Reefer Madness Revisited

Michael E. Schatman, PhD

Michael E. Schatman, Ph.D.
Department of Public Health and Community Medicine
Tufts University School of Medicine
Disclosure

- Consultant/Independent Contractor: Kaleo
- Speaker's Bureau: Kaleo
- Veteran of 31 Grateful Dead/Dead and Company concerts

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
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 32 states plus DC
- 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?

- 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”
- Remains federally “illegal”
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?

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
The Future of Recreational Pot?

- Predictions for legalization in:
  - Arizona
  - Arkansas
  - Connecticut
  - Delaware
  - Florida
  - Illinois
  - Maryland
  - Minnesota
  - Montana
  - New Hampshire
  - New York
  - Ohio
  - Rhode Island


Politics

- Only add to the craziness around medical marijuana
- Obama administration: AG Holder, 2009: “[t]he policy is to go after those people who violate both federal and state law”
- 2011 – Policy reversal, and the Justice Department began to raid dispensaries in selected states, blaming them for letting the industry get out of control
Politics

- 2012 – President Obama announced that cannabis use in states in which it is legal was not a priority for DOJ
- December, 2012 – WA and CO pass recreational MJ laws, Obama administration supported states’ rights
- 2014 – Congress passes the Rohrabacher–Blumenauer amendment, defunding the DOJ from enforcement of federal law in MM states

Politics

- Must be renewed every fiscal year to stay in effect
- 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

- Marijuana contains over 100 cannabinoids
- 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

THC:CBD Ratio

- What kinds of ratios do we see in medical vs. non-medical cannabis?
- Study of over 5000 samples of cannabis seized in CA between 1996-2008:
  - THC levels increased from 4.56% to 11.75%
  - CBD levels decreased from 0.24% to 0.08%
  - Increases in THC thought to be due to shift from traditional strains to sinsemilla
THC:CBD Ratio

- Currently, measurable levels of CBD are rarely found in herbal cannabis
- Niesink RJ, van Laar MW. Front Psychiatry 2013;4:130.
- The THC:CBD ratio is not examined in most studies
  - Most current data come from toxicology following seizures
- 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

- Available as a Schedule III drug (dronabinol/Marinol) since 1985
- Nabilone/Cesamet (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 is dubious
- Consequently, so is clinical utility for pain
Safety Issues Associated with Marijuana

- The myriad safety concerns identified are thought to be due primarily to THC; more THC means more risks
- Can we assume that as the THC levels continue to rise, that safety risks will do the same?
- Smoking remains the most common route of administration
- Recent review – pulmonary effects are even worse than we’d thought – “Marijuana Lung”
- Tars from smoked marijuana contain more carcinogens than do those from tobacco

Physical Safety Issues

- Insufficient data on safety of vaporization – “Preliminary findings do support the idea that vaporization is an improvement over smoking”
- Increases rates of acute myocardial infarction and cardiovascular mortality – doubles rate of MI
- Predicts heart failure and CVA – whether recreational or medical
Physical Safety Issues

- Associated with higher rates of acute ischemic stroke
- Increased duration of marijuana use is associated with increased risk of death from hypertension
- Sexual functioning - THC impairs gonadal function by blocking gonadotropin-releasing hormone (GnRH) release
- Immunosuppressive – Reduces T-Cell activation

Physical Safety Issues

- Cannabinoid Hyperemesis Syndrome
  - Characterized by a syndrome of cyclic vomiting, abdominal pain and compulsive showering in some habitual users
  - Symptoms improve with cessation utilization
  - The prevalence of cannabinoid hyperemesis syndrome seen in EDs has doubled since the liberalization of marijuana laws in Colorado
  - Can masquerade as an eating disorder
  - Estimated 2.75 million cases in the US annually
  - Fatal cases now being reported
Physical Safety Issues

- Cannabis use is associated with higher rates of occupational injuries, injury severity, and prolonged lost workdays among construction workers
- Drugged driving – 96% of cases involve cannabis
- Drugged driving continues to increase, with increases associated with more traffic fatalities

French study: One in two drivers in fatal accidents under the influence of ETOH were also under the influence of cannabis

- High-risk drinking behavior recently found to be related to medical cannabis utilization
  Davis AK, et al. Addict Behav. 2018;77:166-171.
- Older adults – Cannabis use associated with greater physical injury risk and ED visits
- Increases the likelihood of fatal two-vehicle crashes
Physical Safety Issues

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

- Pregnancy – Use of marijuana among pregnant women increased by 69% between 2009 and 2016
- Currently at 22%
- Cannabis use associated with preterm birth
- Likelihood of stillbirth or miscarriage 12 times higher among women using MJ during pregnancy

Physical Safety Issues

- Addiction
  - Not as severe as opioid or benzo addiction
  - Abrupt cessation results in irritability, insomnia, anorexia
- Perceived barrier to quitting MJ – fear of severe withdrawal symptoms
- When used hs, withdrawal’s impact on sleep is particularly problematic
- Reduced MJ use associate with improved sleep quality
Cognitive Safety Issues

- We’ve known about chronic MJ use and its impact on diminution of grey matter in the brain for years
- Of particular concern in the developing brain
- Executive functioning deficits associated with MJ use
- Myriad studies and review indicate that chronic MJ use results in cognitive deficits
  - Long-term and short-term

Cognitive Safety Issues

- Long-term deficits (“residual cannabis effect”) include (from a meta-analysis):
  - Learning
  - Forgetting/Retrieval
  - Abstraction/Executive Functioning
  - Attention
  - Motor Skills
  - Verbal/Language
Mental Health Risks

- Clearly are going to overlap with cognitive risk data, although no consensus regarding the extent of such
- Most studied issue has been early-onset psychosis and recovery from it in marijuana users
- MJ-Psychosis association recognized back to the 1950s
- High THC cannabis increases the risk of psychosis 3-fold compared to non-users, and 5-fold among daily users
  – Particularly problematic in patients using ultra-high-THC wax dabs

Mental Health Risks – Psychosis

- Cannabis use in first episode psychosis is associated with failure of anti-psychotic medications
  – As well as is adherence to anti-psychotic medications
- Extended abstinence from MJ doesn’t seem to reverse symptoms in cannabis-dependent schizophrenics
- A risk factor for violent behavior in early phase psychosis
Mental Health Risks – Bipolar Disorder

- Cannabis using patients with bipolar disease demonstrate poorer treatment adherence
- Cannabis predicts earlier age of bipolar disorder onset
  – The heavier the use, the earlier the onset
- Continued MJ use following diagnosis is associated with higher risk of recurrence and poorer functioning

Mental Health Risks – Bipolar Disorder

- MJ use has been associated with lower remission rates in patients with Bipolar Disorders
- A significant correlation between MJ use and suicide attempts in patients with bipolar disorders
- Cannabinoid hyperemesis syndrome is associated with manic episodes due to lowering of serum mood stabilizer levels
Mental Health Risks - Anxiety

- The acute induction of anxiety associated with THC cannot be ignored
- Early studies found an anti-anxiety effect of MJ
- Recent meta-analysis concludes that THC’s impact on anxiety is not necessarily impressive
  - However, that may have much to do with Indica vs. Sativa strain
- Recent study found that longitudinally, reduction of MJ use was associated with decreased anxiety

---

Mental Health Risks - Anxiety

- PTSD – Once thought to be “treatable” with cannabis
  However chronic MJ use has been found to impair fear extinction
- MJ use after initiating tx associated with worse PTSD symptoms, more violent behavior, and alcohol use
- Indicas may be helpful, activating sativas likely to exacerbate
- Good news: Dispensary employees found to be more likely to recommend an indica or a hybrid for PTDS than a sativa
Cannabidiol (CBD)

- Contrary to popular belief, THC is not the most relevant cannabinoid for medical application
- CBD was first isolated in 1934
- First synthesized in 1967, first easily useable form in 1985
- Ignored for many years
- Seen as something limiting the amount of THC marijuana could potentially contain

CBD

- Of no interest to recreational users….and tragically, for many medical users
- Initially described as “nonpsychotropic”
- However, produces anxiolysis through increasing serotonergic transmission
- Appears to have a mild antidepressant effect with those with low levels of serotonin
- More appropriately called “noneuphoriant”
Rat Cheating on a Forced-Swim Test

CBD Safety Profile

- Safety has been well-established
- Attenuates the “high” caused by THC at 8:1 CBD:THC ratio
- The Director of NIDA wrote, “CBD appears to be a safe drug”
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


- 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

Knight R. DEA clarifies marijuana extract rule and CBD legality. Available at: http://kightoncannabis.com/dea-clarifies-marijuana-extract-rule-and-cbd-legality/

CBD Legal Status

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


- THC will not show up in standard UDT immunoassays
- Now most commonly used for pain, anxiety, depression, and sleep disorders


- Due to lack of regulation, CBD products online are often mislabeled regarding constituents

CBD and Pain

- Much of the existing supportive data is preclinical
- CBD is anti-inflammatory
- Anti-inflammatory, analgesic in arthritis
- Attenuation of early phase inflammation by cannabidiol prevents pain and nerve damage in osteoarthritis

CBD and Pain

- Found to be anti-inflammatory in human cell lines
- Relevance for back pain: CBD has anti-inflammatory effects on rat nucleus pulposus cells
- Reduces chemotherapy-related peripheral neuropathy without diminishing nervous system function or chemotherapy efficacy
- High-dose CBD appears to be hypnotic – increasing sleep, while low-dose CBD has been associated with increased wakefulness
More Recent CBD Research

- Safety established when co-administered with fentanyl
- Enhances fracture healing
- Animal model - Protective effects on lesion-induced intervertebral disc degeneration
- Animal model – synergistic with morphine for certain pain conditions
- Clinical research – Effective for reducing chronic pain in kidney transplant patients (small study)

Marijuana and Pain Research

- Extremely difficult to do in the US
- All federally-funded MM research currently must 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%)
- Why is this a problem?
Marijuana and Pain Research

- Oil or wax dabs available at some dispensaries have THC contents as high as 90%!!!
  - Now being used regularly by 36.5% of cannabis users
- Medical marijuana sold in dispensaries is higher in THC than that sold on the streets
- Recent breakthrough – NIDA has approved a 13.4% THC MJ for research

Edibles

- THC dosing in edibles has been described as “insane” by toxicologists
- Edibles are infused with almost pure THC
- They typically take 30-90 minutes to take effect, reach their peak in 2-3 hours, and can last for 4-12 hours
- Thus, they don’t allow for titration due to a lack of immediate effect
- Labeling of constituents’ content is often inaccurate
Edibles

- This inability to titrate effectively has led to increases in ER visits due to THC intoxication
  

- And multiple deaths
  

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…”
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

**MM and Pain Research**

- Neuropathic pain – first methodologically-robust study conducted in 2008 – found efficacy
  - Higher doses (7% THC) resulted in cognitive deficits
- Similar findings in a 2009 study on neuropathic pain in HIV
- 2010 Canadian study using 9.4% THC MJ – efficacy for neuropathic pain
  Ware MA, et al. CMAJ 2010;182:E694-701.
MM and Pain Research

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

- 2015 study on MJ for pain diabetic neuropathy – higher dose (7% THC) more effective than lower dose (1.29%)…but with more cognitive effects

- Similar findings in 2016 study on neuropathic pain due to spinal cord injury or disease

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
- Recent Australian review suggests that CBD may be better


**MM and Pain Research**

- Musculoskeletal pain and arthritis – “Evidence is Needed”
- Rheumatic conditions – no evidence for efficacy
- Experts recommend against it until more research is available
- Fibromyalgia – No empirical evidence for efficacy
- Headache – very limited evidence for efficacy
- Cancer pain – May have “potential use” – although human studies are of poor quality, limited size, and outdated

**MM and Opioids**

- The most compelling evidence basis for MJ in treating chronic pain was for its opioid-sparing effect
- Medical cannabis laws were associated with lower opioid overdose mortality rates
- Less so, however, as laws on dispensaries have become tougher
- Synergistic with opioids? Likely urban myth…
- Not associated with lower prescription rates and dosages of Schedule II opioids
MM and Opioids

- Perioperative opioid use is significantly higher in MJ-users despite lower subjective pain scores
- MJ use recently found to be predictive of opioid dependence
- Predictive of a 2.5 fold increase in the rate of opioid aberrancy
- Medical marijuana users more likely to use prescription drugs – including opioids – non-medically

“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
“Watcha Smoking, Dude?”

- Sativas are more of a euphoriant, but also more likely to cause anxiety and paranoia
- Do we know which strain is more effective for pain management?
- Head-to-head research is needed

Indica vs. Sativa – Street Reputations

- **Indicas**
  - Relaxing and calming
  - Body buzz or ‘couch lock’
  - Best suited for night use
- **Sativas**
  - Uplifting and energetic
  - Cerebral, spacey or hallucinogenic
  - Best suited for day use

**Treatment Recommendation**

- “The Medicinal Cannabis Treatment Agreement: Providing Information to Chronic Pain Patients via a Written Document”
- Absolutely brilliant!!!!
- “Medical marijuana” is heavily abused
- “….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

- 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

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
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

- 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

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
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

THANK YOU