patients via a Written Document”

B Wilsey, et al. Clin J Pain 2015;31:1087-1096.

- Absolutely brilliant!!!!
- “Medical marijuana” is heavily abused

Meffert BN, et al. Curr Drug Res Rev. 2019;11(1):3-11.

- “....physicians would seem to have an obligation to understand and inform their patients on key issues of the evidence base on cannabinoid therapeutics”

# Medical Cannabis Agreement

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- Covers reduction of diversion, inappropriate utilization, risks of cannabis, vaporizing vs. smoking, Warns against driving a car or operating machinery, “starting low, going slow” when dosing, slowly withdrawing if a patient wants to stop treatment, the need to evaluate the efficacy and appropriateness of therapy on an ongoing basis, not using in public places, medical authorization will NOT protect a patient’s job, and the physician the right to discontinue MM treatment

## Closing Thoughts

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- The future of medical cannabinoids in the US is uncertain
- To assume that marijuana is safe because it's "natural" is neuromysticism
- As is assuming that anecdotal evidence of efficacy provides us with "the truth"
- Improving the quality and quantity of MM research is imperative if MJ is ever to become "medicine"
- CBD, not THC, promises to be the most medically-relevant cannabinoid

## Closing Thoughts

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- If you're going to use MM in your practice, educate yourself and your patient – and do it right
- Take marijuana as a drug seriously – irrespective of what you smoked as a youth
- If you use an opioid agreement, consider using a medical cannabis agreement
- Practicing cannabinoid medicine is challenging when we know so little
- Better data are hopefully just around the corner

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THANK YOU