Marijuana: Clearing the Smoke on Clinical and Policy Issues

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Conflict of Interest Disclosure

• I have no financial relationship or any real or apparent conflict(s) of interest that may have a direct bearing on my presentation.
Why Talk about Marijuana?

- Clinical and political
- Timely
- Treatment for marijuana use vs. marijuana use for treatment
- Your patients want to know
Outline

• What is marijuana?
• Epidemiology and terminology
• U.S. *love-hate* relationship with marijuana
• Neurobiology
• Physiologic effects and other potential risks of marijuana use
• Treatment for marijuana use disorders
• Evidence for and against medical use of marijuana
• Connecticut’s Medical Marijuana Act
  – (Public Act 12-55)
What is Marijuana?

• Dried flowers, leaves, stems and seeds of the *Cannabis sativa* plant
• Usually smoked as a cigarette or in a pipe; can be orally ingested
• More concentrated, resinous form: hashish
• Sticky black liquid: hash oil
• Potency related to concentration of Δ9-tetrahydrocannabinol (THC) and route of administration
Δ⁹-TETRAHYDOCANNABINOL (THC)

- Psychoactive ingredient in *Cannabis sativa*
- Synthetic form is active ingredient of Marinol, approved in 1985 for intractable nausea
- 70+ other cannabinoids, many of which are present to varying degrees in a single C. sativa plant; some non-THC cannabinoids *may* have medical use
Percentage THC in Marijuana Seized by DEA

From the compiled Annual Reports of the Director of the National Institute of Drug Abuse
U.S. Marijuana Use-NSDUH 2013

Young Adults Aged 18-25

- Lifetime: 52%
- Past Year: 32%
- Past Month: 19%
Relative Shifts in Prevalence

% Students Reporting Past Month Marijuana and Cigarettes (by Grade)

SOURCE: University of Michigan, 2011 Monitoring the Future Study
Changes in Attitude Lead to Changes in Use: Marijuana Use and Perceived Risk in 12th Graders

Source: Monitoring the Future, 2011
Street Names for Marijuana and Other Terminology

- Pot
- Cannabis
- Weed
- Mary-Jane
- Reefer
- Ganga
- Hash
- Chronic
- Green
- Wacky-tabacky
- Maui-wowy
- Joint
- Bong
- Blunt
- Roach
- Pipe
- Pot-brownies
Cannabis Use Disorder DSM 5

- A problematic pattern of cannabis use leading to clinically significant impairment or distress, as manifested by two or more of the following within a 12-month period:
  - Cannabis is often taken in larger amounts or over a longer period than was intended
  - There is a persistent desire or unsuccessful efforts to cut down or control cannabis use
  - A great deal of time is spent in activities necessary to obtain cannabis, use cannabis, or recover from its effects
  - Craving, or a strong desire or urge to use cannabis
Cannabis Use Disorder, Cont’d

- Recurrent cannabis use resulting in a failure to fulfill major role obligations at work, school, or home
- Continued cannabis use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of cannabis
- Important social, occupational, or recreational activities are given up or reduced because of cannabis use
- Recurrent cannabis use in situations in which it is physically hazardous
- Continued cannabis use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by use
- Tolerance
- Withdrawal
Cannabis Withdrawal: New to DSM 5

• Cessation of cannabis use that has been heavy and prolonged
• Three or more of the following signs and symptoms develop within approximately one week after the cannabis cessation:
  – Irritability, anger, or aggression
  – Nervousness or anxiety
  – Sleep difficulty (eg, insomnia, disturbing dreams)
  – Decreased appetite or weight loss
  – Restlessness
  – Depressed mood
  – At least one of the following physical symptoms causing significant discomfort: abdominal pain, shakiness/tremors, sweating, fever, chills, or headache
• Cause distress or impairment
• No other explanation for symptoms
US Love-Hate Relationship

Reefer Madness, 1936
“A cautionary tale about the ill effects of marijuana … a trio of drug dealers try to corrupt innocent teenagers with wild parties and jazz music.”

Fast Times at Ridgemont High, 1982...
Jeff Spicoli
US Love-Hate Relationship

• 1937: Marijuana Tax Act - taxes use/possession

• Growing use 1950’s by beat & jazz artists

• 1970: Controlled Substances Act passed by Congress, marijuana listed as schedule I (i.e. no currently accepted medical use, high potential for abuse, and a lack of accepted safety even under medical supervision; limits ability to study effects)

• 1970’s widespread use; 10 states decriminalize

• 1980’s “Say no to drugs,” severe penalties for trafficking
US Love-Hate Relationship

• 1985: Marinol (synthetic THC) approved in the US for treatment of intractable nausea

• 1996: California first state to legalize medical marijuana

• 1997-2014: 22 more states + DC legalize medical marijuana (AK, AZ, CO, CT, DE, HI, IL, ME, MD, MA, MI, MT, NV, NH, NJ, NM, NY, OR, RI, VT, WA)

• 2012-2015: 4 states legalized recreational use (AK, CO, OR, WA)
Cannabinoid Neurobiology

• Cannabinoid Receptors
  – CB1, CB2, GPR55
  – Location:
    • Hippocampus
    • Basal ganglia
    • Cerebellum
    • liver, muscle, gut, and adipose tissue

• Endogenous cannabinoids
  – Anandamide
  – 2-arachidonoylglycerol (AG2)

• SR141617A (Rimonabant) : Cannabinoid antagonist
  – Caused acute withdrawal syndrome in chronic MJ users
  – Caused dysphoria in MJ-naïve patients
Case Presentation #1

- MD is a 19 yo male who comes to your clinic to establish primary care. He is accompanied by his mother. He has no relevant PMH or FH. He takes no medications and has no allergies. He denies alcohol use and smokes ½ PPD for two years. His mother expresses concern over his daily marijuana use.
- Should she be concerned? What should you say?
Physiologic Effects of Cannabinoids

- Neuropsychiatric
  - Mood
  - Memory
  - Cognition
  - Behavior

- Pulmonary
  - Lung function

- Cardiac

- Reproductive

- Gastrointestinal
  - Cannbinoid hyperemesis

- Oncologic risk

- Other
  - Hunger
  - Anti-nociception
  - ↓ Intra-ocular pressure
  - Immunosuppresion
**Effect on Cognition**

<table>
<thead>
<tr>
<th>Level of cannabis use</th>
<th>Model 1 (cannabis use)</th>
<th>Model 2 (cannabis use plus use of alcohol and tobacco)</th>
<th>Model 3 (cannabis use plus age, gender, minority status, and education)</th>
<th>Model 4 (cannabis use plus age, gender, minority status, education, and use of alcohol and tobacco)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\beta$</td>
<td>SE$\dagger$</td>
<td>$\beta$</td>
<td>SE</td>
</tr>
<tr>
<td>Nonusers§</td>
<td>0.28*</td>
<td>0.15</td>
<td>0.22</td>
<td>0.15</td>
</tr>
<tr>
<td>Light users</td>
<td>0.25</td>
<td>0.19</td>
<td>0.17</td>
<td>0.19</td>
</tr>
<tr>
<td>Light users plus use of drugs</td>
<td>0.35*</td>
<td>0.18</td>
<td>0.27</td>
<td>0.19</td>
</tr>
<tr>
<td>Heavy users</td>
<td>0.81</td>
<td>0.71</td>
<td>0.66</td>
<td>0.71</td>
</tr>
</tbody>
</table>

* $p < 0.10$.
† Positive numbers indicate MMSE score increases relative to the reference group; negative numbers indicate relative decreases in MMSE score.
‡ SE, standard error.
§ Reference group.

Lyketsos CG, Am J Epidemiol 1999
Adolescent Vulnerability in IQ Decline

Meier M H et al. PNAS 2012
Post-cessation IQ among Former Persistent Cannabis Users

Meier M H et al. PNAS 2012

Adolescent-Onset (Used Cannabis Weekly Before Age 18)

Adult-Onset (Did Not Use Cannabis Weekly Before Age 18)
Genetic variation in COMT influences the harmful effects of abused drugs

% with schizophrenia disorder at age 26

- No adolescent cannabis use
- Adolescent cannabis use

Pulmonary Effects of Smoked Marijuana

• Acute $\rightarrow$ bronchodilation ($\text{FEV}_1$ increase $\sim 0.15-0.25$ L)

• Long-term $\rightarrow$ cough (OR 2.0, 95% CI 1.32-3.01), phlegm, wheeze; however data were inconclusive regarding an association between long-term marijuana smoking and airflow obstruction

• At low levels of exposure, $\text{FEV}_1$ increased by 13 mL/joint-year and $\text{FVC}$ by 20 mL/joint-year, but at higher levels of exposure, airflow obstruction was observed

2. Pletcher MJ et al. JAMA 2012
## Cardiovascular Complications

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total</th>
<th>Cardiac</th>
<th>Cerebral</th>
<th>Peripheral</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>35</td>
<td>20</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Age (mean±SD)</td>
<td>34.3±8.8</td>
<td>35.5±9.0</td>
<td>32.5±13.4</td>
<td>25.3±3.1</td>
</tr>
<tr>
<td>Male</td>
<td>30</td>
<td>20</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Exposure (A/R/D)</td>
<td>13/6/16</td>
<td>10/2/8</td>
<td>2/0/0</td>
<td>0/0/3</td>
</tr>
<tr>
<td>Cardiovascular history</td>
<td>9</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Associated substances (as quoted in medical file)</td>
<td>24</td>
<td>12</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Tobacco/alcohol</td>
<td>21/6</td>
<td>11/2</td>
<td>0/0</td>
<td>2/2</td>
</tr>
<tr>
<td>None declared</td>
<td>11</td>
<td>9</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cocaine</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Ecstasy</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lysergic acid diethylamide (LSD)</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hospitalization, n (mean duration in days)</td>
<td>18 (15)</td>
<td>10 (20)</td>
<td>0 (0)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Death</td>
<td>9</td>
<td>8</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
Cannabis and Cancer Risk

• Evidence for histopathologic changes supporting the biologic plausibility of an association of marijuana smoking with lung cancer (1)

• 2-fold increased risk of lung CA among chronic, habitual marijuana users in a 40 year cohort study
  – Adjusted for tobacco use, alcohol use, respiratory conditions, and SES (2)

1 Mehra R Archives of Int Med. 2007
2 Callaghan RC Cancer causes and control. 2012
Other Risks with Cannabis Use

• Cannabis use may lead to cannabis use disorder—9%
  – Telescoping: Occurs more rapidly in females (1)
• Associated with use of other substances in adolescents (1)
  – Enrollment in extracurricular activities protective
• Gateway: 2.5 increase risk of subsequent use of prescription opioids (2)
• Increases risk of MV crash 2-fold (3)

1 Schepsis, T JAM, 2011
2 Sullivan LE, Journal of Adolescent Health 2013
3 Asbridge M, BMJ, 2012
Return to Case #1

- There may be an effect on IQ which can persist even with cessation
- Depending on genetics, there is a risk of increase psychotic symptoms
- Smoked marijuana may lead to increased respiratory symptoms and possibly cancer
- Of concern, regular marijuana use may lead to more serious disorders and use of other illicit substances
Fundamental tension

Well-known harms:

• Marijuana use disorders: 3.5% of all U.S. residents 12 and over (NSDUH 2008)

However:

• Intoxication and withdrawal are not fatal
• Overdose is unlikely
• Long-term, moderate use seems to be relatively frequent (compared to other drugs)
• Risk of end-organ damage appears to be lower than several other legal and illegal substances
• Ratio of medical benefit to harm may be equal or better than some controlled substances
Treatment Options

• Behavioral
  – Substance abuse treatment setting
    • cognitive-behavioral therapy, contingency management, motivational enhancement, therapeutic living
  – General medical settings
    • Brief interventions

• Pharmacotherapy
  – No currently approved medication
    • cannabinoid antagonist
    • oral THC for withdrawal, maintenance or short-term treatment?
      • cannabinoid agonist—Levin FR DAD 2011
    • N-Acetylcysteine
A Double-Blind RCT of N-Acetylcysteine in Cannabis-Dependent Adolescents

History of Medicinal Marijuana

The Chinese Emperor Fu His (ca. 2900 BC) noted cannabis possessed both yin and yang.

Cannabis pollen was found on the mummy of Ramesses II, who died in 1213 BC. Prescriptions for cannabis in Ancient Egypt included treatment for glaucoma and inflammation.

Deitch, R. *Hemp: American History Revisited: The Plant with a Divided History*, 2003

Lise Manniche, PhD. *An Ancient Egyptian Herbal*, 1989
In 1850, the U.S. Pharmacopeia listed marijuana as treatment for neuralgia, tetanus, typhus, cholera, rabies, dysentery, alcoholism, opiate addiction, anthrax, leprosy, incontinence, gout, convulsive disorders, tonsillitis, insanity, excessive menstrual bleeding, and uterine bleeding, among others.

In 1942, amidst spreading reports of marijuana’s alleged association with violent crime, it was removed from the U.S. Pharmacopeia.
### Clinical Trials of Cannabinoids, Any Condition: 1990-2012

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Positive trials</th>
<th>Equivocal</th>
<th>Negative trials</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double-blind, placebo controlled</td>
<td>12</td>
<td>7</td>
<td>3</td>
<td>22</td>
</tr>
</tbody>
</table>

A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols* (Sativex®), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis.
Smoked cannabis for chronic neuropathic pain: a randomized controlled trial

Table 2: Pairwise comparisons of the effects of four potencies of smoked cannabis on average daily pain

<table>
<thead>
<tr>
<th>Potency, % of THC</th>
<th>Potency, % of THC</th>
<th>0</th>
<th>2.5</th>
<th>6.0</th>
<th>9.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>2.5</td>
<td>−0.13 (−0.83 to 0.56)</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>6.0</td>
<td>−0.09 (−0.78 to 0.60)</td>
<td>0.04 (−0.64 to 0.73)</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>9.4</td>
<td>−0.71 (−1.40 to −0.02)</td>
<td>−0.58 (−1.27 to 0.11)</td>
<td>−0.63 (−1.30 to 0.06)</td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>

Note: CI = confidence interval, THC = tetrahydrocannabinol.
Major Questions Remain

- Does marijuana provide sustained benefit?
- What are the long term effects in medical populations?
- Is smoked marijuana more effective than synthetic formulations?
- What is the comparative effectiveness of marijuana vs. established treatments?
- What are the appropriate doses for various conditions?
1970: Controlled Substances Act passed by Congress, marijuana listed as schedule I (i.e. no currently accepted medical use, high potential for abuse, and a lack of accepted safety even under medical supervision.)

1985: Marinol (synthetic THC) approved in the US for treatment of intractable nausea

1996: California first state to legalize medical marijuana

1997-2014: 22 more states + DC legalize medical marijuana (AK, AZ, CO, CT, DE, HI, IL, ME, MD, MA, MI, MT, NV, NH, NJ, NM, NY, OR, RI, VT, WA)

2012-2015: 4 states legalized recreational use (AK, CO, OR, WA)
Current State of the Union

- States with medical marijuana laws
- States that have removed jail time for possessing small amounts of marijuana
- States that both have a medical marijuana law and have removed jail time for possessing small amounts of marijuana
- Marijuana is legal for adults and is taxed and regulated similarly to alcohol; state also has a medical marijuana law

D.C. voters made it legal for adults to possess and grow marijuana, but the initiative is undergoing Congressional review; D.C. also has a medical marijuana and decriminalization law

NOTE: Some of the state laws are new and have not yet taken effect or been fully implemented.
2005: Supreme Court decision (Gonzales v. Raich)
Regardless of state laws, federal law enforcement has the authority under the CSA to arrest and prosecute physicians who prescribe or dispense marijuana and patients who possess or cultivate it.

2009: Department of Justice
Issued a memorandum to U.S. Attorneys stating that federal resources should not be used to prosecute providers and patients whose actions comply with their states’ laws permitting medical use of marijuana.

2008-2010: IOM, ACP, AMA
Petitioned DEA/FDA to reschedule marijuana to schedule II …it remains schedule I to this day
Connecticut’s Public Act 12-55

• Qualifying diagnoses:
  – Cancer
  – Glaucoma
  – HIV/AIDS
  – Parkinson's disease,
  – Multiple sclerosis
  – Crohn's disease
  – Post-traumatic stress disorder
  – Damage to the nervous tissue of the spinal cord with objective neurological indication of intractable spasticity
  – Epilepsy
  – Cachexia/Wasting syndrome

• Patient must be at least 18 years old and CT resident.
• Patient must not be an inmate in a Department of Corrections institution or facility.

CT House Bill #5389:
Physician Role

- Must have CT State DEA# and register with CT Prescription Monitoring Program
- Fills out Department of Consumer Protection form certifying:
  - Patient has **qualifying diagnosis**
  - Potential **benefits would likely outweigh the health risks**, based on a medically reasonable assessment.
- This assessment must be made in the course of a **bona fide physician-patient relationship and must include a physical exam**.
- Physician must also **explain potential risks and benefits** to the patient or their legal guardian/designated caregiver.
- Valid for **1 year**, but can be revoked by physician
- Allows patient to possess **1 month supply** at any point.
Patient Responsibilities

• Possess no more than a one-month supply
• Not use marijuana in a way that endangers the health or well-being of others.
• Not use marijuana in a prohibited place:
  – Motor bus, school bus, or other moving vehicle
  – Workplace
  – School grounds, any public or private school, dormitory, college or university property
  – Public place
  – Presence of anyone under 18
One Month Supply

- CT maximum allowable monthly amount = 2.5 oz; physicians may certify a lesser amount

- 2.5 oz = approx. 70,000 mg = 70 grams = 70 large marijuana cigarettes (“joints”) or 140 small marijuana cigarettes

- Cost to patients:
  - Public Act 12-55 contains no comment
  - 2.5 oz costs ~ $500 on the street
  - Not likely to be covered by insurance.
Growers

• Only producers licensed by the Department of Consumer Protection can legally cultivate marijuana.

• The number of licensed producers will be between 3-10

• Any person seeking to be licensed as a producer will have to demonstrate the capacity to build and operate a secure indoor facility that could grow pharmaceutical-grade marijuana

• $25,000 application fee
Dispensing

- *Pharmacists* will be able to obtain a dispensary license from the Department of Consumer Protection.

- *Pharmacies* may not employ more than 5 marijuana licensed pharmacists.

- Pharmacies can prohibit their pharmacists from dispensing marijuana (by not stocking it).

- “Number of pharmacists will not exceed number appropriate to meet needs of qualifying patients. Avoiding over-supply will reduce risk of diversion.”
Case presentation #2

• RJ is a 48 year old man with AIDS, Hepatitis C, wasting syndrome.
• CC: nausea/vomiting, ongoing weight loss
• HPI: BMI 25 → 17 over past 6 months. Reports loss of appetite, nausea/vomiting both of which he says are partially relieved by smoking marijuana, which he started to do again recently on the recommendation of his girlfriend.
• PMHx:
  – HIV/AIDS – former IVDU. Off HAART since 2011, which he discontinued due to nausea/vomiting. CD4 = 34; VL = 1.5 million
  – HCV – type I. Failed IFN/ribavirin due to flu-like symptoms
  – Chronic low-back pain – degenerative disk disease. Percocet discontinued 2011 secondary to cocaine use
  – Gastritis
Case #2, cont’d

• Meds: ranitidine, omeprazole, metoclopramide, tramadol

• Soc Hx:
  – Retired machinist, now on SSDI
  – 1 ppd tobacco; rare alcohol
  – Reports quitting cocaine 6 months ago

• “Doc, since marijuana has been helping, will you certify me to get medical marijuana so that I can use it legally?”
Case # 2 Discussion
Case presentation #3

• JS is a 22-year-old woman with multiple sclerosis, bipolar disorder, generalized anxiety disorder
• CC: painful muscle spasms
• HPI: Started glatiramer acetate 6 months ago with good response: fewer acute MS flares with no hospitalizations. However, painful spasticity limits effectiveness/concentration at her job. Tizanidine caused excess drowsiness so she discontinued it.
• PMHx:
  – Relapsing-remitting MS complicated by ophthalmoplegia, ataxia, and painful spasticity
  – Bipolar disorder, no hx of hospitalization
  – Generalized anxiety disorder, well controlled on sertraline
Case #3, cont’d

• Soc Hx:
  – Works as a paralegal but missed 38 days of work last year because of health problems
  – No tobacco/alcohol, lifetime
  – Denies illicit drug use, lifetime

• Meds: glatiramer acetate, carbemazepine, sertraline

• She says, “I heard in news reports that marijuana can be used now in MS … do you think that might be worth trying?”
Case #3 Discussion
Conclusions

• Marijuana use and marijuana use disorders are prevalent
• Physicians should be aware of the potential physiologic implications of marijuana use
• Treatments are available for marijuana use disorders
• Medical marijuana policies differ statewide
• CT physicians can certify patients with certain qualifying conditions
Thank you

Questions?
Initiates of Illicit Drugs among Persons 12 and Older: 2006

Numbers in Thousands

- **Marijuana**: 2,150
- **Cocaine**: 1,112
- **Ecstasy**: 977
- **Stimulants**: 860
- **Sedatives**: 845
- **Inhalants**: 783
- **LSD**: 267
- **Heroin**: 264
- **PCP**: 91
- **Pain Reliever misuse**: 69
- **Tranquilizer misuse**: 264

Legend:
- [Marijuana](#)
- [Cocaine](#)
- [Ecstasy](#)
- [Stimulants](#)
- [Sedatives](#)
- [Inhalants](#)
- [LSD](#)
- [Heroin](#)
- [PCP](#)