Reefer Madness: Taking the Insanity Out of Medical Cannabinoids

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Disclosure

- Dr. Schatman has no conflicts of interest, other than that he is a veteran of 30 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 29 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? (cont’d)

- 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

The Future of Recreational Pot?

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

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 (cont’d)

- 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 nonmedical 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 (cont’d)

- 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


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

Physical Safety Issues

- Data remain confounded by the fact that so many MM users also smoke tobacco
- Insufficient data on safety of vaporization – “Preliminary findings do support the idea that vapourization is an improvement over smoking”
- Increases rates of acute myocardial infarction and cardiovascular mortality – doubles rate of MI

Physical Safety Issues (cont’d)

- Marijuana use appears to be associated with subclinical atherosclerosis
    – Longer term research needed to determine if it is associated with clinical levels of atherosclerosis
- Associated with higher rates of acute ischemic stroke
- Increased duration of marijuana use is associated with increased risk of death from hypertension
Physical Safety Issues (cont’d)

- Sexual functioning: THC impairs gonadal function by blocking gonadotropin-releasing hormone (GnRH) release
- Cannabinoid hyperemesis syndrome
  - Characterized by a syndrome of cyclic vomiting, abdominal pain and compulsive showering in some habitual users
  - Symptoms improve with cessation of 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

Physical Safety Issues (cont’d)

- 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
  Bonar EE, et al. Addict Behav. 2017[Epub ahead of print].
- Drugged driving continues to increase, with increases associated with more traffic fatalities
Physical Safety Issues (cont’d)

- Increases the likelihood of fatal 2-vehicle crashes

- French study: 1 in 2 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

Physical Safety Issues (cont’d)

- 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

- Cannabis use associated with preterm birth

- Composite neonatal morbidity or death was more frequent among neonates of mothers using marijuana compared to nonusers
Physical Safety Issues (cont’d)

- **Addiction**
  - Not as severe as opioid or benzo addiction
  - Abrupt cessation results in irritability, insomnia, anorexia
- **Perceived barrier to quitting MJ associated with more severe withdrawal symptoms**
- **When used hs, withdrawal’s impact on sleep is particularly problematic**
- **Reduced MJ use associated 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 reviews indicate that chronic MJ use results in cognitive deficits
  - Long-term and short-term
Cognitive Safety Issues (cont’d)

- Long-term deficits (“residual cannabis effect”) include (from a meta-analysis):
  - Learning
  - Forgetting/retrieval
  - Abstraction/executive functioning
  - Attention
  - Motor skills
  - Verbal/language


Cognitive Safety Issues (cont’d)

- Even in adults, imaging studies show structural and functional alterations in the brain

- Recent analysis suggests that cognitive deficits are mediated by interactions between genetics and cannabis use

- Higher THC and lower CBD levels appear to be predictive of greater cognitive deficits
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
- What do we know?
- What do we THINK we know?

Mental Health Risks - Psychosis

- 1960s – Focus was on acute psychosis due to marijuana use
- 1978 – Small case series suggests MJ is a “hazard” to schizophrenics
- 1989 – First longitudinal (15 year) study to conclude that MJ use can play a role in the etiology of schizophrenia
- 2005 – First study demonstrating that THC is associated with exacerbation of core psychotic and cognitive deficits in schizophrenia
Mental Health Risks – Psychosis (cont’d)

- High THC cannabis increases the risk of psychosis 3-fold compared to nonusers, and 5-fold among daily users
  – Particularly problematic in patients using ultra-high THC wax dabs
- 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

Mental Health Risks – Bipolar Disorder

- 1976 Jamaican study – found high incidences of acute hypomania in MJ users
- Continued cannabis use found to result in prolonged manic phase
- 2006 – First study to suggest that cannabis use might predict the development of bipolar disorder
Mental Health Risks – Bipolar Disorder (cont’d)

- 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 (cont’d)

- 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 (cont’d)

- 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
Mental Health Risks – Depression

- MJ’s ability to cause or exacerbate depression is still unclear
- Reduction of use among depressed females found to reduce depressive symptomatology
- Suicide and MJ – Hundreds of studies appear in the literature in regard to adolescents and young adults
- 30-year longitudinal Dutch study – Found that regular MJ use increased risks for suicide, but only among males

Mental Health Risks – Depression (cont’d)

- American study of middle-age and older depressed adults – Found a significant correlation between MJ use and suicidal ideation
- Cannabis use disorder associated with self-injury among US armed forces combat veterans
  Kimbrel NA, et al. Suicide Life Threat Behav. 2017[Epub ahead of print].
- Really hasn’t been studied well enough among medical patients using MJ
**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

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**CBD**

- Of no interest to recreational users….and tragically, for many medical users

- Initially described as “nonpsychotropic”

- However, produces anxiolysis through increasing serotonergic transmission  

- More appropriately called “noneuphoriant”  
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
- 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:
- Sort of….
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
- A few states and local law enforcement are going after CBD’s legality
  Leyes T. Iowa police seize CBD oil without always testing to confirm it's illegal marijuana. Des Moines Register, Jan. 11, 2018.

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 (cont’d)

- 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
- Anxiolytic in humans
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 (cont’d)

- Oil or wax dabs available at some dispensaries have THC contents as high as 90%!!!!
    - Now being used by ¼ of all medical 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 (cont’d)

- 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 (cont’d)

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

- 2015 study on MJ for painful 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:
- Effective in terms of analgesia at higher strengths
- 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 tx option for neuropathic pain

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 is for its opioid-sparing effect
- Medical cannabis laws are associated with lower opioid overdose mortality rates
- Less so, however, as laws on dispensaries have become tougher
- MJ appears to be synergistic with opioids

“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 – more likely to be high in THC, low in CBD
“Watcha Smoking, Dude?” (cont’d)

- Indicas empirically established as preferable for pain management, but cause more sedation than sativas
- 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 (cont’d)

- 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 (cont’d)

- 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 (cont’d)

- 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