Marijuana: Clearing the Smoke on Clinical and Policy Issues

Jeanette M. Tetrault, MD FACP FASAM
Associate Professor of Medicine
Program Director, Addiction Medicine Fellowship
Yale University School of Medicine
Learning objectives

• Define the key components of marijuana as a substance and review relevant epidemiology and terminology

• Explore US policy regarding MJ decriminalization to legalization

• Summarize adverse health effects and other potential risks of marijuana use (and touch on synthetic MJ)

• Examine the tension between treatment for marijuana use disorders vs. marijuana as medicine
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-tetrahydrocannabinol (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*
Marijuana use among individuals age 17 or older

Used Marijuana on 20 or More Days in the Past Month

Used Marijuana on 300 or More Days in the Past Year

NSDUH 2013
Why the increase?

Daily Marijuana Use vs. Perceived Risk of Regular Marijuana Use among 12th Graders, 1975-2013

Source: University of Michigan, 2013 Monitoring the Future Study
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 (e.g., 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

**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.”

**Harold and Kumar Go To White Castle, 2004**
Policy timeline

• 1970: Controlled Substances Act passed by Congress, marijuana listed as schedule I drug
• 1985: dronabinol (synthetic THC) approved in the US for treatment of intractable nausea
• 1996-2015: 28 states + PR medical marijuana, 8 states and D.C. legalize recreational use
• 2005: Supreme Court decision (Gonzales v. Raich)
  – Federal law enforcement has the authority to arrest and prosecute MDs or patients
• 2009: Department of Justice Memorandum
  – Federal resources should not be used to prosecute providers and patients who comply with states laws
• 2008-2010: IOM, ACP, AMA
  – Petitioned DEA/FDA to reschedule marijuana to schedule II …it remains schedule I to this day
• March, 10 2015: CARERS bill introduced in Senate
  – Bipartisan group of senators introduced bill to reschedule marijuana
Current *State of the Union*: 28 states medical marijuana laws, 8 states and D.C. with recreational laws
Moderate acute effects

- Acute marijuana intoxication
  - agitation, psychosis, and anxiety
  - tachycardia and hypertension

- Cannabinoid Hyperemesis Syndrome

- Pediatric Exposures

Kim & Monte Annals of Em Med 2016
## Adverse effects of marijuana use

### Table 2. Level of Confidence in the Evidence for Adverse Effects of Marijuana on Health and Well-Being.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Overall Level of Confidence*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addiction to marijuana and other substances</td>
<td>High</td>
</tr>
<tr>
<td>Abnormal brain development</td>
<td>Medium</td>
</tr>
<tr>
<td>Progression to use of other drugs</td>
<td>Medium</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Medium</td>
</tr>
<tr>
<td>Depression or anxiety</td>
<td>Medium</td>
</tr>
<tr>
<td>Diminished lifetime achievement</td>
<td>High</td>
</tr>
<tr>
<td>Motor vehicle accidents</td>
<td>High</td>
</tr>
<tr>
<td>Symptoms of chronic bronchitis</td>
<td>High</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>Low</td>
</tr>
</tbody>
</table>
• 16 person committee reviewed > 10,000 abstracts published since 1999

• Focused on recently published systematic reviews and high quality primary research for 11 groups of health effects including both harms and therapeutic effects

Addiction to MJ: 9% of users overall, 17% if begin during adolescence, 25-50% of daily users

There is substantial evidence that:

- Initiating cannabis use at an earlier age is a risk factor for the development of problem cannabis use

There is moderate evidence of a statistical association between cannabis use and:

- The development of substance use disorder for substances, including alcohol, tobacco, and other illicit drugs

Adolescent vulnerability in IQ decline

Meier M H et al. PNAS 2012
Other cognitive effects of marijuana

• In a large study of 5115 adults at 18-30yo at baseline followed up for 25 years
• Current use of marijuana associated with worse verbal memory and processing speed
• Cumulative lifetime exposure was associated with worse performance in verbal memory, processing speed and executive function
• For each 5 years of past exposure, verbal memory was 0.13 standardized units lower (95% CI, −0.24 to −0.02; \( P = .02 \))
  – corresponds to remembering 1 word less from a list of 15, for every 5 years of use.

Health effects of cannabis and cannabinoids: Psychosocial domains

There is moderate evidence of a statistical association between cannabis use and:

- The impairment in the cognitive domains of learning, memory, and attention (acute cannabis use)

Association between mood disorder and MJ

Blanco et al. JAMA Psychiatry, 2016
Genetic variation influences harmful effects of marijuana

[Chart showing genetic variation and cannabis use]

BIOL PSYCHIATRY 2012;72:811–816
There is substantial evidence of a statistical association between cannabis use and:

- The development of schizophrenia or other psychoses, with the highest risk among the most frequent users

There is moderate evidence of a statistical association between cannabis use and:

- Better cognitive performance among individuals with psychotic disorders and a history of cannabis use
- Increased symptoms of mania and hypomania in individuals diagnosed with bipolar disorders (regular cannabis use)
- A small increased risk for the development of depressive disorders
- Increased incidence of suicidal ideation and suicide attempts with a higher incidence among heavier users
- Increased incidence of suicide completion
- Increased incidence of social anxiety disorder (regular cannabis use)
- Major depressive disorder is a risk factor for the development of problem cannabis use
Pulmonary effects of smoked marijuana

- Acute → bronchodilation (FEV₁ increase ~ 0.15-0.25L)
- Long-term → 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(1)
- At low levels of exposure, FEV₁ increased by 13 mL/joint-year and FVC by 20 mL/joint-year, but at higher levels of exposure, airflow obstruction was observed(2)

1. Tetrault JM et al. Archives IM 2007
2. Pletcher MJ et al. JAMA 2012
Health effects of cannabis and cannabinoids: Respiratory disease

There is substantial evidence of a statistical association between cannabis smoking and:

• Worse respiratory symptoms and more frequent chronic bronchitis episodes (long-term cannabis smoking)

There is moderate evidence of a statistical association between cannabis smoking and:

• Improved airway dynamics with acute use, but not with chronic use
• Higher forced vital capacity (FVC)

There is moderate evidence of a statistical association between the cessation of cannabis smoking and:

• Improvements in respiratory symptoms

Trends in fatal motor vehicle crashes before and after marijuana commercialization in CO

Salomonsen-Sautel, S. *Drug & Alcohol Dependence*, 2014
Health effects of cannabis and cannabinoids: Injury and death

There is substantial evidence of a statistical association between cannabis use and:
• Increased risk of motor vehicle crashes

There is moderate evidence of a statistical association between cannabis use and:
• Increased risk of overdose injuries, including respiratory distress, among pediatric populations in U.S. states where cannabis is legal (9-4b)

Health effects of cannabis and cannabinoids: Other effects

There is substantial evidence of a statistical association between maternal cannabis smoking and:
• Lower birth weight of the offspring

There is limited evidence of a statistical association between maternal cannabis smoking and:
• Pregnancy complications for the mother
• Admission of the infant to the neonatal intensive care unit (NICU)

There is moderate evidence of no statistical association between cannabis use and:
• Incidence of lung cancer (cannabis smoking)
• Incidence of head and neck cancers

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
Synthetic marijuana: K2, Spice, etc.

• General Information:
  – Marketed as safe legal alternative to marijuana; easily accessible; multiple names (Moon Rocks, Yucatan Fire) generally smoked; very common among adolescents

• Effects:
  – Mild euphoria and relaxation
  – The ‘giggles’
  – Increased sensitivity to external stimuli
  – Distortion of time perception
  – Frank, vivid hallucinations

• Neurobiology: CB receptor agonist; lasts up to 6 hrs

• Adverse effects:
  – Dry mouth, palpitations, rapid heart rate, vomiting, agitation, confusion
  – Evolving chemically and difficult to test for in urine
  – May be adulterated with heavy metal residues
Fundamental tension

- Intoxication and withdrawal of marijuana 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
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.
Health effects of cannabis and cannabinoids: Therapeutic effects

There is conclusive or substantial evidence that cannabis or cannabinoids are effective:

- For the treatment of chronic pain in adults (cannabis)
- As antiemetics in the treatment of chemotherapy-induced nausea and vomiting (oral cannabinoids)
- For improving patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids)

There is moderate evidence that cannabis or cannabinoids are effective for:

- Improving short-term sleep outcomes in individuals with sleep disturbance associated with obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and multiple sclerosis (cannabinoids, primarily nabiximols)

# Cannbinoids for medical use: Pain

<table>
<thead>
<tr>
<th>Study</th>
<th>Cannabinoid Events</th>
<th>Placebo Events</th>
<th>Odds Ratio (95% CI)</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetrahydrocannabinol (smoked)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abrams et al, 2007</td>
<td>13</td>
<td>6</td>
<td>3.43 (1.03-11.48)</td>
<td>6.51</td>
</tr>
<tr>
<td>Nabiximols</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GW Pharmaceuticals, 2005</td>
<td>54</td>
<td>50</td>
<td>0.86 (0.54-1.35)</td>
<td>19.02</td>
</tr>
<tr>
<td>Johnson et al, 2010</td>
<td>23</td>
<td>19</td>
<td></td>
<td>10.87</td>
</tr>
<tr>
<td>Langford et al, 2013</td>
<td>84</td>
<td>56</td>
<td></td>
<td>20.19</td>
</tr>
<tr>
<td>Nurmiiko et al, 2007</td>
<td>16</td>
<td>12</td>
<td></td>
<td>9.84</td>
</tr>
<tr>
<td>Portenoy et al, 2012</td>
<td>22</td>
<td>19</td>
<td></td>
<td>14.04</td>
</tr>
<tr>
<td>Selvarajah et al, 2010</td>
<td>8</td>
<td>8</td>
<td></td>
<td>4.63</td>
</tr>
<tr>
<td>Serpell et al, 2014</td>
<td>34</td>
<td>21</td>
<td></td>
<td>14.91</td>
</tr>
<tr>
<td>Subtotal</td>
<td>241</td>
<td>209</td>
<td>1.32 (0.94-1.86)</td>
<td>93.49</td>
</tr>
<tr>
<td>Overall</td>
<td>254</td>
<td>215</td>
<td>1.41 (0.99-2.00)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

30% decrease in pain with cannabinoid vs placebo: OR 1.41 (95% CI, 0.99-2.00)

Whiting PF et al. JAMA.2015;313(24):2456-2473
## Medical Marijuana and OD risk

### Table. Association Between Medical Cannabis Laws and State-Level Opioid Analgesic Overdose Mortality Rates in the United States, 1999-2010

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Primary Analysis</th>
<th>Secondary Analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate (95% CI)</td>
<td>Estimate (95% CI)</td>
</tr>
<tr>
<td>Medical cannabis law</td>
<td>-24.8 (-37.5 to -9.5)*</td>
<td>-31.0 (-42.2 to -17.6)*</td>
</tr>
<tr>
<td></td>
<td>3.7 (-12.7 to 23.3)</td>
<td>3.5 (-13.4 to 23.7)</td>
</tr>
<tr>
<td>Prescription drug monitoring program</td>
<td>5.0 (-10.4 to 23.1)</td>
<td>4.1 (-11.4 to 22.5)</td>
</tr>
<tr>
<td>Law requiring or allowing pharmacists to request patient identification</td>
<td>-7.6 (-19.1 to 5.6)</td>
<td>-11.7 (-20.7 to -1.7)*</td>
</tr>
<tr>
<td>Increased state oversight of pain management clinics</td>
<td>4.4 (-0.3 to 9.3)</td>
<td>5.2 (0.1 to 10.6)*</td>
</tr>
<tr>
<td>Annual state unemployment rate</td>
<td>2.5 (-2.3 to 7.5)</td>
<td></td>
</tr>
</tbody>
</table>

- All models adjusted for state and year (fixed effects).
- $R^2 = 0.876$.
- All intentional (suicide) overdose deaths were excluded from the dependent variable; opioid analgesic overdose mortality is therefore deaths that are unintentional or of undetermined intent. All covariates were the same as in the primary analysis; $R^2 = 0.873$.
- Findings include all heroin overdose deaths, even if no opioid analgesic was involved. All covariates were the same as in the primary analysis. $R^2 = 0.842$.

Bachhuber MA et al. JAMA 2014
State Level Variation

- Physician certification for patients with certain qualifying diagnoses
- Patient may possess only a one month supply (varies from state to state)
  - CT=2.5 oz; WA=12 oz
- Growers are certified by Department of Consumer Protection to cultivate MJ
  - Application fee often prohibitive
- Pharmacists able to obtain a dispensing license from DCP
  - State regulates amount of licenses
Challenges in conducting research on adverse health effects or therapeutic effects of cannabis

- There are specific regulatory barriers, including the classification of cannabis as a Schedule I substance, that impede the advancement of cannabis and cannabinoid research

- It is often difficult for researchers to gain access to the quantity, quality, and type of cannabis product necessary to address specific research questions on the health effects of cannabis use

- A diverse network of funders is needed to support cannabis and cannabinoid research that explores the beneficial and harmful health effects of cannabis use

- To develop conclusive evidence for the effects of cannabis use on short- and long-term health outcomes, improvements and standardization in research methodology (including those used in controlled trials and observational studies) are needed

Interactive teaching scenario: Morning report/role play

• Set up a “spicy,” public health debate regarding legalization of recreational marijuana using the following citation as a spring board for discussion:
  
  Kilmer B. Recreational Cannabis — Minimizing the Health Risks from Legalization. Perspective. NEJM. February 23, 2017

• Assign report participants to one of two groups:
  – Recreational marijuana SHOULD be legalized in all states nationwide
    • Citing adverse effects of criminalization and potential for increasing state budgets through taxation, potential impact on opioid epidemic
  – Recreational marijuana SHOULD NOT be legalized in all states nationwide
    • Citing current research on adverse health effects and natural experiment data from states that have already legalized recreational marijuana

• All arguments need to be evidence-based and factual
Thank you

Questions?

Acknowledgements: several slides adapted from Dr. William Becker (Yale), Dr. Hilary Kunins (NY DPH), Dr. Jeffrety Hunt (Brown), Dr. Zoe Weinstein (BU)
Association between lifetime marijuana use and cognitive function in middle age: The CARDIA Study

Figure 2. Adjusted odds ratios (log scale) between maximum frequency of cannabis use before age 17 years and young adult outcomes in combined data, compared with individuals who have never used cannabis. Error bars show 95% CIs.
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?