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 29 Grateful Dead/Dead and Company concerts
Goals of Presentation

- 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

The Future of Recreational Pot?

- Predictions for legalization in:
  - Connecticut
  - Delaware
  - Illinois
  - Maine
  - Maryland
  - Michigan
  - Montana
  - New York
  - Rhode Island
  - Vermont (Bernie has to get high, too!)

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
• 2015-2016—Washington State shuts down dispensaries in order to increase tax revenues from recreational pot shops
Politics (cont’d)

- 2016—Trump elected President, said he supports allowing states’ autonomy over marijuana policy
- 2017—Jeff Sessions likely to become AG
  - Has stated that “good people don’t smoke marijuana”
- 2017—“Marijuana Industry Fears If Sessions Is Confirmed, Dispensaries Could Get Shut Down”
- Who can predict what kind of madness will follow?!?!

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%
- THC:CBD ratio—14:1 in 2001, 80:1 in 2014
  - Increases in THC thought to be due to shift from traditional strains to sinsemilla

Synthetic THC

- Available as a Schedule III drug (dronabinol/Marinol) and a Schedule II drug (nabilone/Cesamet) since 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
- Data remain confounded by the fact that so many MM users also smoke tobacco

Safety Issues

- 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
- Associated with higher rates of acute ischemic stroke
Safety Issues (cont’d)

- 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
    Brewerton TD, Anderson O. Int J Eat Disord. 2016 [Epub ahead of print].

Safety Issues (cont’d)

- Psychosis: Potential to induce in genetically prone
- Particularly problematic among the young
- High-THC MJ poses triple the risk for induction of psychosis compared to low-THC
- Continued MJ use has been associated with more negative outcomes in first episode psychosis, along with poorer social functioning trajectories
Safety Issues (cont’d)

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

- Recently found to be particularly problematic among kids with ADHD

- Concerning given ADHD patients’ tendencies toward self-medication

Safety Issues (cont’d)

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

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

- MJ use recently found to be associated with reduced subjective differentiation between threat and safety stimuli during conditioning
Safety Issues (cont’d)

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

- MJ found to be associated with increased impulsivity and interpersonal hostility, while ETOH was not

- Certainly goes against commonly accepted myth . . . .
- So is it really “safer” and “better” than alcohol?

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
**CBD**

- Ignored for many years
- Seen as something limiting the amount of THC marijuana could potentially contain
- Initially described as “nonpsychotropic”
- However, produces anxiolysis through increasing serotonergic transmission


- More appropriately called “noneuphoriant”


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**CBD Safety Profile**

- Safety has been well-established


- Modulates the “high” caused by THC


- 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 is still considered a Schedule I drug
- It is available in all medical marijuana states
- As well as in 13 states with the wisdom to legalize it without MM legalization

Alabama
Georgia
Iowa
Kentucky
Mississippi
Missouri
North Carolina
Oklahoma
South Carolina
Tennessee
Texas
Virginia
Wisconsin

CBD in Pain Management

- Animal model: anti-inflammatory, analgesic in arthritis

- Animal model: reduced neuropathic pain

- Found to be anti-inflammatory in human cell lines

- Relevance for back pain:
  CBD has anti-inflammatory effects on rat nucleus pulposus cells
More Recent CBD Research

- Safety established when coadministered with fentanyl

- Enhances fracture healing

- Animal model: protective effects on lesion-induced intervertebral disc degeneration

- Animal model: synergistic with morphine for certain pain conditions

CBD in Pain Management

- Anecdotally—analgesic in humans

- More research is clearly needed

- Exciting breakthrough—UDT can now detect CBD levels

- U of Mississippi has started growing a low-THC/high-CBD strain
  Reardon S. Nature 2015;519:269-270.

- GW Pharma—Epidiolex®—plant-based CBD
  — Received FDA Orphan Drug Designation for Dravet and Lennox-Gastaut syndromes, and Fast-Track designation for Dravet syndrome
  — Off-label use for pain...?
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
- 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
- Only the NJ law limits the amount of THC in medical marijuana (10%)
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 constituent 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
Marijuana and Pain Research—Why It Stinks

- Should journals publish bad MM research just to say that they are addressing the issue?
- JAMA certainly has . . .

- 2015 Systematic Review/Meta-Analysis
  - Analyzed 79 trials, total of 6462 participants
  - Concluded “moderate-quality” evidence for MM use for pain and spasticity
  - Methodological nightmare

Schatman ME. Medical marijuana and neuromysticism: the data spell the beginning of the end. Painview 2015;11:24-25.

Stinky MM Research

- No uniformity whatsoever!
- Conditions included:
  - Central pain
  - Peripheral pain
  - “Unspecified” neuropathic pain
  - HIV-related sensory neuropathy
  - Pain from “MS or other neurological conditions”
  - “Musculoskeletal problems”
  - Chemotherapy induced pain
Stinky MM Research (cont’d)

- Forms of cannabinoids included:
  - Nabiximols (1:1 THC:CBD ratio)
  - Pure THC oromucosal spray
  - Dronabinol and nabilone (pure po THC)
  - Vaporized whole-plant cannabis (strengths unspecified)
  - Ajuvenic acid capsules
  - Another “unspecified form” of oral THC

Stinky MM Research (cont’d)

- The authors rated levels of potential bias in the studies from “low” to “high”,
  with many rated “high”
- Did they bother omitting those studies?
- Nope. Even though doing so is accepted practice per systematic review methodology
- Did they pay much attention to the myriad adverse events reported in the studies?
- Hell no!!!!!
Adverse Events

- GI disorders
- Psychiatric disorders
- Nervous system disorders
- Cardiac disorders
- Blood disorders
- Renal and urinary disorders
- Metabolic disorders
- Neoplasms
- Skin disorders
- Reproductive disorders
- Visual disorders
- Hepatobiliary disorders
- Infections

and, of course

- Deaths

Science vs “Religion”

- Medical marijuana advocates tend not to let the data get in the way of their opinions
- “There is none so blind as those who will not see...”
Science vs Religion (cont’d)

- It’s all about the “neuromysticism” of MM
- The research is gradually getting better
- Yet opinions are becoming progressively more emotionally based
- Journals publishing lousy systematic reviews and meta-analyses aren’t helping matters
- More confusion for patients . . . as well as the physicians trying to practice good pain medicine

Back to MM and Pain Research

- 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
- Eg, 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 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
**MM and Pain Research (cont’d)**

- Conclusions of MJ for neuropathic pain:
  - 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 tx option for neuropathic pain

**MM and Pain Research (cont’d)**

- 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 significantly lower opioid overdose mortality rates
- MJ appears to be synergistic with opioids

MM and Opioids (cont’d)

- But is this enough to justify MJ’s use in pain treatment?
- The other side of the coin is physicians’ reluctance to prescribe opioids to patients using MJ, even in MM states
- Clearly, more research on the relationship between MJ and opioids are necessary in order to inform practice...
Research Issues

- Why so few efficacy studies?
- American investigators realize that studies using the U of Mississippi MJ are almost meaningless in this day and age
- International investigators are conducting myriad studies on nabiximols (1:1 THC:CBD)
- Nabiximols is now approved in 27 countries—but not in the US
- Thank the good folks at the FDA. . . .

“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