



Reefer Madness Revisited: Taking the Insanity Out of Medical Cannabinoids

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Disclosure

Consultant/Independent Contractor:
Kaleo Pharma; Quest Diagnostics;
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Pharmaceuticals

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



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Learning Objectives

- 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



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

- 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

National Conference of State Legislatures. State medical marijuana laws, 2/11/2019. Available at: <http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx>
- 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



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What is Medical Marijuana?

- 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/djs.shtml>
- Remains federally “illegal”



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What is Medical Marijuana?

- 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?



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

- 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

Governing: State Marijuana Laws in 2019 Map, June 25, 2019.
 Available at: <https://www.governing.com/gov-data/safety-justice/state-marijuana-laws-map-medical-recreational.html>



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The Future of Recreational Pot?

- Predictions for legalization in 2020 for more states, including:
 - ❖ New York
 - ❖ New Jersey
 - ❖ Ohio
 - ❖ Arizona
 - ❖ Florida

William S. USA Today, June 16, 2019.



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Politics

- 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 J.J. 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....



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Cannabinoids

- Marijuana contains over 100 cannabinoids
- Welling MT, et al. Med Cannabis Cannabinoids. 2019;2:1-13.
- Δ9-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



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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 Δ9 -THC, including memory impairment and psychotic-like symptoms”



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THC:CBD Ratio

- ❖ 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



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Synthetic THC

- 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/2/drug-9308-Marinol-Oral-assay/9308/drugname=Marinol-Oral&reportnumber=9>

- 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[Epub ahead of print].



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Safety Issues Associated with Marijuana

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

Romer 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[Epub ahead of print].

- 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.



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Physical Safety Issues

- Vaporization is safer than smoking – fewer toxicants emitted
- Cardiovascular risk: Increased likelihood among young MJ users (18-39) of arrhythmia and stroke

Spindle TR, et al. J Anal Toxicol. 2019[Epub ahead of print].

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

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

- Predicts heart failure and CVA – whether recreational or medical

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

- Cannabis use recently linked to stress-related cardiomyopathy

Kalla A, et al. J Cardiovasc Med (Hagerstown). 2018;19:480-484.

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



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Physical Safety Issues

- **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**
Costinriuk CT, Jenabian MA. AIDS. 2019[Epub ahead of print].



HIV, among others

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Physical Safety Issues

- **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**
Verkatesan T, et al. Neurogastroenterol Motil. 2019;31 Suppl 2:e13606.
 - ❖ **Estimated 2.75 million cases in the US annually**
Habboushe J, et al. Basic Clin Pharmacol Toxicol. 2018;122:660-662.
 - ❖ **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**
Madreddy S, et al. Cureus. 2019;11(8):e5502.



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Physical Safety Issues

- **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**
Aydellotte JD, et al. Accid Anal Prev. 2019[Epub ahead of print].



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Physical Safety Issues

- Perhaps the issue is that users of MJ have been found to have greater **perceived safety** than those who don't
Mason M, et al. Addict Res Theory. 2019[Epub ahead of print].
- **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[Epub ahead of print].
- **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**
Cohen AS, et al. Neurotoxicol Teratol. 2019;68:84-90.



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Physical Safety Issues

- **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**
Zvolensky MJ, et al. Addict Behav. 2018;76:45-51.
- **When used hs, withdrawal’s impact on sleep is particularly problematic**
Livne O, et al. Drug Alcohol Depend. 2019;195:170-177.
- **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.



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Cognitive Safety Issues

- **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



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Cognitive Safety Issues

▪ Long-term deficits include (from a 2019 narrative review of systematic reviews and meta-analyses):

- ❖ Learning
- ❖ Memory
- ❖ Abstraction/Executive Functioning
- ❖ Attention
- ❖ Motor Skills
- ❖ Verbal/Language

Kroon E, et al. Addiction. 2019[Epub ahead of print].

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

Meier MH, et al. J Psychiatry Neurosci. 2019[Epub ahead of print].



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Mental Health Risks

▪ Most studied issue has been early-onset psychosis and recovery from it in marijuana users

▪ MJ-Psychosis association recognized back to the 1950s

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

▪ One third to one half of new cases of psychosis in London & Amsterdam linked to daily high-potency MJ use

Hawkes N. BMJ. 2019;364:1290.

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

Meier MH, et al. Pediatrics. 2019;144(3). pii: e20190338.



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Mental Health Risks – Psychosis

▪ 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

Reid S, Bhattacharyya S. Psychiatry Res. 2019;280:112523.

▪ 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

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



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Mental Health Risks - Anxiety

- 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 K1, Conrad R. Psychopathology. 2019;52(1):26-32.
 - ❖However, this may have much to do with Indica vs. Sativa strain
- Longitudinally, reduction of MJ use is associated with decreased anxiety
Cuellette MJ, et al. Can J Addict. 2019;10(3):30-37.



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Mental Health Risks - Anxiety

- 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[Epub ahead of print].



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Cannabidiol (CBD)

- 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



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CBD

- Of no interest to recreational users....and tragically, for many medical users
- Initially described as “non-psychoactive”
- 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.



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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[Epub ahead of print].
- The Director of NIDA wrote, “CBD appears to be a safe drug”
Volkow N. Huffington Post July 23, 2015.
- Dosing? We’re clueless...
Millar SA, et al. Br J Clin Pharmacol. 2019;85(9):1888-1900.
- Attenuates the “high” caused by THC at 8:1 CBD:THC ratio
Kim PS, Eisman M. Curr Pain Headache Rep. 2017;21(4):19.



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CBD Availability

- 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
Traynor K. Am J Health Syst Pharm. 2018;75:1088-1089.
- 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
McGarrell SL, Maguire TC. National Law Rev. December 20, 2018. Available at: <https://www.nationallawreview.com/article/2018-farm-bill-signed-law-includes-major-changes-involving-hemp>.



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CBD Legal Status

- 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 pain, anxiety, depression, and sleep disorders
Corroon J, Phillips JA. Cannabis Cannabinoid Res. 2018;3:152-161.
- 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.



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CBD and Pain

- Much of the existing supportive data is preclinical
- CBD is anti-inflammatory to cultured skin fibroblasts
Gegotek 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
Chen J, et al. Mol Med Rep. 2016;14:2321-2327.



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More CBD Research

- 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[Epub ahead of print].



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More CBD Research

- Animal model - Protective effects on lesion-induced intervertebral disc degeneration
Silveira JW, et al. PLoS One 2014;9:e113161.
- Animal model – synergistic with morphine
Neelakantan H, et al. Behav Pharmacol. 2015;26:304-314.
- But we have to watch the preclinical researchers and their sneaky lab animals...



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Rat Cheating on a Forced-Swim Test



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CBD and Pain - Clinical

- 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
Cunetta 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"



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Marijuana and Pain Research

- 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?



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Marijuana and Pain Research

- 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
- Devenport 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



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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].



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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(6):569-570.

- Myocardial infarction

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

- And multiple deaths

Calandrello SP, Fulton KJ. University of Washington School of Law Research Paper No. 2019-07, 2019. Available at: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3163729.



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Science vs. "Religion"

- 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..."



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MM and Pain Research – What DO We Know?

- 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



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MM and Pain Research

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

Wiseley B, et al. J Pain 2008;9:506-521.
 Ellis PJ, 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.
 Wiseley B, et al. J Pain 2016;17:982-1000.

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

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



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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

Wiseley B, et al. J Pain Headache Rep. 2019;23(8):59.



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MM and Pain Research

- 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[Epub ahead of print].

- 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[Epub ahead of print].

- 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”

Wiseley B, et al. Schmerz. 2019[Epub ahead of print].



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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. 2018[Epub ahead of print].
- Synergistic with opioids? Likely urban myth...



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MM and Opioids

- 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”
Olsson 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[Epub ahead of print].



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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[Epub ahead of print].
- Predictive of a 2.5-fold increase in the rate of opioid aberrancy
Chen J, et al. Schatman ME, et al. Pain Med. 2018;19:1997-2008.



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MM and Opioids

- MJ use associated with higher prescription opioid use following traumatic musculoskeletal injury
Bhaskyam 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[Epub ahead of print].
- MJ users were found to have a sedation requirement significantly higher than non-users for operative procedures
Twardowski MA, et al. J Am Osteopath Assoc. 2019[Epub ahead of print].
- MJ users have considerably more risks associated with anesthesia
Echeverria-Villalobos M, et al. J Clin Anesth. 2019;57:41-49



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“Watcha Smoking, Dude?”

- 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.



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Treatment Recommendation

- “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”



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Medical Cannabis Agreement

- Covers reduction of diversion – particularly to vulnerable children and adolescents
- Addresses inappropriate utilization by the authorized patient
 - ❖We must not lose sight of the data indicating that marijuana is indeed addictive
- Discusses the risks of marijuana generally and to specific populations
- Recommends vaporization over smoking



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Medical Cannabis Agreement

- Warns against driving a car or operating machinery
- Emphasizes “start low, go slow” when dosing – particularly with new strains
- Covers potential benefits of FDA-approved cannabinoids over smoked marijuana
 - ❖Based on empirical evidence...and clinical experience, I disagree
- Recommends withdrawing slowly if a patient wants to stop
- Addresses the need to evaluate the efficacy and appropriateness of therapy on an ongoing basis
- Covers not using MM in public places



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Medical Cannabis Agreement

- Warns that medical authorization will NOT protect a patient’s job
- Gives the physician the right to discontinue MM treatment
- Respect for patient autonomy is contingent upon the doctrine of informed consent
 - Dalla-Vorgia P, et al. J Med Ethics 2001;27:59-61.
- This is exactly what these agreements are providing
- Thus – they constitute ethical pain medicine practice
- And perhaps even protect the physician as well as the patient



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Closing Thoughts

- 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



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Closing Thoughts

- 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



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